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Universidad Rey Juan Carlos

**NEUROPATHIC PAIN
IN SPINAL CORD INJURY
PATIENTS:**

**BEDSIDE-QUANTITATIVE SENSORY
TESTING
AND QUALITY OF LIFE**

Silvia Huelbes Alonso

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D. JULIAN SCOTT TAYLOR, JEFE DEL GRUPO DE INVESTIGACIÓN SENSITIVO-MOTORA Y NEUROLOGÍA EXPERIMENTAL DEL HOSPITAL NACIONAL DE PARAPLÉJICOS DE TOLEDO, COMO DIRECTOR DE ESTE TRABAJO Y D. CARLOS GOICOECHEA GARCÍA, PROFESOR TITULAR DE ESCUELA UNIVERSITARIA DE LA FACULTAD DE CIENCIAS DE LA SALUD DE LA UNIVERSIDAD REY JUAN CARLOS, QUE ACTÚA COMO TUTOR EN ESTE DEPARTAMENTO,

CERTIFICAN:

Que el trabajo de investigación "Neuropathic Pain In Spinal Cord Injury Patients: Bedside-Quantitative Sensory Testing And Quality Of Life", ha sido realizada por Dña. Silvia Huelbes Alonso en el Hospital de Paraplégicos de Toledo y en la Fundación "Pain Relief Foundation" de Liverpool, opta a Tesis Doctoral Europea, y como tal autorizamos su lectura.

y para que así conste a los efectos oportunos, firmamos la presente en Toledo, a 1 de junio de 2006.


J. S. Taylor
Director





S. Huelbes


C. Goicoechea
Tutor



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Abbreviations/Abreviaturas

7day VAS	Average pain intensity during the last week with the VAS	Media de la intensidad de dolor durante la última semana con el VAS
%	Percentage	Porcentaje
25P	25th Percentile	Percentil 25
75P	75th Percentile	Percentil 75
Aaw	Activities away from home	Actividades lejos de casa
Aβ	A beta fiber	Fibra A beta
ACC	Anterior Cingulated Cortical area 24	Área 24 cortical anterior cingulada
Ad	A delta fiber	Fibra A delta
Aff	Affective Distress	Angustia afectiva
AMHs	Mechano- and heat-sensitive A fibre nociceptors	Nociceptores de fibras A sensibles a estímulos de calor y mecánicos
AMPA	a-amino-3-hydroxy -5-methyl-4-isoxazole propionate	a-amino-3-hydroxy -5-methyl-4-isoxazole propionate
ANOVA	Analysis of Variance	Análisis de varianza
ASIA	American Spinal Injury Association	Asociación Americana de Lesión Medular
at	At the level of SCI	Al nivel de lesión
AU	Arbitrary Units	Unidades Arbitrarias
below	Below the level of SCI	Por debajo del nivel de lesión
BST	Bedside Sensory Testing	Pruebas semi-cuantitativas de sensibilidad
C	Cervical lesion	Lesión Cervical
C 7 (e.g)	Lesion at the 7th cervical vertebrae	Lesión en la 7ª vértebra cervical
CaMKII	Calcium/calmodulin-dependent protein kinase II	Proteína quinasa II dependiente de calcio/calmodulin
Cat	Catastrophizing	Catastrofismo
CEPs	Cerebral event related potentials	Potenciales relacionados a eventos cerebrales
cerv	Cervical site	Sitio cervical
CL	Central lateral nucleus	Núcleo lateral central
cm	Centimeter	Centímetro
CNS	Central nervous system	Sistema nervioso central (SNC)
Com	Complete lesion (ASIA A)	Lesión completa (ASIA A)
Cop	Coping Self Statements	(Auto-)Afrontamiento
CPG	Central Pain Generator	Generador de dolor central
CRPS	Complex Regional Pain Syndrome	Síndrome de dolor regional complejo
CSQ	Coping Strategy Questionnaire	Cuestionario de Estrategias de Afrontamiento
CSQ-R	Coping Strategy Questionnaire-Revised	Cuestionario de Estrategias de Afrontamiento-Revisado
DC	Dorsal Column	Columna dorsal
df	degrees of freedom	grados de libertad (gl)
DiR	Distracting Responses	Respuestas Distractoras de los otros
DN4	Douleur Neuropathique 4 questions questionnaire	Cuestionario de Dolor Neuropático de 4 preguntas
DNIC	Diffuse noxious inhibitory controls	Controles inhibitorios nocivos difusos
DREZ	Intervention on the entry of the dorsal root area	Intervención en la entrada del área de la raíz dorsal
Dsta	Distancing	Distanciamiento del Dolor
Dstr	Distraction	Distracción de la Atención
e.g.	For example	Por ejemplo
EMG	Electromyogram	Electromiograma

EMM	Estimated Marginal Means	Medias Marginales Estimadas
e-VAS	Electronic Visual Analogue Scale	Escala Análoga Visual electrónica
g	Gram	Gramo
GABA	Gamma-aminobutyric acid	Ácido gamma-aminobutírico
HCh	Household Chores	Actividades Domésticas
HPC	Heat-pinch-cold	Frío-pinchazo-calor
HRQOL	Health-related quality of life	Calidad de vida relacionada con la salud
HV	Healthy Volunteers	Voluntarios sanos
Hz	Hertz	Herzio
i.e	For example	Por ejemplo
IASP	International Association for the Study of Pain	Asociación Internacional para el Estudio del Dolor
IC	Insular Cortex	Corteza Insular
Ign	Ignoring pain	Ignorancia de las Sensaciones Dolorosas
Incom	Incomplete lesion (ASIA B or C)	Lesión incompleta (ASIA B o C)
Int	Interference	Interferencia en su vida
L4 (p.g)	Lesion at the 4th lumbar vertebrae	Lesión en la 10ª vértebra lumbar
Lco	Life Control	Control de su vida
LTP	Long-term potentiation	Potenciación a largo plazo
m	Month	Mes
MAS	Mechanical Allodynia/Sensibility	Alodinia/sensación mecánica
Max VAS	The highest pain score with the VAS	La tasa más alta de dolor con el VAS
MHS	Mechanical Hyperalgesia/Sensibility	Híperalgesia/sensación mecánica
Min VAS	The lowest pain score with the VAS	La tasa más baja de dolor con el VAS
mm	Milimeter	Milímetro
mN	Milinewton	Milinewton
MPI	Multidimensional Pain Inventory	Inventario de Dolor Multidimensional
MPI-SCI	Multidimensional Pain Inventory – Spinal Cord Injury Version	Inventario de Dolor Multidimensional- Versión para Lesión Medular
MPQ	McGill Pain Questionnaire	Cuestionario de dolor de McGill
MRI	functional magnetic resonance	Imagen de resonancia magnética
MTP	Medium-term potentiation	Potenciación a medio plazo
n	Number of patients	Número de pacientes
N	Number of patients (total sample)	Número de pacientes (muestra total)
NeR	Negative Responses	Respuestas Negativas de los otros
NK1	Neuropeptide receptors NK1	Receptores Neuropeptídicos NK1
NMDA	N-methyl-D-aspartate	N-metil-D-aspartato
No.	Number	Número
NO/PKG	Nitric oxide/protein kinase G	Proteína kinasa G/ Óxido nítrico
NoNP	Non Neuropathic Pain	Sin Dolor Neuropático
NP	Neuropathic Pain	Dolor Neuropático (DN)
NPQ	Neuropathic Pain Questionnaire	Cuestionario de Dolor Neuropático
NT	Not Tested	Sin examinar
°C	Degrees centigrade	Grados centígrados
°C/s	Degrees centigrade per second	Grados centígrados por segundo
Owo	Outdoor work	Actividades fuera de casa
p	Probability/level of significance	Probabilidad/nivel de significación
PAG	Periaqueductal grey formation	Formación gris periacueductal
Para	Praying	Rezo
PET	Tomography of Emission of Positrons	Tomografía de Emisión de Positrones
PHN	Post-herpetic neuralgia	Neuralgia post-herpética
PKA	protein kinase A	Proteína kinasa A
PKC	Protein kinase C	Proteína kinasa C
PS	Post-stimulus Sensations	Sensaciones post-estímulo

QoL	Quality of Life	Calidad de vida
QST	Quantitative Sensory Testing stimulation	Estimulación por examen sensorial cuantitativo
Rad Pain	Radiating Pain localised in another area of the body	Dolor irradiado localizado en otro área del cuerpo
rCBF	regional cerebral blood flow	Fluido sanguíneo cerebral regional
s/sec	Seconds	Segundos
Sac	Social Activities	Actividades fuera de casa
SCI	Spinal Cord Injury	Lesión medular (LM)
SEPs	Somatosensory <i>evoked</i> potentials	Potenciales evocados somatosensoriales
Sev	Pain Severity	Severidad del Dolor
SF-MPQ	Short Form McGill Pain Questionnaire	Forma reducida del Cuestionario de Dolor de McGill
SI	primary somatosensory cortex	Corteza Somatosensorial Primaria
SII	secondary somatosensory cortex	Corteza Somatosensorial Secundaria
SMT	Spinomesencephalic tract cells	Células espinomesencefálicas
SoR	Sollicitous Responses	Respuestas Solícitas de los otros
SPECT	Single-photon emission topography	Topografía de emisión de fotones
SRT	Spinoreticular tract neurons	Neuronas del tracto espinoreticular
STP	Short-term potentiation	Potenciación a corto plazo
STT	Spinothalamic tract cells	Células del tracto espinotalámico
Sup	Support	Apoyo
SYR	Syringomyelia	Siringomielia
t	Student's t	T de Student
T	Thoracic lesion	Lesión Dorsal
T 10 (e.g)	Lesion at the 10th thoracic vertebrae	Lesión en la 10ª vértebra dorsal
TA	Thermal Allodynia/Sensibility	Alodinia térmica
thor	Thoracic site	Sitio dorsal
TS	Temporal Summation to Pin-prick	Sumación Temporal al pinchazo de alfiler
TSAR	Thermal Stimulus And Response System	Sistema de Estímulo Térmico y Respuesta
Unpl.	Sensations of discomfort provoked by the pain during the last week	Molestia provocada por el dolor en la última semana
VAS	Visual Analogue Scale	Escala Análoga Visual
vF	von Frey filament	Filamento de von Frey
VLP	Ventral posterior lateral nucleus	Núcleo lateral posterior ventral
VMpo	Ventro medial pontinus nucleus	Núcleo ventro medial pontinus
VPI	Ventral posterior inferior nucleus	Núcleo inferior posterior ventral
VPM	Ventral posterior medial nucleus	Núcleo medial posterior ventral
WDR	Wide-dynamic-range neurons	Neuronas de rango dinámico ancho
WHYMPI	West Haven-Yale Multidimensional Pain Inventory	Inventario de Dolor Multidimensional West Haven-Yale
yrs	Years	Años

CHAPTER 1. GENERAL INTRODUCTION

1.1. Human Pain Mechanisms

Pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage (**IASP definitions on-line**). Physiological pain is an essential early warning device that alerts us to the presence in the environment of damaging stimuli. All living organisms need to be able to react to noxious stimuli, and a major evolutionary drive for the development of a plastic nervous system might have been the acquisition of the capacity to detect and remember danger. Pain is not homogeneous, and comprises of three categories: physiological, inflammatory and neuropathic pain, the latter being the aim of this study (**Woolf et al., 2000**).

Pain in the uninjured organism is an essential mechanism which initiates an organized defensive reaction to the presence of a potentially damaging stimulus in the environment. Nociception is the response of a receptor preferentially sensitive to a noxious stimulus or to a stimulus which would become noxious if prolonged. Neuropathic Pain is the category which is initiated or caused by a primary lesion or dysfunction in the nervous system (**IASP definitions on-line**).

Woolf et al. (1999) have suggested that pain hypersensitivity is an expression of neuronal plasticity, the duration of which is determined by three distinct processes: *activation, modulation, or modification* (**Fig 1.1**) in the nociceptive process. The process of *modulation* represents reversible changes in the excitability of primary sensory and central neurons mediated by post-translational alterations induced in receptors/ion channels by activation of intracellular signal transduction cascades. *Modification* represents long-lasting alterations in the expression of transmitters, receptors, or ion channels or in the structure, connectivity and survival of neurons, such that the nociceptive system is grossly modified, distorting its normal response characteristics to noxious and innocuous stimuli. These forms of neuroplasticity in nociception have also been suggested to constitute a continuum encompassing the diverse reactions of neurons confronted with continually changing stimuli in the environment. Indeed nociception is an active process within both the peripheral and central nervous system (CNS) affected by multiple processes that determine the gain of the system. (**Woolf and Salter, 2000**).

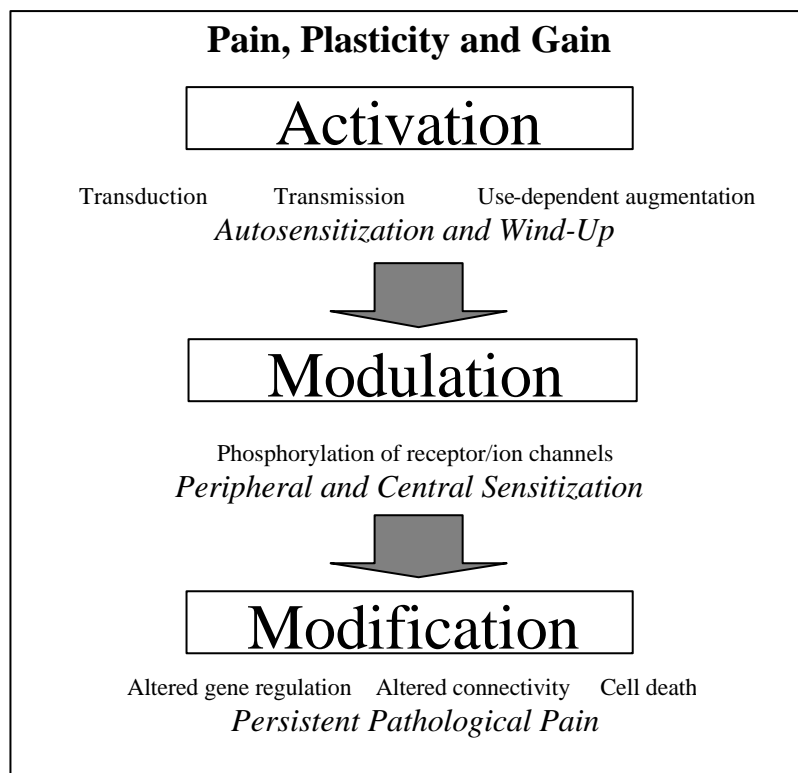


Fig.1.1. Forms of neural plasticity within the nociceptive process proposed to increase gain in the somatosensory system which produces pain hypersensitivity (Woolf and Salter, 2000).

1.2. Classification of Cutaneous Afferent Nerve Fibres.

Nerve fibres have been classified according to their conduction velocity and axon diameter into A- ($A\alpha$, $A\beta$, and $A\delta$) and C- fibre types. $A\alpha$ fibres have a diameter of 12-20 μm , and a conduction velocity of 70-120 m/s. The primary function of these fibres is one of proprioception. $A\beta$ fibres have a diameter of 5-12 μm with a conduction velocity of 30-70 m/sec and are responsible for the transmission of touch and pressure. $A\delta$ fibres have a diameter of 2-5 μm with a conduction velocity of 12-30 m/s and are responsible for the transmission of pain, temperature, and touch. C-fibres are unmyelinated and have a diameter of 0.2-2 μm with a conduction velocity of 0.5-2 m/s. Their functions involve heat, cold, and pressure.

1.3. General principles of central processing of cutaneous sensory information.

The primary afferent fibres from nociceptors end in the dorsal horn of the spinal cord. $A\beta$ fibres constitute the medial division of dorsal roots, mediate sensory modalities consisting of touch, perception of texture, perception of form, and modality termed proprioception, mediated by the dorsal column-medial lemniscal pathways (Willis, 1991). Afferent cutaneous $A\delta$ nociceptive fibres (respond almost exclusively to mechanical nociceptive stimuli) end mainly in laminae I and V whereas C polymodal nociceptors (respond to mechanical, thermal and chemical stimulation) terminate chiefly in laminae I and II based on Rexed's laminar scheme. Neurons exclusively activated by low threshold sensory receptors are called mechanoreceptors. The response of the dorsal horn neurons (either nociceptive or WDR) are not only dependent by the nature of the nociceptive afferent information but also by the interaction of the intrinsic neural systems, descendent or peripheral, that facilitate/inhibit the afferent impulse transmission (Cervero and Laird, 1995; Zhang et al., 1991). Nociceptive neurons within the dorsal horn include wide-dynamic-range and high-threshold cells. Discrimination of painful stimuli depends on signals carried by wide-dynamic-range (WDR) neurons. The main

pathway for pain sensation, the spinothalamic tract, crosses at the segmental level and ascends in the anterolateral quadrant. The ventral posterior lateral thalamic nucleus is a pain centre that probably accounts for sensory discrimination of pain stimuli in man (**Treede, 1999**).

Neurons in several different ascending pathways have been found to respond to noxious stimuli. The activity of WDR neurons shows parallels with second-pain sensation (**Price et al., 1977**). Such neurons demonstrate temporal summation (**Wagman and Price, 1969**), which could account for the increment in second-pain sensation that is produced by repetitive stimulation of C fibres. Stimulation of the axons of presumed WDR spinothalamic tract neurons results in sensations of burning, aching, cramping, and/or sharp pain (**Mayer et al., 1975**).

The spinothalamic tract that projects to the intralaminar complex and to the medial thalamic nuclei, as well as the spinoreticular and spinomesencephalic tracts, contribute to the motivational-affective and other aspects of the pain reaction (**Willis, 1985**). There are also neurons in the spinocervical tract and the postsynaptic dorsal column pathway that are nociceptive, and there may even be direct projections of nociceptors through the dorsal columns to the dorsal column nuclei. One route for pain information outside of the ventrolateral quadrant contralateral maybe mediated by an ipsilateral spinothalamic tract component.

Clinical case studies also indicate that the chief pathway carrying nociceptive information to the human brain is crossed and ascends in the anterolateral quadrant. For instance, anterolateral cordotomies can produce long-lasting analgesia on the contralateral side of the body below the lesion (**Gybels and Sweet, 1989**). The area of pain relief corresponds somatotopically to the sector of spinal cord interrupted, and all forms of pain sensation are abolished if the cordotomy is done bilaterally. Alternative pathways are thought to assume a role in the mediation of pain sensation, since in about half of the cases an anterolateral cordotomy provides relief of pain only for a matter of months (**White and Sweet, 1979**), with the development of central neuropathic pain (**Vierck et al., 1997**). The existence of a component of the spinothalamic tract in the posterior lateral funiculus in human could account for this return of pain. Other possibilities include the ipsilateral component of the spinothalamic tract, the spinocervical tract and the postsynaptic posterior column pathway. **Nathan and Smith (1986)** also suggested the existence of relays that transmit sensations of ongoing dysesthesias across spinal lesions to higher pain centres.

1.4. Sensory processing of Touch-Pressure and Vibration

The sensory receptors thought to signal information about the intensity and duration of prolonged mechanical contact of a stimulus with the skin are the SA I mechanoreceptors. Projected receptive fields of afferent fibres evoking touch-pressure sensation when stimulated through microneurographic electrodes usually coincide with the receptive fields of SA I units (**Ochoa and Torebjörk, 1983**). The gradient of receptive-field size parallels the gradient of the capacity of the human hand for tactile discrimination. Furthermore, the density gradient of SA I receptors (as well as fast adapting FA I receptors, see below) in the glabrous skin of the human hand correspond to the gradient of threshold for two-point discrimination (**Johansson and Vallbo, 1979, 1983**). SA I receptors have a dynamic and a static response; in humans SA I receptors can be entrained by vibratory stimuli (**Järvilehto et al., 1976**) and are most sensitive to frequencies of 2-32 Hz and could contribute to the detection of stimuli having frequency components below 4 Hz (**Johansson et al, 1982**).

The second subtype, SA II, play a less clear role. SA II receptors seem to be involved in touch-pressure (**Harrington and Merzenich, 1970**) but another hypothesis is that they contribute to position sense (**Knibestöl and Vallbo, 1970**). There is no gradient for SA II receptors located on the distal versus the proximal hand surface (**Johansson and Vallbo, 1979, 1983**). Furthermore, the receptive fields are very large. An analysis of the number and spatial distribution of the receptive fields of SA II units indicates that they would not be able to provide the information required for two-point discrimination (**Johansson and Vallbo, 1980**).

Another channel that is involved in mechanoreception is responsible for the sensations of flutter and vibration. The most obvious types of receptors that are candidates for the sense of flutter are the rapidly adapting sensitive mechanoreceptors, which include FA I receptors (Meissner's corpuscles) in glabrous skin and hair follicle and field receptors in hairy skin; and for vibratory sensation is the FA II receptor (Pacinian corpuscle). **Johansson and Vallbo (1979, 1983)** reported that the density of FA I receptors in the human glabrous skin corresponds to the gradient of sensitivity of two-point discrimination, as does the density gradient of SA I receptors (**Bolton et al., 1966**). An analysis of receptive field overlap is consistent with the hypothesis that both FA I and SA I receptors contribute to two-point discrimination (**Johansson and Vallbo, 1980**). Flutter sensation probably results from information that is transmitted by several different routes, including direct projections in the dorsal columns, as well as by activation of neurons belonging to the postsynaptic dorsal column pathway, the spinothalamic tract, and the spinothalamic tract. Vibratory sensation appears to depend upon direct projections in the dorsal columns and upon activation of neurons of the postsynaptic dorsal column pathway.

Clinical observations indicate that recognition of contact with the skin is mediated not only by the posterior columns but also by axons of the anterolateral quadrant. The patients with lesions of the posterior columns could still feel tactile stimuli, but had disturbances in two-point discrimination and difficulty in judging the intensity of pressure stimuli (**Nathan et al., 1986**). These deficits may have been due in large part to interruption of the touch-pressure sensory channel. More clinical evidence indicates that vibratory sensation in humans depends upon transmission of information in the posterior columns, but the spinothalamic tract is sufficient for contact recognition (**Noordenbos and Wall, 1976; Nathan et al., 1986**). Conversely, the patients with lesions of the anterolateral quadrants retained vibratory sensation (**Nathan et al., 1986**). The patient of **Noordenbos and Wall (1976)** with transection of all the spinal cord except for one anterolateral quadrant could still sense mechanical contact bilaterally. However, this probably depended upon rapidly adapting mechanoreceptors.

1.5. Sensory processing of pain

Several types of pain can be described: *superficial and deep pain*. Superficial pain results from intense stimulation of the skin and can be well localized. Deep pain arises from skeletal muscles, tendons, periosteum, and joints and is poorly localized. Visceral pain shares many of the attributes of deep pain, including a tendency to be referred to superficial structures and to induce powerful autonomic responses. Superficial pain can be further subdivided into pricking pain and burning pain. Synonyms are *first* and *second pain*; since a noxious stimulus applied to some parts of the body may evoke the two kinds of superficial pain in temporal succession (early evidence is reviewed by **Lewis, 1942**). It has been proposed that *first and second pain* are produced by activation of *Ad and C fibres*, respectively, and that the temporal lag between the pains is due to different peripheral conduction velocities of the nociceptive afferent fibres that are involved (**Treede et al., 1998**).

In addition to the sensory experience called pain, strong stimuli produce other behavioral events, including flexor withdrawal reflexes (**Sherrington, 1906**), autonomic responses (**Schmidt and Weller, 1970**), arousal, aversive behavior, endocrine changes, and other motivational-affective responses (**Melzack and Casey, 1968; Bonica, 1990; Price, 1999**). Stimuli that evoke a pain reaction are said to be noxious (**Sherrington, 1906**), meaning that they threaten or actually produce damage. Another major consideration in experiments on nociceptive neurons is that it is possible to separate the sensory mechanism from other aspects such as motivational-affective mechanisms. Pain has been experienced in patients in the absence of obvious activity in nociceptive afferents. This *neuropathic pain* is common following damage to peripheral nerves or to certain parts of the central nervous system (**Yeziarski and Burchiel, 2002**).

1.5.1. Nociceptors

Pain receptors (nociceptors) can be found in the skin, muscle, joints, or viscera, and terminate as unencapsulated endings that are generally supplied with either finely myelinated A δ or unmyelinated C

afferent fibres. Nociceptor subtypes include cutaneous A δ mechanical, A δ mechanoheat, C polymodal, C mechanoheat and C heat nociceptors (**Treede et al., 1998**).

1.5.2. Properties of Nociceptors

Mechanothermal unit receptors (AMH) are innervated by A δ fibres in the human skin and respond to more than one modality of noxious stimulation (**Bromm et al. 1984**). The responses to noxious heat can occur without prior heating and the discharge rate can be higher than that shown by C polymodal nociceptors. They can account for the pricking pain that heat pulses provoke (**Lewis, 1942; Treede et al., 1998**). In an experiment by **Kleinbohl et al. (2006)** short-term sensitization was observed to occur only at frequencies above 0.3 Hz and was affected by both stimulus frequency and intensity, but the AMH-fibre (Mechano- and heat-sensitive A fibre nociceptors) related sensitization depended on activation frequencies of over 0.6 Hz; and multiple stimulation of the same skin area during the medium-term resulted in habituation. Differentially, C-fibre innervated mechano-heat-responsive units (CMH, polymodal nociceptors) respond to heat below 50°C (**Schmidt et al. 1995**).

C polymodal nociceptors in the skin of the human hand and foot respond to noxious mechanical, thermal and chemical stimuli (**Bromm et al. 1984**). The receptive fields, larger than in animals, vary in dimensions from 1 by 1 mm up to 6 by 17 mm and often include two to seven spot-like areas. Thresholds for von Frey hairs range from 0.7 to 13.1 g. The C fibres do not show *spontaneous* activity, so that weak mechanical stimuli that activate mechanoreceptors such as air puffs, hair bending, stroking with cotton or skin stretch are ineffective. Moderate-intensity, non-painful mechanical stimuli could cause discharges at low rates, but noxious stimuli produce the highest discharge rates in these units (50-60 impulses/s). The responses are slowly adapting and may present afterdischarges observed following strong stimulation. Repeated stimulation cause receptor fatigue. Cooling is rarely effective in activating these units and warming to 40-45 °C can excite some of them.

Higher levels of activity in these receptors correlated well with pain when the afferent fibres were activated by noxious heat or chemical stimuli, but not with mechanical stimuli (**Van Hees and Gybels, 1981**). The concomitant activation of A β and C fibres by mechanical stimuli result in inhibitory interactions that prevent pain. Noxious heat and chemical stimuli would activate nociceptors without exciting A β fibres, so pain could result from such stimuli without interference from an intrinsic the inhibitory system. Another factor that affects the adequate stimulation of nociceptors may be the spatial characteristics of the mechanical stimulus, since spatial summation makes an important contribution to pain (**Slugg et al., 2000**).

1.5.3. Sensations Evoked by Nociceptors

Activating a population of A δ or C fibres in a human cutaneous or mixed nerve produces considerable pain, but does following single impulse stimulation or with low-frequency afferent discharge. Stimulation of A δ nociceptors in human nerves through microneurography electrodes produces pricking pain, meanwhile C polymodal nociceptors generally produces dull or burning pain, depending on whether the afferent fibres innervate glabrous or hairy skin (**Ochoa and Torebjörk, 1989**). Therefore, the sensations depend upon the activation of small groups of axons. During their repetitive stimulation, no sensation is *evoked* until the stimulus frequency exceeds the threshold activation rate of 3 Hz. Above this threshold, the intensity of the sensation is proportional to stimulus frequency and the sensation is a sustained itch rather than pain (**Torebjörk and Ochoa, 1983**). Polymodal C-fibre nociceptors from a given area of the skin travel together for long distances in peripheral nerves (the localization of a painful heat stimulus is accurate to within a mean distance of 17.1 mm, compared with 11.8 mm for tactile localization (**Jfrum et al., 1989**)).

1.5.4. Pain intensity Coding

Psychophysical tests of the relationship between individual C polymodal nociceptor activation following noxious heat stimulation and the estimation of pain magnitude may be linear in humans (**LaMotte et al., 1982**). Since A δ mechanothermal receptors have a higher threshold for noxious heat pulses than do C polymodal nociceptors, these latter must be responsible for the discrimination of heat pain from threshold (43-45°C) up to levels that can damage the skin (above 50°C). Magnitude ratings depend upon the integrated input from a number of nociceptors. Cutaneous pain in humans depends upon spatial and perhaps temporal summation of the activity of nociceptors (**Adriaensen et al., 1980**); for example in the situation of prolonged mechanical skin compression despite adaptation in C polymodal nociceptor discharge, with an increase in pain intensity.

Andrew and Greenspan (1999) distinguished between slowly and rapidly adapting A δ nociceptors and found that the incrementing pain responses depended on enhanced nociceptive responses in central neurons, as well as an intermittent increase in the discharge rate of A δ nociceptors. Stimulus intensity corresponds more closely to the total number of nociceptor discharge rather than a decrease in interspike intervals.

1.5.5. Peripheral chemical mediation of pain

Peripheral skin damage results in the exposure of nociceptive terminals to algogenic chemicals, including K⁺, H⁺, peptides such as bradykinin, monoamines such as serotonin and histamine, and prostaglandins. Combinations of these inflammatory mediators may excite and/or sensitize chemically responsive nociceptors, resulting in enhanced pain (**Petho et al., 2001**). The membranes of different type of nociceptors contain different combinations of transducer molecules for chemical, mechanical, or thermal stimuli (**Beck and Handwerker, 1974**).

1.5.6. Referred pain

Some subjects with pain refer visceral or deep pain to superficial structures. The *convergence-projection theory* of **Ruch (1946)** is the most likely mechanism, which assumes that somatic and visceral nociceptive afferent fibres converge onto a common pool of neurons in the spinal cord (including spinothalamic tract cells) and transmit somatic pain to the brain. In addition to pain referral, viscerosomatic convergence can help explain the superficial tenderness that may develop secondary to visceral disease. Presumably a change in central excitability occurs, similar to that found in secondary hyperalgesia following damage to the skin.

1.5.7. Inhibitory interactions: Counterirritation.

Strong stimulation of the skin (called “*counterirritation*”) helps alleviate pain, but the exact mechanism is still not clear following stimulation of large afferent fibres. The *gate theory* as an explanation (**Melzack and Wall, 1965**) has been questioned, and it is possible that inhibitory interactions occur in other levels of the nervous system rather than the spinal cord. Furthermore, noxious stimuli in fine afferent fibres are more effective in inhibiting nociceptive transmission than that produced by large afferent fibre or innocuous stimuli (**Chung, 1984**). The functional organization of the system of “*diffuse noxious inhibitory controls*” (**DNIC, Cervero and Wolstencroft, 1984**) appears to involve the activation of pathways that ascend to the brain stem to trigger discharges in inhibitory pathways and which descend as a long loop from the brain stem.

1.5.8. Hyperalgesia and allodynia following skin damage.

According to the IASP, *hyperalgesia* is defined as an increased response to a stimulus which is normally painful; and is a condition in which pain *evoked* by suprathreshold stimuli is more intense (**Hardy et al., 1952**). *Allodynia* is the pain due to a stimulus which does not normally provoke pain (**IASP online definition www.iasp-pain.org**). Primary hyperalgesia and allodynia occur in the

immediate area of skin damage, and sensitization of nociceptors helps account for primary hyperalgesia. Secondary hyperalgesia and allodynia develop in the surrounding undamaged skin area. Repeated application of a noxious stimulus may sensitize nociceptors or suppress their responses, depending upon the intensity of the stimulus. There has been a controversy about the peripheral and central mechanisms implicated. Some authors like **Lewis (1942)** have suggested that secondary hyperalgesia and allodynia is due to a peripheral mechanism, whereas **Hardy et al. (1952)** and more recent evidence indicate that these mechanisms changes depend on changes in central nervous system processing (**Baumann et al.,1991**)

1.6. Temperature sensation and central processing.

The threshold for thermal sensation depends upon factors like the rate of temperature change, the amount of change (°C), the surface area stimulated and the original or “adapting” temperature (**Molinari et al., 1977**). Cold receptors show little change in discharge at midrange (27-33°C) temperatures, but notable changes at higher and lower temperatures. At the extremes of the temperature range (above 45°C and below 18°C) the subject feels heat pain (**LaMotte and Campbell, 1978**) or cold pain (**Wolf and Hardy, 1941**).

1.6.1. Thermal receptors

Thermal pain is *evoked* by the activation of a different set of receptors from those responsible for thermal sensation, even when some responses are activated following slowly adapting mechanoreceptor discharge. Evidence suggests that warm and cold sensation channel are independent. For example, spinal cord disease can produce a dissociated loss of either cold or warm sensation (**Head and Thompson, 1906**). **Defrin et al. (2002)** found that warm and cold stimuli produced a sensation of pricking pain in areas lacking any thermal sensibility. Cold stimuli were perceived as warm in areas in which only warm sensation was preserved, and vice versa. These data suggest that the integrity of non-noxious thermal systems is essential for the normal perception of thermal pain, and that the subjective sensation of pain depends on the integration of information from nociceptive and non-nociceptive channels.

1.6.2. Warm Receptors

Warm receptors have spot-like receptive fields (**Konietzny and Hensel, 1979**) and have been estimated to lie about 0.6 mm below the surface of human skin (**Bazet et al., 1930**), though their structure is unknown. When the skin temperature is increased from a neutral level of 32° C to 43° C, warm receptors discharge more vigorously, and the intensity of the sensation of warmth increases in parallel (**Konietzny, 1984**). There is a low-threshold subgroup that produce static discharge at 32° C and have a bell-shaped stimulus-response curve with maximal activation at 38-43 °C; and a high-threshold group that begins to discharge only when the skin temperature is raised above 35-38° C with a maximum firing rate observed at or above 45° C (**Konietzny, 1984**). However, as the temperature increases into the noxious range, the discharges of the high threshold warm receptors decrease (**Iggo, 1969; Hallin et al., 1981**) though they may evoke the sensation of heat (**Konietzny, 1984**). Heat pain in the range of 43-45 °C can be attributed to the activation of C polymodal nociceptors. A “central threshold” for warm sensation requires summation of input from warm receptors (**Konietzny and Hensel, 1979**) and a population of 50 warm receptor innervated fibres would be required (**Johnson et al., 1979**).

1.6.3. Cold receptors

The receptive fields of cold receptors in humans are small spots of about 1mm in diameter and are situated on average 0.15 mm from the surface of the skin. The maximum discharge rate for a given receptor occurs at a temperature somewhere between 18 and 34° C (**Iggo, 1969**). But some cold fibres also discharge more vigorously when the temperature is elevated to 45-50° C. This effect is called the

“paradoxical response” of cold receptors (**Kenshalo and Duclaux, 1977**) and is apparently mediated by changes in vasomotor tone (**Long, 1977**). The bell-shaped stimulus-response curve for cold fibres makes it difficult to understand how a human subject can discriminate the intensity of thermal stimuli (**Järvilehto, 1973**). Intensity coding may be explained by the total amount of neural activity that is *evoked* by a thermal stimulus (**Erickson, 1973**); it may also depend on the recruitment of other types of cold receptors (**LaMotte and Thalhammer, 1982**) with a monotonic stimulus-response curve at low temperatures (10-30° C). When cold becomes extreme (less than about 15° C), cold nociceptors are activated, leading to cold pain (**Simone and Kajander, 1997**).

At a given adapting temperature, the response of a cold receptor is linearly related to the amplitude of the ramp change in temperature (**Kenshalo and Duclaux, 1977**). The threshold for detection of cooling transients is about 0.02-0.05° C (**Hardy and Oppel, 1938; Kenshalo et al., 1968**), well below the threshold for discrimination of static temperature levels. Activation of a single cold receptor may not evoke a cold sensation unless the discharge rate reaches a high level. This presumably reflects the need for summation to reach the “central threshold” for cold sensation. **Järvilehto (1973)** estimated that a cold sensation *evoked* from a cold spot can be correlated with a discharge frequency of 80 impulses/s in a single cold fibre.

The neural system for judging thermal stimulus intensity acts like an integrator, summing the neural activity during the dynamic response. When ramp stimuli are used, a change in the slope of the ramp does not alter the estimate of intensity, but rather the time at which the maximum intensity is experienced (**Kenshalo and Duclaux, 1977**). According to **Johnson et al. (1973)** decisions can be made about which of two cold stimuli is colder within 2 s and the total information from 16 cold fibres is required. Due to the latencies of cold and warm fibre responses, the sensation of coolness is distinctly slower than that for the sensation of warmth (**Kenshalo and Duclaux, 1977**).

1.6.4. Central projection of thermoreceptors

It is likely that afferent A δ and C fibres from cold and warm receptors also end in one or more of the laminae I, II and V, especially in the superficial laminae. However, individual labelled thermoreceptive afferent fibres have not been traced to their endings. Cold pulses may produce dynamic and then static responses in second-order cells; these responses are graded with stimulus intensity (**Iggo and Ramsey, 1976**). However, some units have only static or only dynamic responses (**Hellon and Misra, 1973**).

In some studies, a high proportion of the thermoreceptive neurons of the dorsal horn were found to project contralaterally at least to the level of the cervical spinal cord (**Iggo and Ramsey, 1976**). **Norrzell (1983)** demonstrated that the ascending thermosensory pathway is located in the middle of the lateral funiculus, but in humans the question of whether axons of lamina I spinothalamic tract cells also ascend in more posterior areas of the lateral funiculus than axons of spinothalamic neurons in deeper laminae. Neurons that respond to cold have been recorded in the thalamus, in the region of the VMPO thalamic nucleus in humans (**Davis et al., 1999**).

1.6.5. Clinical Correlations

Spinal cord lesions produce a differential loss of thermal or pain sensation (**Head and Thompson, 1906**), attributed to a partial separation of the temperature and pain pathways, with the thermal projection lying more posterior in location than the pathway that mediates pain sensation (**Foerster and Gagel, 1932**). Thermal sensations may be *evoked* by stimulation in the anterolateral quadrant of the cord (**Mayer et al., 1975**). Thus, a crossed pathway in the anterolateral quadrant mediates thermal sensation in humans; this pathway is presumably the spinothalamic tract. The tract of Lissauer distributes thermal information over several segments along the ipsilateral side of the cord, as it does pain information (**Hyndman, 1942**).

1.7. Descending control of ascending sensory pathways.

Spinothalamic tract cells (STT cells) are subject to a of powerful descending controls that can suppress pain (Mayer and Price, 1976). They can be inhibited following electrical stimulation of the nucleus raphe magnus (Gerhart et al., 1981), medullary reticular formation (McCreery and Bloedel, 1975), periaqueductal gray (PAG) and midbrain reticular formation (Hayes et al., 1979), parabrachial region (Brennan et al., 1987), periventricular gray (Ammons et al., 1986), VPL nucleus (ventral posterolateral nucleus of the thalamus, Gerhart et al., 1981), and the primary sensory and posterior parietal cortex (Yeziarski et al., 1983). STT cells are sometimes excited following stimulation in the medial brain stem (Haber et al., 1980), especially in the reticular formation (Basbaum and Fields, 1984), and often following stimulation of the motor cortex or pyramid (Yeziarski et al., 1983).

Spinoreticular tract neurons (SRT neurons) are under the influence of descending modulatory systems. Some SRT neurons are inhibited by stimulation of the reticular formation (or by stimulation of the vagus nerve, Haber et al., 1982). Others are excited by reticular formation stimulation (Giesler et al., 1981). Such neurons may in turn excite other spinal cord neurons and thus account for part of the excitatory receptive fields of neurons such as the STT cells that project to the CL nucleus (central lateral nucleus), SRT neurons with complex receptive fields, and many neurons that receive visceral afferent input (Cervero et al., 1985). Alternatively or additionally, excitation of SRT neurons may reflect activity in spino-bulbo-spinal loops that produce a prolonged action in inhibitory circuits, such as the diffuse noxious inhibitory control (DNIC) system (Cervero and Wolstencroft, 1984).

Spinomesencephalic tract cells (SMT cells) can be inhibited or excited by stimulation in the nucleus raphe magnus, modularly reticular formation, PAG, or midbrain reticular formation. Frequently, the inhibition is preceded by excitation (Yeziarski, 1990). Little is known about the descending control of the spinomedullary pathway to nucleus Z or of the spinohypothalamic and other spinolimbic system pathways.

1.8. Neuropathic pain after CNS injury: Characteristics and mechanisms.

Neuropathic pain (NP) results from lesions or chronic alterations in peripheral or central nerve pathways. It may develop and persist in the absence of an evident nociceptive stimulus in contrast to normal nociceptive somatic pain. The symptoms may be focal or more generalized. Characteristically, the symptom is presented as a tonic painful or burning sensation (dysesthesia) accompanied with exaggerated response (hyperalgesia), or the perception of a non-nociceptive stimulus as painful (allodynia). These terms are grouped in hyperpatia and are characteristic of an altered hypersensitivity (**IASP definitions on-line**, see above). Central pain is common in patients with stroke, multiple sclerosis, syringomyelia, and spinal cord injury. It frequently develops after a delay of weeks or months, is associated with a sensory change involving the spinothalamic pathways, and has a poor prognosis for *spontaneous* remission. Possible hypotheses that explain the varied clinical manifestations can be divided into two categories: those stressing aberrant neural activity in the deafferented circuits and those focussing on the postlesion imbalance between facilitatory and inhibitory neural pathways. All models inherently assume a degree of specialization of cerebral structures in pain processing (Nurmikko, 2000).

The clinical features of NP may include some of the following:

- Only a fraction of individuals who develop a CNS lesion associated with central neuropathic pain develop such a pain state (Boivie, 1994).
- Time of onset varies from immediately after injury to years after the lesion (Pagni, 1998). A rapid onset suggests that damage to the CNS interrupts or alters maintained functional activity, such as tonic inhibition of pain transmission neurons. NP is often permanent (Boivie, 1994; Pagni, 1998)

- A strong relationship between the presence of central neuropathic pain and abnormalities in somatic sensation.
- Central neuropathic pain may be projected to a large area of the body and the distribution corresponds somatotopically to the site of the lesion.
- The pain in central neuropathic pain can have any quality (**Boivie, 1994; Beric et al., 1988**) though burning pain seems to be the most common.
- Neuropathic pain may have different qualities (**Davidoff et al., 1987**) including “intermittent, shooting, or lancinating” (**Pagni, 1998**).
- There does not seem to be any strong correlation between pain quality and the location of the causal lesion (**Boivie, 1994**).
- Central neuropathic pain can be influenced by stimulation of the skin, movement, visceral stimuli and psychological state, including emotional responses (**Boivie, 1994; Pagni, 1998**).

1.8.1. Enhanced excitability: Irritable focus

This is a region of nervous tissue in which neural circuits become hyperexcitable and activity of the irritable focus evokes central pain (**Dejerine and Roussy, 1906; Pagni, 1998**). Ascending sensory projection cells, such as hyperexcitable STT neurons following a spinal cord lesion may consequently increase their activity and produce pain (**Riddoch, 1938**). A parallel mechanism in peripheral neuropathic pain is the upregulation of sodium channels in the primary afferent neurons after nerve damage and the development of ectopic discharges from the region of the neuroma or from dorsal root ganglion cells (**Lyu et al., 2000**), and observations following SCI suggest upregulation of NAV 1.3 channels in the thalamus and spinal cord (**Hains and Waxman, 2006**). Haemoglobin from haemorrhage into a spinal lesion may also increase excitability of neurons in the gray matter whose axons ascend in the ipsilateral lateral funiculus (**Vierck and Light, 1999**).

1.8.2. Enhanced excitability: Central sensitization

Central sensitization to stimuli in several experimental models has been studied extensively at the level of the spinal cord in models of acute inflammation; for example, intradermal injection of capsaicin results in an enhanced responses of primate STT neurons (**Baumann et al., 1991**). Central sensitization depends on the activation of both ionotropic and metabotropic glutamate receptors and neuropeptide receptors such as NK1 receptors (**Dougherty and Willis, 1991; 1992**). These neurotransmitter events lead to the activation of intracellular signal transduction pathways involving a number of protein kinases, including calcium/calmodulin-dependent protein kinase II (CaMKII), protein kinase C (PKC), nitric oxide/protein kinase G (NO/PKG), and protein kinase A (PKA, **Lin et al., 1996; 1997; 1999**). Consequences of the activation of protein kinases include phosphorylation of N-methyl-D-aspartate (NMDA) receptors (**Zou et al., 2000**) and of α -amino-3-hydroxy-5-methyl-4-isoxazole propionate (AMPA) receptors (**Fang et al., 2000**). Phosphorylation of excitatory amino acid receptors can enhance their responsiveness (see “Modulation” in Fig. 1.1., **Cheng and Huang, 1992**). These mechanisms are similar to those involved in long-term potentiation (LTP) in brain structures such as the hippocampus, and so it is reasonable to consider central sensitization in the spinal cord to be a form of LTP (**Willis, 2001; see Discussion chapter 3**), which presumably requires changes in gene expression (see “Modification” Fig 1.1). These changes may be initiated in response to activation of immediate early genes, such as c-fos (**Wu et al., 2000**).

1.8.3. Disinhibition

Disinhibition could contribute to central neuropathic pain that originates from injury to the spinal cord, essentially interrupting inhibitory pathways that descend from the brain to the spinal cord, known as the endogenous analgesia system (**Fields and Besson, 1988**). Transynaptic loss of dorsal horn inhibitory interneurons after PNS/CNS injury may contribute to peripheral neuropathic pain (**Sugimoto et al., 1990**) and central pain (**Drew et al., 2004**). The loss of dorsal horn interneurons may relate to excitotoxicity produced by release of an excessive amount of glutamate from A β fibres that

sprout grow into the superficial dorsal horn (**Woolf et al., 1992; Coggeshall et al., 2001**) and from the liberation of glutamate following SCI (**Yeziarski et al., 1996**).

At the higher level central sensitization may also involve disinhibition due to loss of effectiveness of inhibitory mechanisms within the spinothalamo-cortical pathway. Another suggestion is that disinhibition is produced by interruption of corticothalamic inhibitory projections that end in the lateral thalamus, resulting in an increased responsiveness within the thalamus (**Head and Holmes, 1911**). Alternatively, interruption of projections from the reticular nucleus of the thalamus could lead to disinhibition of thalamic neurons (**Cesaro et al., 1991**) following a lesion that impinges on the thalamus. Thalamic pain initiated by interruption of the dorsal column-medial lemniscus pathway has been suggested to result from disinhibition of transmission through the STT and associated nociceptive pathways (**Foerster, 1927**). This is consistent with the fact that stimulation of the dorsal column can be used to relieve pain (**Shealy et al., 1967**), possibly by inhibiting nociceptive transmission at a supraspinal level (**Gybels and Sweet 1989; Meyerson 1990**). However, evidence shows that central neuropathic pain can occur with no deficit in dorsal column-medial lemniscus sensory modalities, including touch, vibratory sense and proprioception (**Biernacki 1956; Beric et al., 1988; Boivie et al., 1989**).

1.8.4. Alternative nociceptive pathways following Interruption of the spinothalamic tract

Surgical interruption of the spinothalamic system does not relieve central neuropathic pain (**Tasker, 1990**) and this argues against the idea that hyperexcitable spinothalamic neurons are responsible for central neuropathic pain after a spinal cord lesion. The presence of an irritable focus could develop excite spinal neurons which give to the activation of other alternative nociceptive pathways other than the STT. Another theory of central neuropathic pain is that when nociceptive transmission is completely interrupted in the spinothalamic system on one side, nociceptive transmission may occur through alternative nociceptive pathways (**Craig, 1991**), such as the ipsilateral STT, the postsynaptic dorsal column pathway, the spinocervical tract, the spinoparabrachial tract, the spinothalamic tract, spinolimbic tracts, and the spinoreticular tract (**Willis and Coggeshall, 1991**).

1.8.5. Deafferentation induced pain in thalamic pain centres

Central neuropathic pain may occur after lesions that interrupt the spinothalamic pathways, whether or not the dorsal column-medial lemniscus system is also affected (**Boivie et al., 1989; Pagni, 1998**). The nuclei in the ventroposterior thalamus that receive nociceptive spinothalamic and trigeminothalamic projections include the ventral posterior lateral (VPL) nucleus, its trigeminal equivalent, the ventral posterior medial (VPM) nucleus, and the ventral posterior inferior nucleus (VPI), as well as parts of the posterior complex (**Mehler et al., 1960; Zhang et al., 2000; Willis et al., 2001**). Nociceptive responses have been recorded from neurons in all of these nuclei (**Pollin and Albé-Fessard, 1979; Lenz et al., 1994**). Damage to the STT pathway may induce *spontaneous* activity in thalamic pain centres and perhaps heightened responsiveness to inputs from other pathways (**Levitt and Levitt, 1981**). Evidence in support of this is the observation of burst discharges in thalamic neurons in human patients and the development of novel receptive fields following SCI (**Lenz, 1989**). The electrical stimulation in the ventrocaudal nucleus of the thalamus or the rostromedial part of the medial brain of patients with NP provoke referred pain in the desafferented part and it is similar to the own patient's pain (**Lenz et al., 1998**), and it seems to be related to *evoked* pain. The mechanisms are not clear, but they may be caused by a reduced GABAergic inhibition, a perturbed balance between the medial and lateral thalamus, disinhibition between the spinothalamic pathways, or changes in the afferent excitatory conduction of the spinothalamic tract transection (**Jensen and Lenz, 1995**). The projection towards the cortex may explain the somatotopic and conscious representation of pain. Another way in which upstream neurons could be affected by the loss of a major input would be through upregulation of neurotransmitter receptors, a form of denervation supersensitivity. Another change could be transneuronal degeneration and subsequent reorganization of the remaining postsynaptic neurons.

1.8.6. Genetic and psychological susceptibility to pain

The liability for developing chronic pain state following peripheral nerve injury may also have a genetic component (**Mogil et al., 1999a,b**) and it would not be surprising if a similar genetic dependence applies to central pain. Recently a psychophysical study in man indicates a correlation between subjects who utilize “catastrophizing” as a cognitive strategy with the degree of central sensitization to pain (**Widerström-Noga et al., 2006**).

1.9. Experimental pain methods

Studies of pain mechanisms in normal, pain-free individuals provide a degree of experimental control not found either in clinical pain studies or with laboratory animals. The goals of pain studies in normal individuals can be divided into at least five overlapping categories: measurement, development and validation of pain measures; assessment of analgesic efficacy; evaluation of underlying mechanisms of pain and pain control; studies of psychological variables and constructs involved in pain experience/report; and finally use of experimental methods as an adjunct to clinical pain assessment. Once an external stimulus is applied to create the experience of pain, this experience can be evaluated by a number of verbal, behavioural and physiological measures.

1.9.1. Sensory stimulation

Heat is one of the most commonly used methods of evoking experimental pain sensations. The temporal and spatial properties are easily varied and the stimulation excites a known group of nociceptors. Heat pain is commonly applied by contact or by radiant sources. Objects heated by water baths or by contact thermodes can administer contact heat. Modern contact thermodes use the Peltier principle in which a direct current through a semiconductor substrate results in a temperature increase on one side and a temperature decrease on the other. The magnitude and direction of stimulus change is proportional to the magnitude and polarity of the stimulating current (**Kenshalo and Bergen, 1975; Marchand and Arsenault, 2002**). Other contact stimulators use circulating fluid, or electrical heaters, which may be cooled by circulating fluid (**Petzke et al., 2003**). Radiant heat is a classic stimulation method (**Hardy et al., 1952**). Modern adaptations employ a laser stimulus source (**Greffrath et al., 2002**).

Cold stimuli are administered by contact stimulators described above, by administration of coolant sprays or by immersion in fluid. These methods can be divided into those delivering discrete stimuli and methods producing continuous stimulation.

Mechanical pressure is a classic method in which pain sensations are *evoked* by deformation of the skin via von Frey hairs and needles, by application of gross pressure, by pinching, by high velocity impact via probes or projectiles, and by balloon or fluid distension of viscera. Phasic or tonic stimulation with sharp or punctuate mechanical probes is useful in studies of nociceptor function and phenomena such as temporal summation (**Andrew and Greenspan, 1999**).

Electrical stimulation is applied to the skin (**Donaldson et al 2003**), teeth (**Motohashi et al., 2002**), muscle (**Kosek and Hansson, 2002**) and stomach or intestine (**Arendt-Nielsen et al., 1997**) and is applied directly to peripheral (**Weidner et al., 2002**) and central (**Davis et al., 2000; Lenz et al., 1998**) neurons.

Chemical stimulation has been applied to intact, punctured or blistered skin amongst others. (**Drewes et al., 2003**). The use of topical or intradermal capsaicin, the pungent ingredient in chilli pepper, is a special case in which the primary pain of the application is of less interest than the phenomena of primary heat hyperalgesia and secondary mechanical allodynia and hyperalgesia (**Byas-Smith et al., 1999; Gottrup et al., 2000; Wang et al., 2000**).

1.9.2. Psychophysical techniques for pain measurement

Pain is both a somatic sensation and a powerful feeling state which evokes behaviours that minimize bodily harm and promote healing (**Wall, 1979**). The sensory and affective (unpleasantness) aspects of the pain experience have been assessed by a number of scaling methods. In some cases, different types of scale were used to measure the two dimensions. The results of several studies suggest that the combination of instructions to the subject and the labels on a VAS (“the most intense pain sensation imaginable”, “the most unpleasant feeling imaginable”) are sufficient for discrimination of intensity and unpleasantness (**Price 1988**).

The “pain threshold” is used to describe general pain sensitivity and its use is associated with the concept of variability between different individuals. This high threshold implies a difference in the nervous system such that it takes extra input for such a person to feel pain and a greater input to feel the same level of pain as a person with a more normal threshold. Unfortunately, the threshold is also associated with the labels chosen to describe the sensation processed by the nervous system. The pain threshold can be determined by the classical “Method of Limits” (**Engen, 1971**) which administers ascending and descending trials, the “Method of Adjustment” in which the subject adjusts stimulus intensity, and the “Method of Constant Stimuli” in which a set of fixed stimuli are presented several times in a random sequence (**Chen et al., 1996**).

Tolerance measures and the threshold procedures described above can be considered to be “stimulus-dependent” methods since the dependent variable is an amount of stimulus intensity (or time) corresponding to a fixed response of pain threshold. In contrast, many of the suprathreshold scaling procedures can be classified as “response-dependent” methods. These methods deliver a series of discrete stimuli of varying but fixed intensity in random sequence. The dependent variable is some measure of subjective response; including both discrete numerical (1-10) or verbal (mild, moderate, severe) categorical scales, and bounded continuous response dimensions such as the visual analogue scale (VAS). Theoretically unbounded measures, such as numbers or time duration, are used with psychophysical scaling techniques of magnitude estimation and cross-modality matching. The use of these pain scales is able to characterize pain signalling, when quantitative stimuli are employed to determine the threshold and the intensity of pain (**Price, 1999**). Ratio scales like the VAS are the most useful for the evaluation of pain intensity and are very reproducible when are applied to groups of patients during different temporal moments (**Price, 1999**).

1.9.3. Neurophysiological techniques for pain measurement

Microneurography recording of afferent activity in animals has provided a wealth of information about the function of nociceptors. **Andrew and Greenspan (1999)** recently linked such methods to human pain responses by presenting identical stimulus protocols, including diagnostic nerve blocks, to humans and rats, comparing the human psychophysical responses to the physiological responses in the rat. The observed increase in perceived sensation during tonic mechanical stimulation could be attributed to central summation of activity from C fibre and possibly Ad afferents, and also from possible peripheral mechanisms including delayed excitation of both C fibre and Ad nociceptors.

Most studies of *pain-related reflexes* assess spinally mediated electromyogram (EMG) response to a brief intense stimulus. Several measures of reflex activity, such as the H reflex, the nociceptive (RIII) reflex, jaw inhibitory reflexes and the blink reflex have been investigated in human subjects. These reflexes are commonly elicited by electrical stimulation (also by laser). These measures have been shown to correlate with verbal report and serve as a marker for nociceptive threshold when compared to the results of the compound action potential (**Dowman, 1993**). Reflex measures of pain sensitivity may also be relatively resistant to psychological factors that influence verbal reports of pain.

There is also an increasing employment of both methods used to assess *supraspinal processing* and in the knowledge gained from these methods. Application of a temporally controlled stimulus can evoke

a small, synchronized response in the EEG embedded in non-synchronized (noise) EEG activity. Averaging multiple trials reduces the influence of random, non-synchronized activity, revealing a waveform of about 1s in duration that can be characterized by the amplitude and latency of positive and negative peaks. Early, short-latency components of the waveform have been associated with sensory components of these inputs. Termed cortical *evoked* potentials, cerebral event related potentials (CEPs) or somatosensory *evoked* potentials (SEPs), these measures have been studied extensively and under certain conditions correlate with both stimulus intensity and verbal report. These studies use CEPs *evoked* by electrical, laser, contact heat and mechanical stimulation to assess a number of research goals. Many of these methods have examined the waveform and topography of *evoked* responses to stimuli applied to various locations including comparisons within the hand, skin and muscle (**Niddam et al., 2001**), and oesophagus and colon (**Rossel et al., 2001**). Despite the accelerated growth of functional brain imaging of pain, the results of these CEP studies clearly demonstrate an important advantage of these methods in that they provide a high resolution in the time domain that complements the spatial resolution provided by methods such as fMRI.

The electrical currents measured by the EEG can also be assessed by measuring the minute *magnetic fields* generated by variation in these currents. The EEG and magnetic methods discussed above can provide spatial information by the use of numerous detectors and appropriate analysis software. Advances in functional brain imaging have resulted in a number of techniques that visualize brain function in three dimensions by assessing glucose utilization or by changes in regional cerebral blood flow (rCBF). Although methods such as rCBF assessment in pain states have been performed with single-photon emission topography (SPECT) and by inhalation of tracers or MRI spectroscopy, the predominant methods are PET and fMRI.

1.10. Psychological mechanisms of pain affect.

Unpleasant emotional feelings are integral components of pain because of unique sensory qualities and because these qualities often occur within a context that is threatening, such as during disease or physical trauma. Thus, pain contains both sensory and affective dimensions and is often accompanied by desires to terminate, reduce, or escape its presence (**Melzack and Casey, 1968; Price 1999**). Part of the affective dimension of pain is the moment-by-moment unpleasantness of pain, made up of emotional feelings that pertain to the present or short-term future, such as distress or fear. Pain unpleasantness is often, although not always, closely linked to the intensity of the painful sensation. Another component of pain affect, "secondary pain affect," includes emotional feelings directed toward long-term implications of having pain (e.g., "suffering").

The multidimensional scaling of verbal descriptor items has examined the structure of the McGill Pain Questionnaire (MPQ), which is probably the most widely used multidimensional instrument. Results of experiments confirm the two main dimensions of sensory intensity and affect/unpleasantness, but they have resulted in different category assignments and variations in the overall organizational scheme of hierarchical categories (**Kwilosz et al 1983**). Non-verbal measures are also necessary in some populations, such as infants or in adults with poorly developed language skills.

Multiple factors contribute to pain unpleasantness. Several sensory attributes of pain dispose unpleasant emotional feelings. The foremost among these is that sensations of pain are often more intense than other types of somatic sensations. In addition, pain presents characteristics of slow adaptation (i.e., persistence), temporal summation (for some types of pain), spatial spread of sensation at suprathreshold levels, spatial summation, and unique sensory qualities, as implied by words such as stinging, burning, and aching (**Melzack and Casey, 1968; Price, 1999**). Sensory attributes dispose us to perceive pain as invasive and intrusive for both the body and consciousness (**Price, 1999**). Both neural and psychological processes related to pain-related sensation can be conceived as important causal links in the production of pain-related emotional disturbance. The persistence of pain enhances unpleasantness over time.

Nociceptive, exteroceptive (e.g., sight and sound), and interoceptive sensory processes (e.g., startle and increased autonomic responses) may provide parallel contributions to pain affect (**Price, 1999**). Consistent with **Damasio's (1994)** neurological view of emotion mechanisms, pain unpleasantness reflects the contribution of several sources, including pain sensation, arousal, autonomic, and somatomotor responses, all in relation to meanings of the pain and to the context in which pain presents itself. Psychophysical studies demonstrate that pain sensation and pain unpleasantness represent two distinct dimensions of pain that demonstrate reliably different relations to nociceptive stimulus intensity and are separately influenced by various psychological factors. Some psychological factors, (i.e. Hypnotic suggestions given for enhancing and decreasing only pain unpleasantness, **Rainville et al., 1999**) selectively influence pain unpleasantness and others alter pain unpleasantness in response to changes in pain sensation (**Price, 1987; 1999**).

Unlike pain unpleasantness, secondary pain affect is based on more elaborate inner reflection related to that which one remembers or imagines. This involves meanings such as perceived interference with one's life, difficulties of enduring pain over time, and the implications for the future (**Price, 1987; 1999**). Pain is often experienced not only as a threat to the present state of one's body, comfort, or activity but also to one's future well-being and life in general. The perceived implications that present distress holds for future well-being and functioning support the link between pain unpleasantness and secondary pain affect.

Using **Eysenck and Eysenck's** personality inventory (**1975**) in myofascial pain dysfunction, patients were found to have the personality trait of neuroticism, but this factor had no influence on sensory ratings of experimental heat pain or clinical pain. Neuroticism has been associated with a small but statistically significant enhancement of patients' unpleasantness ratings of both experimental and clinical pain. Finally, patients with a high neurotic score rated emotions of secondary pain affect (i.e., depression and anxiety) as much more negative in comparison with low neurotic score patients. Extroverts and introverts did not differ in their ratings of any pain dimensions (**Harkins et al., 1989**).

The same overall pattern of results was obtained in a study of 205 chronic pain patients (**Wade et al., 1992**). Both studies demonstrated that neuroticism exerted its largest influences not on the early stages of pain sensory processing and pain unpleasantness, but on the secondary pain affect. The sequential model of intensity-unpleasantness-secondary affect was also supported by multivariate (linear structural relations) analysis of pain dimension ratings by 1008 chronic patients.

1.10.1. Impact of pain on quality of life (QoL) measures.

Neuropathic pain is associated with changes in mood states and function independent of the evolution of pain development. Psychological factors are related with the presence and severity of pain and with more depressive symptoms and perceived stress in central pain syndromes (**Siddall et al., 2003**). Measures of pain-related physical function often confound the measurement of physical and psychosocial function. While health-related QoL measures do not provide a complete solution to this challenge, in many situations health-related QoL measures complement, and may even be preferable to pain-specific measures. Indeed the combination of pain intensity scales like the VAS (**Woolf et al., 1999**), combined with cognitive scales (CSQ and MPI; **Widerström-Noga et al., 2002**), are techniques that may facilitate the comparison of data obtained with psychological and neurophysiological methods.

QoL remains an ill-understood concept in medicine. Studies in the area suggest three important approaches to standardize and measure QoL: Health-related quality of life (HRQOL), Well-being, and QoL as a superordinate construct. To measure HRQOL and well-being various instruments are used such as the SF-36, Sickness Impact Profile, Satisfaction With Life Scale and finally the Life Satisfaction Questionnaire – LiSat. Inspection of the QoL measure is necessary to identify QoL domains; most measures lack sufficient evidence of reliability and validity, and longitudinal studies starting in the early phase of rehabilitation are necessary to reveal the course and predictors of QoL of persons with central injuries such as SCI (**Post et al., 2005**).

Thus, the QoL is considered the main aspect in clinical research and health promotion, and it is especially useful for people with SCI and pain, where the impairment is incurable or insufficiently understood. The Coping Strategies Questionnaire *CSQ* (**Rosenstiel and Keefe, 1983**) is used to identify the psychological response to pain. The CSQ rates the frequency of the patients to adopt seven different coping strategies when they feel pain. Several studies identified *catastrophizing*, but not other coping strategies, as consistently associated with psychological anxiety and pain interference in the activity. Higher levels of pain are related with lesser autoefficiency. Although more longitudinal studies are needed, it may be concluded that the higher catastrophizing by the SCI patient, the higher pain intensity and psychological stress (**Turner et al., 2002**). Other scales of QoL in SCI pain patients have been used MPI-SCI (**Widerstom-Noga et al., 2002**).

1.11. NP after SCI: Epidemiology, classification, characteristics and mechanisms

The incidence of spinal cord injury (paraplegia and tetraplegia) is between 12,000 and 15,000 people each year in the US, with 10,000 of these suffering from a permanent paralysis, many of which die as a consequence of these lesions. The majority of these traumas occur in young individuals, more often in male population between 15 and 35 years old. A British study (1993-1995) revealed that the aetiology of spinal lesions are mainly due to work and domestic accidents (37%), sports (20.5%) and car accidents (36%), reflecting that the incidence of the lesions is higher at the cervical level (44%) and thoracic level (41%) rather than the lumbar level (15%). The incidence of traumatic SCI in Spain is estimated to be 2.5 cases out of 100,000 habitants per year (aproximately 1,000 people a year). Spinal lesions due to atraumatic medical origins represent 25% of the total (**Fundación ONCE**).

Neuropathic pain associated to spinal cord injury is an unpleasant and incapacitating symptom, which interferes with the rehabilitation process and the reinsertion of the patient in the community due to a progressive deterioration in their quality of life after the initial trauma (**Siddall et al., 2003**). The symptoms persist over several years, are associated with a severe intensity of pain, impede the patient's daily activity and do not respond to conventional analgesic treatments. The majority of studies indicates that a third of the patients with chronic pain suffer intense or severe pain (**Bonica, 1991; Finnerup et al., 2001; Siddall et al., 2001**). The prevalence of pain after SCI reaches 81 % of the total patients, whilst NP components may be present in 41% at level and 34% below the level of the lesion (**Siddall et al., 2003**).

Based on the IASP (International Association for the Study of Pain) definition of SCI pain, two different types of pain exist: nociceptive and neuropathic. Nociceptive pain includes the musculoskeletal and visceral types. Two categories of neuropathic pain exists after SCI: *at level* (pain in the dermatomes at the level of the trauma), *below level* (pain in the dermatomes below the level of the trauma) and *above level* (**Siddall et al., 2000**). Whilst NP below the level of the lesion is considered as a *central* pain caused by impairment in the spinal cord (in those patients with a lesion above the T10 level), neuropathic pain at the level of the lesion may have peripheral and central components which are difficult to separate.

The typical characteristics of NP after SCI include *spontaneous* and continuous pain, or *ongoing pain*, with features of *dysesthesia* (an abnormal, unpleasant, *spontaneous/evoked* sensation) below the level of SCI (**Siddall et al., 2003**), combined with the presence of *evoked pain* signs at the level of SCI (**Eide et al., 1996**). These *evoked pain* signs may be *allodynia* and *hyperalgesia*. Often characteristics may include temporal summation to repeated application of innocuous or noxious stimuli (**Price et al., 1989**).

Bouhassira et al. (2000) and **Defrin et al. (2001)** concluded that in SCI patients changes were not revealed in the sensory function for the thermal and mechanical modalities in patients with and without pain, although allodynia was present with NP. However **Finnerup et al. (2003)** revealed that patients with central NP frequently presented dysesthesia and *evoked* pain to brush, cold and pin prick at the level of SCI (see **Huelbes et al., 2004**). In summary, these studies suggest either altered function in

thalamic pain centres and/or an area of hyperexcitability at the local area of SCI in the development of NP. Changes in peripheral nervous system components may also be involved in SCI NP (**Wall and Melzack, 2006**).

Other mechanisms of SCI-NP pain have also been suggested. **Beric et al. (1988)** proposed an imbalance between the spinothalamic and dorsal column systems as the main underlying mechanism of dysesthesia due to a misinterpretation of residual peripheral input. These authors also suggested that the term “*central dysesthesia syndrome*” to include the presence of *spontaneous*, uniform, diffuse, unpleasant, burning sensations in patients with a disproportionate dysfunction of spinothalamic and dorsal column systems. The term *central* indicates the apparent absence of dysfunction of the peripheral nervous system, suggesting a supraspinal dysfunction. *Dysesthesia* is used because most of the patients can differentiate between the unpleasant ongoing sensations and other pain types that they have. The distinction may help to separate those pains which may have a peripheral origin or at least peripheral triggering mechanisms. The diagnosis of the syndrome would not only include a patient description and identification of the cause of complaint, but also psychophysiological evaluation of spinothalamic and dorsal column system functions and clinical neurophysiological assessment of peripheral nerve and spinal cord functions below the level of the lesion.

Finally, recent studies have described the quality of life (QoL) in SCI pain patients using specific questionnaires such as the *MPI-SCI* (Multidimensional Pain Inventory – Spinal Cord Injury version) that measures a wide range of psychosocial factors associated with acute and chronic pain syndromes (**Widerström-Noga et al., 2002**). Importantly, the *MPI-SCI* also measures the interference of pain in day to day activities. Indeed SCI pain has been shown to be the most significant factor which affects all levels of daily activity, as well as difficulty in enduring other aspects of SCI such as paralysis or depression. In addition, affective pain may be directly related with the ability of the pain patient to successfully cope with the impact of SCI (**Widerström-Noga et al., 2002**).

In the following chapter we present, in a longitudinal study, the role of the Central Pain Generator at the level of SCI and its effect on NP development below the level of the lesion (Chapter 2). After that, we examine the differences between SCI-NP patients and subjects without NP using standard QST tests and thermal stimulation applied with the TSAR system, and assess the possible involvement of the Central Pain Generator operating at, below and above the level of the injury (Chapter 3). And finally, we show the change in the most important Quality of Life (QoL) factors over the time of injury, derived from both the CSQ-R and *MPI-SCI*, and relate these changes to *spontaneous* pain intensity and unpleasantness (Chapter 4).

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--VERSIÓN RESUMIDA EN ESPAÑOL--**CAPÍTULO 1.
INTRODUCCIÓN GENERAL****1.1. Mecanismos de Dolor en Humanos.**

El dolor fisiológico es un mecanismo temprano y esencial advertencia que nos alerta de la presencia en el ambiente de estímulos dañinos. Todos los organismos vivos necesitan ser capaces de reaccionar a estímulos nociceptivos, y una mayor evolución para el desarrollo de un sistema nervioso plástico podría haber sido la adquisición de la capacidad de detectar y recordar el peligro. El dolor no es homogéneo, y comprende tres categorías: dolor fisiológico, inflamatorio y neuropático, objetivo de este estudio. (Woolf et al., 2000). Nocicepción es la respuesta de un receptor sensitivo a un estímulo nociceptivo o a estímulos que se vuelven nocivos si son prolongados. Dolor Neuropático (DN) es el iniciado o causado por una lesión primaria o disfunción en el sistema nervioso (**definiciones de la IASP en su página web**).

Woolf et al. (1999) ha sugerido que la sensibilidad al dolor es una expresión de su plasticidad neuronal, su duración está determinada por tres distintos procesos: *activación*, *modulación* (cambios reversibles en la excitabilidad de neuronas sensoriales y centrales mediadas por alteraciones post-translacionales) o *modificación* (alteraciones a largo plazo en la expresión de receptores, canales iónicos o en la estructura, conectividad y supervivencia de las neuronas, como el que el sistema nociceptivo se halle modificado gravemente, distorsionando la respuesta normal de los estímulos) (**Fig 1.1**) en el proceso de dolor. Nocicepción es un proceso activo que incluye al sistema periférico y central (SNC) (Woolf and Salter, 2000).

1.2. Clasificación de Fibras de Nervios Aferentes Cutáneos

Las fibras nerviosas han sido clasificadas, de acuerdo a su velocidad de conducción y diámetro de axón, en A-B y C-fibras. Las A α tienen un diámetro de 12-20 μ m, y una velocidad de conducción de 70-120 m/s. Las A β , diámetro de 5-12 μ m y una velocidad de conducción de 30-70 m/s (transmisión del tacto y presión); las fibras A δ , diámetro de 2-5 μ m y una velocidad de conducción de 12-30 m/s (transmisión del dolor, temperatura y tacto). Las fibras C diámetro de 0.2-2 μ m y una velocidad de conducción de 0.5-2 m/s. Sus funciones incluyen el dolor simpático y calor, frío y presión.

1.3. Principios Generales del procesamiento central de la información sensorial cutánea

Las fibras nociceptivas aferentes cutáneas A δ (responden casi exclusivamente a estímulos mecánicos nociceptivos) terminan principalmente en la lámina I y V mientras que los nociceptores polimodales C (responden a estimulación mecánica, térmica y química) terminan en la lámina I y II basado en el esquema laminar de Rexed.

Estudios clínicos indican que la principal vía que transporta información nociceptiva al cerebro humano se cruza y asciende en el cuadrante anterolateral (Gybel and Sweet, 1989).

1.4. Procesamiento sensorial de la modalidad Táctil-Presión y Vibración

Se piensa que los receptores sensoriales señalan la información en intensidad y duración del contacto mecánico prolongado de estímulos con la piel son los receptores mecánicos SA I. Los SA II juegan un papel menos claro. Estudios de microneurografía de fibras aferentes coinciden con campos de SA I (Ochoa and Torebjörk, 1983). La densidad del gradiente de los receptores SA I (como los FA I) en la palma de la mano humana corresponde al umbral para la discriminación entre dos puntos (Johansson and Vallbo, 1979a; 1980; 1983). Los receptores SA I respondieron a estímulos vibratorios (Järvilehto et al., 1976) y los SA II a tacto-presión (Harrington and Merzenich, 1970). Los pacientes con lesiones en la columna posterior tienen distorsionada la discriminación entre dos puntos y del estímulo de presión (Nathan et al., 1986), debido en gran parte a la interrupción del canal de tacto-presión. La sensación de movimiento probablemente se transmite por las proyecciones en la columna

dorsal y neuronas postsinápticas de las vías medulares dorsales, el tracto espinocervical y el espinotalámico. La sensación de vibración, por las proyecciones en la columna dorsal y neuronas postsinápticas de las vías medulares dorsales.

1.5. Procesamiento Sensorial del dolor

El dolor *superficial* resulta de una intensa estimulación y se puede localizar bien, mientras que el *profundo* proviene de los músculos, tendones, periostium y articulaciones y no se puede localizar fácilmente. El dolor *primario* y el *secundario* son sinónimos (Lewis, 1942), y son producidos por activación de fibras *A δ* y *C*, respectivamente. El retraso entre los dos es debido a diferente velocidad de conducción periférica de las fibras aferentes nociceptivas involucradas (Treede et al., 1998). Aparte del dolor, se pueden producir reflejos de retirada de flexores (Sherrington, 1906), respuestas autonómicas (Schmidt R.F and Weller, 1970), excitación, conducta aversiva, cambios endocrinos y otras respuestas afectivo-motivacionales (Melzack and Casey, 1968; Bonica, 1990; Price, 1999). Se ha evidenciado presencia de DN en pacientes con ausencia de actividad en aferentes nociceptivos, común después de daño en nervios periféricos o ciertas partes del sistema nervioso central (Yeziarski and Burchiel, 2002).

1.5.1. Nociceptores

Incluye fibras mielínicas mecánicas *A δ* cutáneas, *A δ* mecanotérmicas, y amielínicas *C* polimodales, *C* mecanotérmicas y nociceptores *C* al calor (Treede et al., 1998).

1.5.2. Propiedades de los nociceptores

Existe una substancial población de receptores con fibras *A δ* que responden en humanos a más de una modalidad de estimulación nociceptiva mecanotérmica (Bromm et al., 1984). Kleinbohl et al. (2006) observó sensibilización a corto plazo solo a frecuencias por encima de 0.3 Hz, afectada por la frecuencia e intensidad del estímulo, pero las fibras mecanotérmicas *A* lo hacían sólo por encima de 0.6 Hz, y múltiple estimulación a medio plazo resultó en habituación. Diferencialmente, los nociceptores polimodales *C* de respuesta mecanotérmica al calor respondieron a más de 50°C (Schmidt et al., 1995). Estímulos nociceptivos de calor y químicos activarían los nociceptores sin excitar fibras *A δ* y así el dolor podría no tener interferencia del sistema inhibitorio.

1.5.3. Sensaciones Provocadas por Nociceptores.

La activación de una población de fibras cutáneas *A δ /C* o nervios mixtos produce dolor considerable, pero no con un simple impulso o descarga de frecuencias bajas. La estimulación de las *A δ* mediante electrodos de microneurografía produce dolor tipo pinchazo, mientras que en las *C* polimodales es de tipo sordo o quemazón, dependiendo de si las fibras aferentes inervan piel con o sin vello (Ochoa and Torebjörk, 1989), así las sensaciones dependen de la activación de pequeños grupos de axones dependiendo también de la frecuencia que excede el umbral (3Hz), por encima de la cual la intensidad de la sensación es proporcional a la frecuencia de estímulo y la sensación es un picor continuo más que de dolor (Torebjörk and Ochoa, 1983).

1.5.4. Código de Intensidad de dolor.

Ya que los receptores mecanotérmicos *A δ* tienen umbrales más altos para los pulsos nociceptivos de calor que los *C* polimodales, estos deben ser responsables de la discriminación entre el dolor al calor desde el umbral (43-45°C) hasta niveles que puedan dañar la piel (por encima de 50°C). El dolor cutáneo en humanos depende de la sumación espacial y quizá temporal de la actividad sobre los nociceptores (Adriaensen et al., 1980), como ocurre con la compresión mecánica prolongada a pesar de la adaptación de descargas de los nociceptores polimodales, y el dolor tiende a incrementarse. Andrew and Greenspan (1999) distinguieron entre nociceptores de adaptación rápida o lenta y encontraron que el incremento de las respuestas de dolor dependía de las respuestas nociceptivas incrementadas en neuronas centrales, así como incrementos intermitentes en las tasas de descarga de los nociceptores *A δ* .

1.5.5. *Mediación Química del Dolor periférica.*

Combinaciones de mediadores inflamatorios (bradikinina, monoaminas como la serotonina y la histamina, y prostaglandinas) sensibilizan químicamente los nociceptores, resultando en dolor incrementado (**Petho et al., 2001**).

1.5.6. *Dolor Referido.*

La *teoría de convergencia-proyección* asume que las fibras aferentes nociceptivas somáticas y sensoriales convergen en un grupo de neuronas de la médula espinal (incluidas las del tracto espinotalámico) y transmite dolor somático al cerebro. Presumiblemente ocurre un cambio de excitabilidad central similar a la de la hiperalgesia secundaria.

1.5.7. *Interacciones Inhibitorias.*

La estimulación fuerte de la piel (llamada “*counterirritation*”) ayuda a aliviar el dolor, pero no está claro cómo se consigue la consiguiente estimulación de las grandes fibras aferentes, ya que la *teoría de la puerta de entrada* ha sido cuestionada. La organización funcional del sistema de “*controles inhibitorios nociceptivos difusos*” (DNIC) involucra la activación de vías que ascienden al tallo cerebral para liberar descargas en las vías inhibitorias descendentes.

1.5.8. *Hiperalgesia y Alodinia*

La hiperalgesia es definida como el incremento de respuesta a un estímulo que normalmente es doloroso (**IASP**), o una condición en la cual el dolor provocado por estímulos por encima del umbral es más intenso (**Hardy et al., 1952**). La alodinia es el dolor debido a estímulos que normalmente no provocan dolor (**IASP**). La hiperalgesia y la alodinia primaria ocurren en el área del daño, con sensibilización de nociceptores, mientras que la secundaria se desarrolla en el área circundante no dañada. Los posibles mecanismos implicados se hallan en controversia, algunos autores (**Lewis, 1942**) piensan que ambas son debidas a un mecanismo periférico mientras que otros **Hardy et al. (1952)** y recientes evidencias (**Baumann et al., 1991**) indican que dependen de cambios en el sistema de procesamiento central.

1.6. Sensación de Temperatura.

Los umbrales para la sensación térmica dependen de factores como la tasa de cambio de temperatura, la cantidad de cambio, la superficie del área afectada y la temperatura de “adaptación” (**Molinari et al., 1977**). En los extremos del rango de temperatura (por encima de 45° C y por debajo de 18° C) el sujeto siente dolor al calor (**LaMotte and Campbell, 1978**) o dolor al frío (**Wolf and Hardy, 1941**).

1.6.1. *Receptores Térmicos*

El dolor térmico es provocado por diferentes grupos de receptores responsables para la sensación térmica, pero también existen respuestas de los receptores mecánicos de adaptación lenta. Los canales para las sensaciones de calor y frío son independientes, como lo demuestran observaciones en lesión medular (**Head and Thompson, 1906**).

1.6.2. *Receptores de Calor*

Los receptores de calor presentan campos de puntos (**Konietzny and Hensel, 1979**) y se sitúan a unos 0,6 mm bajo la superficie de la piel humana (**Bazet et al., 1930**), aunque su estructura es desconocida. Existe un grupo de umbral bajo (con descargas a 32° C y curvas acampanadas estímulo-respuesta con máximo de 38-43° C) y de umbral alto (que empiezan a liberar sólo a 35-38° C con una tasa máxima por encima de 45° C (**Konietzny, 1984**)). El dolor al calor en el rango de 43-45° C puede atribuirse a los nociceptores C polimodales.

1.6.3. *Receptores del Frío*

En humanos son pequeños puntos de cerca de 1 mm de diámetro situados a una media de 0,15 mm desde la superficie de la piel. La tasa máxima de respuesta para un receptor dado ocurre a una temperatura entre 18 y 34° C (**Iggo, 1969**), aunque algunas fibras del frío también producen una vigorosa descarga a 45-50° C (“respuesta

paradójica”) (Dodt and Zotterman, 1952; Kenshalo and Duclaux, 1977) y aparentemente es mediada por cambios en el tono vasomotor (Long, 1977). La intensidad se explica por la cantidad total de actividad neural provocada por el estímulo térmico (Erickson, 1973) y por el reclutamiento de otros tipos de receptores de frío (LaMotte and Thalhammer, 1982) con curvas estímulo-respuesta monotónicas a bajas temperaturas (10-30° C).

1.6.4. Proyección Central de termorreceptores.

Una gran proporción de neuronas termoreceptivas del asta dorsal se encontraron proyectando contralateralmente en la médula espinal cervical (Iggo and Ramsey, 1976); y Norrsell (1979; 1983) ha demostrado que la vía ascendente termosensitiva se localiza en la mitad del funículo lateral. Se han registrado neuronas respondientes al frío en la región del núcleo VMpo del tálamo en humanos (Davis et al., 1999).

1.6.5. Correlaciones Clínicas.

Las lesiones de la médula espinal producen pérdida de la sensación térmica o dolorosa (Head and Thompson, 1906), atribuida a la separación parcial de las vías de temperatura y dolor. Las sensaciones térmicas pueden ser provocadas por estimulación en el cuadrante anterolateral de la médula (Sweet et al., 1950; Mayer et al., 1975) y presumiblemente este es el tracto espinotalámico.

1.7. Control Descendente de Vías Ascendentes Sensoriales.

Las células del tracto espinotalámico (células STT) son susceptibles a potentes controles descendientes que pueden suprimir el dolor (Mayer and Price, 1976). Pueden ser inhibidas tras estimulación eléctrica en el núcleo magno del rafe (Gerhart et al., 1981a), formación medular reticular (McCreery and Bloedel, 1975), formación medular periacueductal gris y del cerebro medio (Hayes et al., 1979), región parabraquial (Brennan et al., 1987), periventricular gris (Ammons et al., 1986), núcleo VPL del tálamo (Gerhart et al., 1981c; 1983), y la corteza parietal sensorial primaria y posterior (Yeziarski et al., 1983).

Las neuronas del tracto espinoreticular (neuronas SRT) están bajo la influencia de sistemas moduladores descendientes. Algunas neuronas SRT son inhibidas por estimulación de la formación reticular (Haber et al., 1982) y otras son excitadas por ella (Giesler et al., 1981b). La excitación de estas neuronas puede reflejar actividad en los bucles espino-bulbares que producen prolongada acción en circuitos inhibitorios, como el sistema DNIC (Cervero and Wolstencroft, 1984). Las células espinomesencefálicas (células SMT) pueden ser inhibidas o excitadas (primero) por estimulación del núcleo magno del rafe, formación reticular modular, gris periacueductal, o formación reticular del cerebro medio.

1.8. Dolor Neuropático después de la Lesión Medular: Características y Mecanismos.

El Dolor Neuropático (DN) es el resultante de lesiones o alteraciones crónicas en nervios periféricos. Puede desarrollarse y persistir en ausencia de estímulo nociceptivo evidente, no así en el dolor somático. Característicamente se presenta como sensación basal dolorosa o quemante (disestesia), con hiperalgesia (respuesta exagerada) o percepción dolorosa de un estímulo no nociceptivo (alodinia) (IASP).

El dolor central es común en pacientes con trauma, esclerosis múltiple, Syringomyelia y lesión medular; se desarrolla después de semanas o meses, se asocia con cambios en las vías espinotalámicas y tiene una mala remisión. Dos hipótesis pueden explicar las manifestaciones clínicas: actividad neural aberrante en los circuitos desaferentados y desequilibrio entre vías neurales facilitatorias e inhibitorias (Nurmikko, 2000).

El DN asociado a LM puede ser incapacitante, interferir con la rehabilitación y la reinserción por un deterioro de la calidad de vida después del trauma inicial (Siddall et al., 2003; Yeziarski, 1996; Finnerup and Jensen, 2003). El DN tras la LM es de más del 81 % de los pacientes, y está presente en el 41 % al nivel de la lesión y en el 34 % por debajo de la lesión (Siddall et al., 2003). Existen muy pocos estudios de dolor después de la LM que analicen los mecanismos presentes.

El tiempo de comienzo varía desde ser inmediato (lo que sugiere que el sistema nervioso central altera la actividad funcional mantenida) a años después de la lesión (Pagni, 1998), fuerte relación entre presencia de DN central y anomalías en la sensación somática, el DN central puede ser proyectado a un área mayor del cuerpo y la distribución corresponde somatotópicamente al lugar de lesión, puede presentar cualquier cualidad (Boivie, 1994; Davidoff et al., 1987) (aunque el dolor quemante es el más común; Beric et al., 1988), frecuentemente es

permanente (Boivie, 1994; Pagni, 1998), puede estar influenciado por estimulación de la piel, movimiento, estímulos viscerales y estado psicológico incluidas las respuestas emocionales (Boivie, 1994; Pagni, 1998).

1.8.1. Excitabilidad incrementada: Foco de Irritabilidad

Es una región del tejido nervioso en el que los circuitos neurales se vuelven hiperexcitables y su actividad provoca dolor central (Dejerine and Roussy 1906; Pagni 1998), causado por sustancias sanguíneas que causan excitabilidad incrementada en la materia gris cuyos axones ascienden en el funículo ipsilateral (Vierck and Light 1999).

1.8.2. Sensibilización Central.

Depende de neurotransmisores que llevan a la activación intracelular de las vías neurales, como proteínas quinasas (CaMKII, PKC, NO/PKG y PKA) (Lin et al., 1996a; 1997; 1999). La subsiguiente fosforilación de los receptores aminoácidos excitatorios puede incrementar su respuesta (Cheng and Huang 1991; 1992). Así, la potenciación a largo plazo (LTP), en el hipocampo por ejemplo, es similar a ese proceso (Willis 1997; 2001b) y quizá requiere cambios en la expresión génica.

1.8.3. Desinhibición

El DN central no sólo necesita de déficit en la modalidad sensorial lemniscal de la columna medial (Biemond 1956; Beric et al., 1988; Boivie et al., 1989), sino que también puede involucrar desinhibición causada por la pérdida de mecanismos inhibitorios dentro de la vía espinotalámica-cortical. Otra explicación podría ser que la desinhibición es producida por interrupción de proyecciones inhibitorias corticotalámicas que terminan en el tálamo lateral (Head and Holmes, 1911).

1.8.4. Vías Nociceptivas Alternativas tras la interrupción del tracto espinotalámico.

Estas podrían ser las STT ipsilaterales, la vía postsináptica de la columna dorsal, el tracto espinocervical, el tracto espinobraquial, el tracto espinotalámico, los tractos espinolímbicos y el espinoreticular (Willis and Coggeshall, 1991).

1.8.5. Dolor inducido por Desafrentación en centros de dolor talámicos.

Las neuronas del sistema ascendente de transmisión del dolor desarrollan actividad espontánea y quizá respuesta aumentada a inputs sobre otras vías (Levitt and Levitt, 1981), como se puede observar en descargas de neuronas talámicas en pacientes y el desarrollo de nuevos campos receptivos tras la LM (Lenz, 1989). También podrían estar afectadas por alguna clase de supersensibilidad denervada. Otro cambio podría ser la degeneración transneuronal y subsecuente reorganización de neuronas postsinápticas.

1.8.6. Susceptibilidad Genética.

Se ha encontrado para dolor crónico periférico (Mogil et al., 1999a,b) y no sería sorprendente encontrarlo también para el dolor central.

1.9. Métodos de Estimulación Experimental de Dolor.

1.9.1. Estimulación Sensorial

Estudios con individuos sanos proporcionan desarrollo de las medidas y validación, valoración de la eficacia analgésica, evaluación de los mecanismos y control del dolor, estudios de variables psicológicas y constructos involucrados en la experiencia de dolor y su informe, y el uso de métodos experimentales para su evaluación clínica.

El *calor* es uno de los métodos más comunes para provocar sensaciones experimentales de dolor, clásicamente mediante calor radiante (Hardy et al., 1952) o más recientemente, con láser (Greffrath et al., 2002). El *frío* puede administrarse mediante los mismos estimuladores con estimulación discreta o continua. La presión mecánica es otro método clásico en el que la sensación de dolor se provoca por deformación de la piel mediante filamentos de von Frey entre otros. La estimulación tónica o fásica es útil en estudios de la función nociceptiva y

la sumación temporal (**Andrew y Greenspan, 1999**). Otros métodos son la estimulación eléctrica (**Donaldson et al., 2003**); y química aplicada a la piel para estudiar hiperalgesia y alodinia (**Gottrup et al., 2000; Wang et al., 2000**).

1.9.2. Técnicas psicofísicas para la medida del dolor

El “umbral de dolor” es utilizado para describir la sensibilidad general al dolor y es asociado a la variabilidad entre individuos. Estos métodos, junto con las medidas de tolerancia son considerados métodos “estímulo-dependientes”, en contraste, muchos de los procedimientos de escalas supraumbral son “respuesta-dependientes”, entre ellos la escala visual análoga (VAS) de dos dimensiones, y discrimina entre intensidad y desagradabilidad (**Price, 1988**). El cuestionario de McGill es la escala de descriptores verbales multidimensional más utilizada.

1.9.3. Las técnicas neurofisiológicas para la medición del dolor

Los registros *microneurográficos* de actividad aferente proporcionan información de la función de los nociceptores C y posiblemente Ad (**Andrew y Greenspan, 1999**). La mayoría de estudios de reflejos relacionados con dolor evalúan la respuesta electromiográfica a un estímulo intenso corto (EMG), y ésta correlaciona con el informe verbal y sirve como marca para el umbral nociceptivo comparado con el potencial de acción (**Dowman, 1993**); también se han estudiado potenciales corticales evocados, potenciales relacionados con eventos cerebrales (CEPs) o potenciales evocados somatosensoriales (SEPs), los cuales correlacionan con el informe verbal y la intensidad del estímulo. Los EEG y los métodos de campos magnéticos proporcionan información espacial para el uso de detectores y análisis mediante software (los más usados son el PET y fMRI).

1.10. Mecanismos Psicológicos de la Influencia del Dolor.

Los sentimientos emocionales de desagradabilidad son componentes integrantes del dolor por las cualidades sensoriales únicas que ocurren en un contexto amenazante; así el dolor posee ambas dimensiones sensoriales y afectivas (**Melzack y Casey, 1968; Price, 1999**). Varios atributos sensoriales del dolor disponen las sensaciones emocionales de desagradabilidad. Procesos neurales y psicológicos relacionados con la sensación de dolor pueden ser concebidos como importantes vínculos causales en la producción de la alteración emocional del dolor. Estudios psicofísicos demuestran que las sensaciones de dolor y desagradabilidad representan dos dimensiones distintas de dolor que demuestran diferentes relaciones a la intensidad del estímulo y están influenciadas por factores psicológicos distintos. La influencia secundaria del dolor supone la interferencia vital percibida, las dificultades para soportar el dolor en el tiempo y las implicaciones para el futuro (**Price, 1987; 1999**).

1.10.1. Impacto en las medidas de Calidad de Vida (QoL)

Se ha probado que los instrumentos para medir la calidad de vida pueden facilitar medidas de la función física mejor que las medidas existentes, y aunque no son la solución completa, en muchas situaciones complementan las medidas de dolor en su comparación de intervenciones (**Wall y Melzack, 2006**).

El DN está asociado con cambios de humor independientemente de la evolución del dolor, y se ha demostrado que los factores psicológicos están relacionados con la gravedad del dolor y más síntomas depresivos y estrés percibido (**Siddal et al., 2003**). La aplicación de escalas psicofísicas como el VAS (**Woolf et al., 1999**), combinadas con escalas cognitivas para la evaluación psicológica (CSQ y MPI; **Widerström-Noga et al., 2002**) son técnicas que facilitan la comparación de los datos obtenidos por métodos psicológicos y neurofisiológicos, en grupos de pacientes y diferentes momentos temporales (**Price, 1999**). Así, la calidad de vida se considera el principal aspecto en investigación clínica y promoción de la salud, y es especialmente útil en personas con LM y dolor, donde el daño no es suficientemente entendido. El cuestionario *CSQ* (“Coping Strategies Questionnaire” de **Rosenstiel y Keefe, 1983**) mide la frecuencia con que los pacientes adoptan siete diferentes estrategias cuando sienten dolor, y el mayor nivel de catastrofismo en pacientes con lesión medular ha sido asociado con mayor intensidad de dolor y estrés psicológico (**Turner et al., 2002**). El *MPI-SCI* (“Multidimensional Pain Inventory – Spinal Cord Injury version” de **Widerström-Noga et al., 2002**) es un instrumento exhaustivo para la evaluación de factores psicológicos en dolor agudo o crónico y también determina la interferencia de subtipos de dolor en la calidad de vida.

1.11. DN después de la LM: Epidemiología, clasificación, características y mecanismos.

La incidencia es de 12.000-15.000 personas cada año en EE.UU. y 10.000 de ellos sufren parálisis permanente. La mayoría ocurren en individuos jóvenes, más frecuentemente en hombres entre 15-35 años y de causas por trabajo y accidentes domésticos en su mayoría, según un estudio inglés. La incidencia en España sólo de casos traumáticos es estimada en aproximadamente 1.000 personas al año. (**Enciclopedia Microsoft ® Encarta ® 2003; Fundación ONCE**).

Basados en la IASP (Asociación Internacional para el Estudio del Dolor), existen dos diferentes tipos de dolor: Nociceptivo y Neuropático, este último puede ser en los dermatomas *al nivel* del trauma, o en los que se encuentran *por debajo* del nivel (**Siddall et al., 2000**). Un dermatoma es un área localizada de la piel que tiene sensación por un nervio proveniente de una raíz nerviosa de la médula espinal. Mientras el DN por debajo del nivel de lesión se considera *central* causado por daño en la médula, el DN al nivel puede presentar componentes periféricos y centrales difíciles de separar. Típicamente presenta dolor *continuo* con características *disestésicas* por debajo del nivel de lesión (**Siddall et al., 2003**) y la presencia de signos de dolor *provocado* al nivel de la LM (**Eide et al. 1996**), como *alodinia*, *hiperalgesia* (**IASP definitions on-line**) y *sumación temporal* (**Price et al., 1989**). **Beric et al. (1988)** sugirió que el “síndrome de disestesia central” incluye la presencia de sensaciones espontáneas y de quemazón, entre otras, en pacientes con disfunción en los sistemas espinotalámico y de la columna dorsal. Recientemente, **Finnerup et al. (2003)** expuso que los pacientes con DN central presentaban más frecuentemente disestesia e hipersensibilidad al nivel de la LM (**Huelbes et al., 2004**), lo que sugiere la existencia de un área de hiperexcitabilidad en la médula espinal en el desarrollo del DN tras la LM.

En el siguiente capítulo presentamos el papel del CPG al nivel de la LM y su efecto en el desarrollo por debajo del nivel de lesión (Capítulo 2). Después examinaremos las diferencias entre los pacientes con LM-DN y sujetos sin DN usando QST estándar y estimulación térmica aplicada con el sistema TSAR, y evaluaremos la posible implicación del CPG actuando al nivel, por debajo y por encima de la lesión (Capítulo 3). Y finalmente, mostraremos los factores más importantes de Calidad de Vida (QoL) a lo largo del tiempo de lesión, derivados del CSQ-R y MPI-SCI, y relacionaremos estos cambios a la intensidad de dolor espontáneo y desagradabilidad (Capítulo 4).

CHAPTER 2.

NEUROPATHIC PAIN DIAGNOSIS AFTER SPINAL CORD INJURY: LONGITUDINAL ANALYSIS OF PHYSIOPATHOLOGICAL MECHANISMS PRESENT AT AND BELOW THE LEVEL OF THE LESION.

2.1. Introduction

2.1.1. Characteristics of Neuropathic Pain At Level and Below the Level of The Lesion After SCI.

Neuropathic Pain and *dysaesthesia* (unpleasant abnormal sensations) are seen in areas with sensory abnormality. The qualities can be burning, smarting, shooting, aching, pricking, and tingling and is a persistent pain present long after the injury, despite the availability and use of many treatment (**Siddall et al., 2000; Widerström-Noga and Turk, 2003**). Abnormal sensations that are not unpleasant are termed *paraesthesias*, which might include *dysaesthesias*. Pain and *dysaesthesias* in SCI can either be *spontaneous* or *stimulus-evoked*. *Stimulus-evoked* pain may present itself as allodynia (the elicitation of pain by non-noxious stimulation, for example with light touch or innocuous cold or warmth) and hyperalgesia (an increased pain response to a noxious stimulus). Other features frequently seen in NP are wind-up-like pain (abnormal temporal summation of pain), aftersensations (pain continuing after stimulation has ceased), and referred pain (pain felt in a place apart from the stimulated area) (**Siddall et al., 2000**).

The typical characteristics of SCI-NP include *spontaneous* and continuous pain - *ongoing pain*-, with features of *dysesthesia*, an abnormal and unpleasant *spontaneous/evoked* sensation, below the level of SCI (**Siddall et al., 2003**), and the presence of *evoked pain* signs at the level of SCI (**Eide et al. 1996**). The prevalence of pain after SCI has been reported to be as high as 81 % in patients (61% in **Damirel et al., 1998** and 67% in **Ravenscroft et al., 2000**), whilst the NP subtype may be present in 41 % at level and 34 % of patients below the level of the lesion (**Siddall et al., 2003**). In the majority of clinical studies a third of the patients have been reported with chronic pain associated with an intense or severe intensity (**Bonica, 1991; Finnerup et al., 2001; Siddall et al., 2001**). Neuropathic Pain (NP) *below* the level of the SCI is considered to be a central pain condition caused by spinal cord damage (**Siddall et al., 2000**), and involve an abnormal spinothalamic function with altered sensibility to temperature and pin prick (**Bowsher, 1996**), though spinothalamic lesion is a necessary but not sufficient condition (**Finnerup et al, 2003b**). **Siddall et al., (2003)** has identified the component of NP more debilitating for the patients after SCI: the development of a dysesthesia below the level with a more than a year since the initial trauma is associated with a severe intensity of NP.

On the other hand, **Finnerup et al. (2003a,b)** examined sensory detection and pain thresholds above injury level in SCI patients with central NP, SCI patients without NP, and in 20 control subjects. The SCI pain group had significantly higher cold and warm detection thresholds compared with the pain free subjects and higher tactile detection thresholds compared with the SCI pain free group and found no difference in pain or pain tolerance thresholds among pain and pain free SCI patients. These data suggested changes in somatosensory function (hyperexcitability) in dermatomes rostral to the segmental injury level linked to the presence of central NP in SCI patients, and also changes in pain inhibitory and facilitating systems.

2.1.2. Correlation between At and Below Level of SCI: The “Central Pain Generator” (CPG) Hypothesis.

One of the most interesting clinical hypothesis of local SCI-NP generation has recently been suggested by **Finnerup et al. (2004)** and **Vierck et al. (2000)**. The exact localization of the neuronal hypersensitivity responsible for the *evoked* pain or dysesthesia after SCI is not yet known. Indeed in humans, the intervention on the entry of the dorsal root area (DREZ) seems to have some relief effect in pain at level (**Loeser et al., 1968**). **Melzack and Loeser (1978)**, performed a cordectomy above the level of the original spinal lesion and failed to eradicate pain below the level of injury, suggesting that the original site of the pain generator was located at a more rostral level of SCI. In contrast, several authors describe pain relief using local anesthetic blockade. Specifically, **Pollock (1951)** described that NP below the level of the lesion could be eliminated by the application of “local anesthetics” above the level of the lesion, but not when there was a “spinal liquid blockage”; indicating that a spinal centre was critical in maintaining NP below the level of injury. These results also support the role of neuronal *hyperexcitability* at and below the level of SCI. Furthermore other studies indicate that the administration of lidocaine relieved pain at and below the level of SCI, suggesting the existence of a “Central Pain Generator” or “CPG”, in some patients (**Loubser and Donovan, 1991**). Recently **Loubser and Clearman (1993)** demonstrated that Lidocaine applied at the level of SCI eliminated pain and “spasticity”. Neurological sensory testing in patients with pain present below the level of the lesion significantly showed more *sensory hypersensitivity* at level than non-pain patients (**Finnerup et al., 2004**), and the same group has identified a correlation between *evoked* pain at level and the intensity of dysesthesia below the level of injury (**Finnerup et al., 2003b**), suggesting a common pathophysiological mechanism acting at and below pain. Indeed the degree of grey matter injury at the rostral end of the injury, observed by magnetic resonance, may be the anatomical correlate for this site of spinal neuronal hyperexcitability or CPG (**Finnerup et al., 2003a**).

In animal models, SCI of the grey matter and adjacent hyperexcitability to have been related to pain (**Yeziarski and Park, 1993**) and recent evidence suggest that abnormal dorsal horn activity below the level of SCI may also be present (**Hao et al., 2004**). Pharmacological studies also support the importance of neuronal hyperexcitability for NP after SCI. The administration of Lidocaine a voltage-sensitive sodium channel antagonist and other similar antagonists such as Lamotrigine (**Finnerup et al., 2002**) showed some efficacy in reducing *spontaneous* and *evoked* NP. In parallel the administration of Ketamine and other NMDA receptor antagonists (and therefore the inhibition of glutamatergic excitation) are effective in reducing NP pain at and below the level of the lesion (**Eide et al., 1995**; **Gonzalez-Valdizan et al., 2004**).

Taken together, current data suggests that damage to the spinothalamic pathway by itself does not totally explain central pain in SCI patients, and that *neuronal hyperexcitability* caused by excitotoxic changes and injury to inhibitory neurons may be an important additional mechanism for the genesis of below level pain. Some authors have suggested that the combination of ascending tract deafferentation and an activation of supraspinal targets by other spinal sources of activity, possibly through the propriospinal system (**Vierck et al., 2000**), could be responsible for SCI-NP. Thus, SCI central pain may be the result of supraspinal neuroplastic changes in response to the deafferentation and abnormal input from a spinal generator (**Finnerup et al., 2004**). However, not all patients with SCI present signs of spinal hyperexcitability (**Finnerup et al., 2003b y 2004**), indicating that other possible pathophysiological mechanisms may be active. Indeed SCI-NP may represent an heterogeneous pain condition which depends on several different mechanisms operating in parallel (**Finnerup et al., 2004**). Another possibility for the failure to identify clinical signs of hyperexcitability may reflect the poor sensibility of the testing methodologies adopted, or that spinal sensibility may only be present during the acute/subacute phase (0-6 months) after SCI (**Siddall et al., 1999**).

2.1.3. Longitudinal Studies of SCI-NP Mechanisms at the Local Level.

It is clear that useful information regarding the development of pain signs and therefore physiopathological mechanisms could be identified at the local spinal level using longitudinal studies from acute SCI patients up to one year after injury. An approximation towards an understanding of pain mechanisms would involve substantial progress in characterizing NP physiopathology and the development of more precise tools to discover which mechanisms contribute to the pain syndrome (**Woolf and Decosterd, 1999**). Indeed **Finnerup and Jensen (2004)** have suggested the utility of performing repeated assessment of central SCI-NP signs and symptoms when significant pain begins to develop within the area of sensibility loss.

In one of the few studies into the longitudinal development of SCI-NP, **Siddall et al. (1999; 2003)** studied a large sample of patients with traumatic SCI to determine the time of onset, prevalence and severity of different types of pain, including NP at and below the injury up to five years following injury. Up to 6 months they concluded that experienced allodynia was present predominantly in patients with incomplete spinal lesions at the cervical rather than thoracic level, and also with central cord syndrome. SCI patients presented either NP at level (36%) or below level pain (19%) at an early onset time (2 weeks) lasting up to the time of study (5 years). The mean onset time for at-level NP was the shortest (mean 1.2 years), while below level NP generally had a later onset (1.8 years) for chronic patients, and 2 weeks for the acute patients. Patients with NP at level were less than 40% during both the acute (0-6 months) and chronic SCI phase (6 months to 5 years), while below level NP increased from 15% (at 2 weeks) to 35% (at 5 years). While a similar prevalence rate for at level NP was observed in patients with cervical and thoraco-lumbar injury, below level NP was identified in 50% of patients with cervical lesion compared to only 20% of patients with thoraco-lumbar lesions. Patients with incomplete lesions presented slightly more at level pain intensity than complete SCI, at any time point (**Siddall et al., 1999**). In general, NP was more likely to be described as “severe” or “excruciating” than musculoskeletal pain, and a significant correlation between the presence of at-level NP at 5 years and earlier time points was identified. The severity, early onset and prevalence of SCI-NP in general, 5 years after injury and its high correlation with pain intensity at earlier time points appears to indicate a SCI-NP type that occurs early, is difficult to tolerate and which persists continuously despite attempts at its management. It appears from this data that if a patient has NP early after SCI it is likely to be both severe and persistent *at* and *below* the level of the injury. In contrast, below level NP is present in a slightly lower proportion of patients at later onset times (1, 2, 3 and 6 months) but with similar levels of intensity. This is consistent with previous reports suggesting that at-level NP occurs within days to weeks following injury and NP below-level within the first weeks to years following injury (**Beric et al., 1988**). Similar to at level NP, the below level pain is severe and persistent with high correlations between earlier time points and pain intensity at 5 years following injury. The late onset of below level NP may reflect a difference in the underlying mechanisms responsible for the generation of pain or perhaps a relatively slow process of neuronal degeneration, maybe of the spinothalamic system, that eventually leads to deafferentation and neuronal hyperactivity of supraspinal structures (**Vierck et al., 2000**).

Standard neurological tests of pain signs (**Jensen et al., 2003**) permit an approximation to the central mechanisms present after SCI and include signs like dynamic allodynia, mechanical hyperalgesia and hyperalgesia to cold present at level of the injury though temporal summation was not present (**Finnerup et al, 2003b, Eide et al., 1996**). It is noticeable that the majority of NP patients included in the study of **Finnerup et al. (2003b)** were SCI patients with complete lesions and therefore physiopathological processes that provoke a central sensitization were not so much intact than in NP patients with incomplete lesion. Based on this research, SCI patients with *central* pain presented hypersensitivity more frequently in the dermatomes corresponding with at level of the lesion than those without pain and found a significant correlation between the intensity of dysesthesia *evoked* by brush at level of SCI and *ongoing* pain below the level of lesion. In **Siddall et al. study (2003)**, allodynia was present in a relatively small percentage of patients (mainly in the very early 2 months), more in patients with cervical lesions. However, **Siddall (1999; 2003b)** did not provide any information in between months 2 and 6, and then up to 5 years, which did not give information of the

evolution of pain intensity in time (only the prevalence), and then is not enough to follow a changing mechanism like the CPG. Furthermore, only mechanical allodynia but not other pain signs like hyperalgesia or thermal allodynia were measured.

In this study the measures of sensory function after SCI were periodically assessed at and below the level of injury during the acute SCI phase in order to identify central NP mechanisms. In particular neuropsychological measurement techniques such as psychophysical ratio scales (Visual Analogue Scale, VAS) (Price et al., 1983; Woolf et al., 1999) which have successfully been used in SCI patients (Widerström-Noga et al., 2001; Defrin et al., 2001; Finnerup et al., 2003) were employed in the SCI-NP patients to assess five measures of ongoing *spontaneous* pain intensity and *evoked* pain measures using standard “bedside sensory tests” of sensory function after either incomplete or complete SCI. We achieved this by repeated measures ANOVA for *spontaneous* pain with respect to the SCI level (at and below level); the chi-square non-parametric test was performed on the prevalence of pain *evoked* signs at and below the level of injury; and correlational analysis of *spontaneous* and *evoked* signs at and below the level of SCI was attained at 2 and 6 months after SCI using the Spearman’s Rho test.

2.2. Objectives

2.2.1. The Role of the Central Pain Generator At the Level of SCI and its Effect on Neuropathic Pain Development Below the Level of the Lesion.

The object of the study was to determine the role of the local spinal pathophysiological mechanisms during the development of NP at and below the level, up to one year after the injury, either in incomplete or complete SCI. For this purpose measures of pain signs were recorded using a global and semi-directive pain questionnaire and a neurological exam using standard “bedside sensory testing” at 2, 3, 4, 6 and 12 months, to identify changes in mechanisms of sensibility with evidence specifically for dysesthesia, mechanical and thermal allodynia, mechanical hyperalgesia and temporal summation to repeated pinprick. Longitudinal statistical analyses was performed to study the relationship between *spontaneous* and *evoked* pain in general between at and below level SCI pain, followed by specific analysis of cervical and thoracic injured patients.

2.2.2. Study Hypothesis

The Central Pain Generator is responsible for the development of NP at and below the level of injury in the majority of patients, and simple VAS ratio scales and bedside sensory testing methods are valid instruments for its assessment.

2.3. Methods

2.3.1. Criterion of Selection

2.3.1.1. Inclusion Criteria

The subjects of the present study were recruited at the Paraplegic National Hospital of Toledo (Spain), and covered all the Spanish population territory. We revised a total of 258 clinical histories of in-patients identifying that 30 of them were appropriate for longitudinal “bedside sensory testing” (BST) of pain signs after their injury. These patients participated as volunteers, from the 1st of July 2003 to the 1st of March 2005. Their aetiology of SCI was either traumatic or atraumatic. Ages were comprised between 18 and 75 years, understood and spoke Spanish and agreed and signed the consent form. Each patient received standard hospital treatment that included analgesics prescribed after the first assessment of pain in this study. BST was performed at 2, 3, 4, 6, and 12 months after spinal cord lesion onset.

Neuropathic pain patients, who usually presented “burning” and/or “pressuring” sensation mainly, at any dermatomal level of the body above the conus medullaris (T10) and motor-sensitive complete or incomplete spinal lesion (according to the SCI scale “ASIA” by the American Spinal Injury Association : categories A (complete sensitive and motor lesion), B and C (incomplete sensitive/ motor lesion)); evaluated since two months after the trauma (acute phase depending on their neurological stability). Patients were required to have a pain intensity greater than 3 on the Visual Analogue Scale ratio scale (VAS), equivalent to “moderate” on the MPQ PPI scale (Mild, Moderate, Severe, Agonizing, Unbearable; **Lázaro et al., 2001**) two months after the SCI. Patients could also manifest any other type of pain distinct from neuropathic (nociceptive, osteomuscular, oncologic, etc) as long as that it was less severe. Patients with spasms related to NP were permitted, independently of their level localization.

2.3.1.2. Exclusion Criteria

Patients presenting psychogenic pain, multiple sclerosis, peripheral neuropathies, complex regional pain syndrome (CRPS), cognitive impairment, incapacity for verbal communication, severe hypoacusia or demency, were excluded, as well patients who were not able to be tested on the first assessment (before pharmacological treatment began). Patients with spasms unrelated to NP were also excluded from the study.

2.3.1.3. Experimental Groups

Patients with NP were selected according to three physical characteristics defined by: location, description and origin (**Siddall et al., 2003**). Comparisons were made between the presence of pain at or below the SCI in NP patients: a) Neuropathic Pain at level of the spinal lesion; the pain was described as “acute” and “burning” and/or “pressing” within the two dermatomes above and below the level of the SCI; and b) Neuropathic Pain below the level of the spinal lesion; the pain was described as “acute” and “burning” and/or “pressing” in an area more than four dermatomes below the level of the SCI.

Comparisons were also made between NP patients according to the vertebral level of their SCI, cervical versus thoracic lesions; and grade of injury, complete versus incomplete lesions.

2.3.1.4. Patient Study General Design

All procedures were approved by the Human Ethics Committee (Comité Ético de Investigación Clínica del “Complejo Hospitalario de Toledo-SESCAM”) in accordance with the Declaration of Human Rights, Helsinki, 1975. The patients were informed of the nature and purpose of the study and voluntarily signed the informed consent form by which they entered to participate in our research project, allowing them to abandon the study of their own free will.

2.3.2. Instruments

2.3.2.1. ASIA Assessment

Neurological examination was performed for each patient according to the standard SCI scale “ASIA”, developed by the American Spinal Injury Association. This scale characterizes the SCI into several categories depending on the impairment grade: “ASIA A” representing complete motor and sensitive SCI; “ASIA B” and “ASIA C”, motor or sensitive incomplete lesions (**Ditunno et al., 1994**). The ASIA examination was attained by the specialized rehabilitation physicians from our hospital, all of them with several years of experience in the management and treatment of SCI patients.

2.3.2.2. Visual Analogue Scale (VAS)

The VAS scale is a standard psychophysics ratio scale that simplifies the assessment of the patient's pain. The patient must choose a score between a minimum ("0" or "no pain sensation at all") and maximum ("10" or "the worst imaginable pain"). The words "no sensation" and "maximum pain" were placed at the ends of the scale, and a mark was placed in point 2 of the scale to indicate the threshold for non nociceptive sensations and the patient starts to feel pain ("almost pain"). This is based on preliminary studies pointing that are necessary the use of this type of modified VAS in Bedside Sensory Testing evaluation (**Vierck**, unpublished). In the present study five different scores of *spontaneous* pain intensity were used: 7 day (the average pain intensity during the last week given by the patient); Maximum and Minimum pain intensity (the highest and lowest pain score given by the patient); Present intensity (the pain score given by the patient at the particular moment of the assessment) and finally, 7 day pain Unpleasantness intensity (sensations of discomfort provoked by the pain during the last week). This facilitated the periodic and objective follow-up of the patient.

2.3.2.3. Neuropathic Pain Based on Mechanisms Interview

With the objective of developing a semi-directive interview for the identification of the pathophysiological characteristics of pain after the SCI, we have designed two complete questionnaires, one for the assessment of the NP below the level of the lesion and other similar for the NP at the level of the lesion, based on the mechanisms questionnaire proposed by **Woolf (1999)**.

The interview combines information regarding the localization of the patients' pain, with the area of dysesthesias (abnormal painful sensations) and paraesthesias (abnormal and unpleasant but not painful sensations) drawn on the involved dermatomes; areas of normal or abnormal sensitivity, pain definition using the patients description according to several pre-defined adjectives, the nature and intensity of the stimuli that evoke pain (static or dynamic mechanical or thermal stimuli), characterization of *spontaneous* or *evoked* pain with 10 pre-defined adjectives (burning, pulsing, pricking, stinging, stabbing, cutting, cramping, pressuring, tingling, itching), and the continuity of *spontaneous* pain (**See Protocol 2.1 and 2.2 in Appendix**). Importantly 7 day, Maximum, Minimum, Present and Unpleasant pain intensity assessment used 10 cm lines, for description of pain at and below the level of the SCI.

2.3.2.4. Bedside Sensory Testing (BST)

Patients used the modified VAS scale described previously (**See 2.3.2.2 section**) to quantify from 0 to 10, where "2" depicted pain threshold, the magnitude of *evoked* pain intensity following standard neurological tests designed to evaluate the presence of pain signs and pathophysiological characteristics either for nociceptive or neuropathic pain. **Table 2.1** lists the relationship between pain types and signs, and the tools that may be used to characterize them (last column shows the tests that were available in the hospital at the time of the study, c.f. **Chapter 3**). The same adapted VAS scale was used to assess *non evoked* pain for paraesthesias (VAS < 2) and dysesthesias (VAS > 2).

We measured several neuropathic pain signs: mechanical and thermal allodynia/dysesthesia, sensation/hyperalgesia to pin-prick, post-stimulus sensations after pin-prick stimulation and temporal summation to repeated pin-prick stimulation. Based on standard bedside sensory testing tools, we used: a soft thin brush, manual soft static pressure applied with one finger, one pin-prick ("safety pin") or four repeated applications of the pin (less than 1 sec between them) and a drop of acetone on the skin by a dropper were used (**see Appendix Picture 2.3.**).

Bedside Sensory Testing for <i>Evoked</i> Pain Signs			
Type of Pain	Assessment tools	Signs	Bedside Sensory Testing Tools
Nociceptive Pain: Musculoskeletal Origin	Algometer	Sensation/ Allodynia to Static Mechanical Stimulation	Soft static pressure
Neuropathic Pain: Central Origin	Brush	Sensation/ Allodynia to Dynamic Mechanical Stimulation	Brushing the skin
	513 or 745mN von Frey	Sensation/ Hyperalgesia to pin-prick	1 “safety pin”-prick application
	Thermal Roller	Sensation/ Hyperalgesia to heat	-
	Thermal Roller	Sensation/ Hyperalgesia to cold	1 drop of acetone
	513 or 745mN von Frey	Temporal Summation of nociceptive responses	4 “safety pin”-prick applications (< 1 sec between them)
	513 or 745mN von Frey	After stimulus sensation	Time (s) until sensation persisted after the last of the 4 pin-prick applications

Table 2.1. Semi-quantitative and bedside sensory tests for *evoked* central SCI pain signs

2.3.3. Clinical Procedure

Before accomplishing the relevant testing procedures for the project, a similar pilot study with 10 patients was completed. Thus, it was established that an initial pre-treatment (standard pharmacological treatment adopted in the Pain Unit) diagnostic session measure was necessary for the overall study, to reflect treatment effects, and in which it was determined that the change in pain intensity along the different temporal measures could be of great importance. This small pilot study, with pre and post-treatment diagnostic sessions (from 6 weeks after SCI) was performed between June and November 2003. In three of these patients post-treatment measures could be reliably assessed were therefore included in the definitive study. However, we changed the first measure from 6 weeks to 2 months, since our patients fulfilled the inclusion criteria at that time ($VAS \geq 3$)

A total of thirty spinal cord injury patients participated in our study; all volunteers with cervical and thoracic SCI lesions selected from the eight areas of the in-patient rehabilitation service at the Hospital Nacional de Paraplégicos de Toledo (Spain), with the exclusion of those patients to whom the first pre-treatment assessment session could not be achieved. A total of 258 in-patients from 1st of July 2003 to the 1st of July 2004 (according to hospital's data base) were revised according to the strict inclusion criteria defined above. No patients who initially agreed to participate in the study abandoned it.

All patients received the standard pharmacological treatment prescribed by the Pain and Spasticity Unit required in each case. The first diagnostic session and the remaining bedside sensory testing sessions were performed before analgesic medication, while the remaining test sessions were made during the standard prescription during the development of the patient's pain, according to the

practitioner's guidelines. The follow-up testing times were at 2, 3, 4, 6 and 12 months after spinal cord injury onset. The number of follow-up testing sessions depended on each patient's time of pain onset; for instance, in a patient that started their pain at 4 months after SCI, the subsequent evaluations were performed at 4, 6 and 12 months after the time of SCI.

In each session, the pain intensity -present pain- was ascertained first, together with the maximum, minimum, 7 day and unpleasant pain intensity, at and below the level of the lesion. Immediately afterwards, the quality of pain was characterized using the pre-defined adjectives included in the *Neuropathic Pain Based on Mechanisms Interview*. Next, bedside sensory testing of the patient was performed using the different measures of sensibility/pain following skin stimulation with brush, manual pressure, "safety pin" prick/s and one drop of acetone. The duration of the complete testing session was variable in each case, but in general reached approximately 30 minutes.

2.3.4. Statistical Data Analysis.

The data was collected in the form of several clinical protocols designed in the clinical laboratory of the Sensorimotor Function Group of the Hospital Nacional de Paraplégicos. The statistical comparison of the patients' data was analyzed by using the software SPSS version 12.0.1, either with parametric and non-parametrical tests. For the pain intensity study, the Greenhouse-Geisser test was chosen to perform repeated measures ANOVA for pain with respect to the SCI level (at and below level) in thirty patients. The Greenhouse-Geisser test is an adjustment in the uni-variate repeated measures test when the sphericity assumption is broken, and is a conservative measure for a small sample of data. Different SCI groups were compared using this test, such as complete/incomplete and cervical/thoracic SCI lesions.

The chi-square non-parametric test was performed on the prevalence of pain *evoked* signs at and below the level of injury. Correlational analysis of *spontaneous* and *evoked* signs at and below the level of SCI was attained at 2 and 6 months after SCI using the Spearman's Rho test.

Due to the lack of patients/missing data some analysis could not be performed by the ANOVA and correlational analysis with the SPSS program.

Cochran's analysis was achieved for common *evoked* signs at and below the level of SCI from 2-6 months following the lesion.

2.4. Results

2.4.1. Demographic and Diagnostic Data

A total of 30 patients were recruited from the Hospital Nacional de Paraplégicos de Toledo (Spain), originally from most of the Spanish territory. The average age in our sample (n=30 patients) was 39 years (SD +/- 13) with a range between 21 and 71 years. One third of these were women (33.3 %). The most frequent cause for SCI in our hospital was Traffic Accident (40%) followed closely by Atraumatic Injury (36.7 %); other causes such as Fall (13.3 %), Diving Accident (6.7 %), Gun Shot Wound (3.3 %) were lesser prevalent. The level of SCI was cervical for half of the patients: 26.7 % high cervical lesion (C2-C4), 23.3 % low cervical lesion (C5-C8), 16.7 % high thoracic lesion (D1-D4) and 33.3 % low thoracic lesion (D5-D10). Complete SCI (ASIA A) represented two thirds of the total population (63.3 %) with incomplete SCI being divided as 10% (ASIA B) and 36.7 % (ASIA C) respectively.

2.4.2. Time of Spontaneous NP Onset

Although NP in the acute phase presents a variable onset, the large majority of the 30 patients started to perceive dysesthetic symptoms (VAS \geq 3) between the second (40.0%) and third month (46.7%) after the injury, in agreement with other studies (Siddall et al., 1999). Only one patient began at the fourth month and three of them during the sixth months after the injury (3.3 and 10 % respectively, Fig. 2.1).

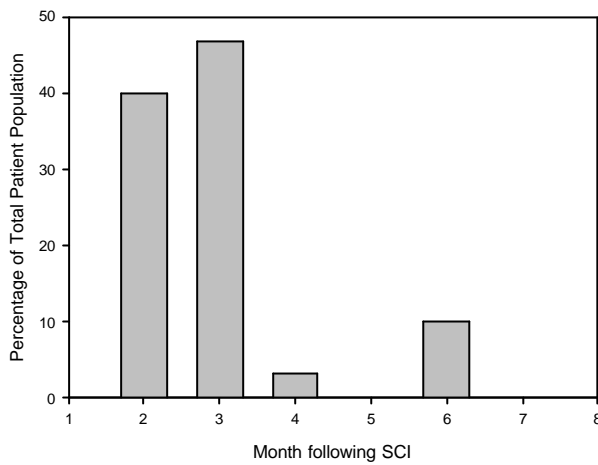


Fig 2.1. Percentage of patients with pain at 2, 3, 4, and 6 months following SCI.

The prevalence of *spontaneous* NP at and below the level of SCI in each month evaluated for the 30 patients is represented in **Fig.2.2**, observing that in the second month after SCI the NP below the level is 30% and then rises to more than double in one month. At level NP exceeded 50% for all the months examined.

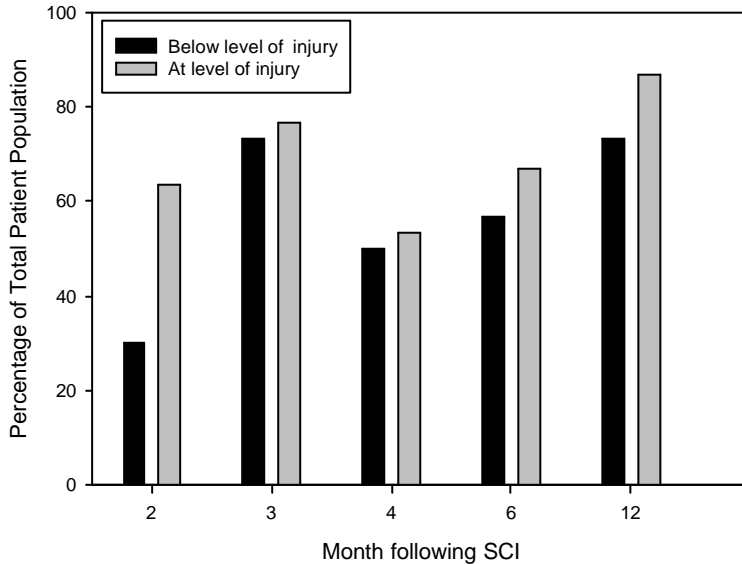


Fig 2.2. Prevalence of *spontaneous* NP at and below level of SCI for each month.

Evoked NP prevalence at and below the level of SCI evaluated during the third and sixth month after SCI indicated that at both times, sensation to pinprick/mechanical hyperalgesia was the most prevalent either at or below level, and was present in 50% of the patients at level 6 months after injury. In general more *evoked* pain signs were observed at level than below the level at 6 months (n=30, **Fig. 2.3 and 2.4**); whilst thermal allodynia below the level decreased to half at 6 months and then rose to double at the level of the lesion during the same month.

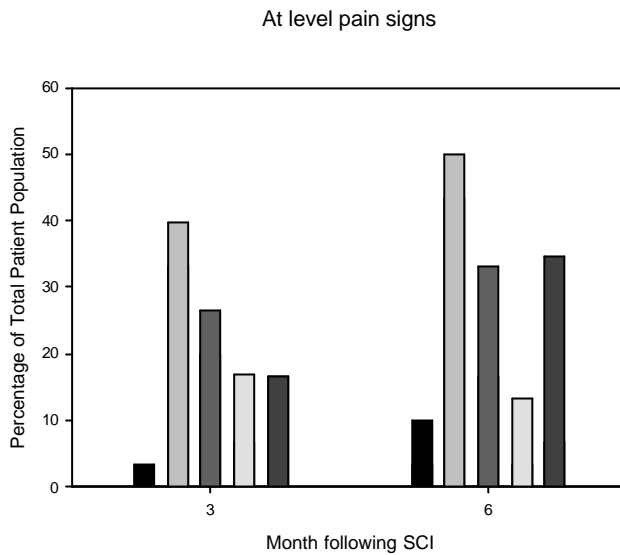


Fig.2.3. Prevalence of *evoked* NP at the level of SCI at 3 and 6 months after SCI. MA= Mechanical Allodynia/Sensibility; MH=Mechanical Hyperalgesia/ Sensibility; TS= Temporal Summation to Pin-prick; PS= Post-stimulus Sensations; TA= Thermal Allodynia/ Sensibility; below= below the level of SCI; at =at the level of SCI.

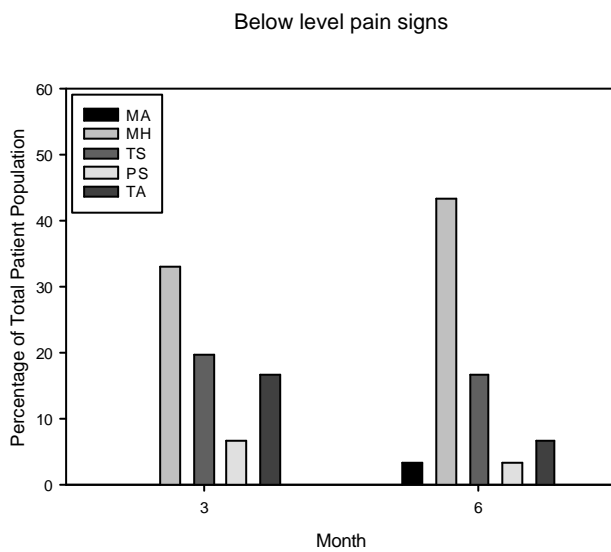


Fig.2.4. Prevalence of *evoked* NP signs below the level of SCI at 3 and 6 months after SCI. MA= Mechanical Allodynia/Sensibility; MH=Mechanical Hyperalgesia/ Sensibility; TS= Temporal Summation to Pin-prick; PS= Post-stimulus Sensations; TA= Thermal Allodynia/ Sensibility; below= below the level of SCI; at =at the level of SCI.

2.4.3. Intensity of Spontaneous Pain

Repeated measures analysis of different *spontaneous* pain intensity at the level of SCI indicated a general increase from 2 to 12 months after SCI. **Table 2.3** showed a progressive increase at level NP intensity (where for example, the 7 day mean pain intensity at level was 1.6 at 2 months and 4.3 at 12 months following injury) associated with a higher unpleasant pain intensity (6.6 at 2 months 4.9 at 12 months following injury). Maximum pain intensity at the level of lesion also increased from 3.5 at 2 months to 5.4 at 12 months after SCI while present pain intensity showed a similar increase from 3.8 to 3.5 at the equivalent time periods.

Below the level of the lesion, the 7 day and maximum pain intensity also increased from 2 to 12 months. Unpleasant pain intensity was maintained at a very high level while present pain intensity decreased from 2 to 12 months after SCI.

In the remaining analysis presented here the 7 day pain intensity was adopted since we considered the values to be more homogeneous (see the size of the SD), informative and reliable as the other patient’s report scores of VAS. Furthermore, the analysis was not significant or could not be done because of the missing data of the patients in the majority of the time measures (moreover, the observed power was close to 1.00).

Months	Pain Intensity Measure	At Level of SCI				Below Level of SCI			
		N	Mean	SD	SE	N	Mean	SD	SE
2	7 day	30	1.6	3.2	0.6	30	1.9	3.4	0.6
	Unpleas.	11	6.6	3.0	0.9	11	6.0	3.8	1.1
	Max	12	3.5	3.8	1.1	12	6.3	3.6	1.0
	Present	12	3.8	3.5	1.0	12	4.5	4.1	1.2
3	7 day	30	1.2	3.2	0.6	30	1.6	2.8	0.5
	Unpleas.	17	4.3	3.8	0.9	17	4.3	3.9	0.9
	Max	20	4.4	4.3	1.0	20	4.4	4.3	1.0
	Present	20	2.7	3.6	0.8	20	3.0	3.4	0.8
4	7 day	27	2.9	3.5	0.7	27	2.4	3.4	0.7
	Unpleas.	26	3.6	3.7	0.7	26	3.3	3.9	0.8
	Max	27	4.2	4.1	0.8	27	3.5	4.1	0.8
	Present	27	2.4	3.4	0.7	27	2.2	3.5	0.7
6	7 day	24	3.4	3.9	0.8	24	2.7	3.5	0.7
	Unpleas.	22	4.5	4.1	0.9	22	4.1	4.0	0.9
	Max	24	4.7	4.0	0.8	24	4.0	4.1	0.8
	Present	24	2.9	3.7	0.7	24	2.4	3.1	0.6
12	7 day	18	4.3	3.5	0.8	18	3.1	3.3	0.8
	Unpleas.	18	4.9	3.7	0.9	18	4.4	3.5	0.8
	Max	18	5.4	3.7	0.9	18	4.2	3.8	0.9
	Present	18	3.5	3.4	0.8	18	3.0	3.6	0.8

Table 2.3. Means, standard deviations and standard errors of the 7 day, unpleasantness, maximum and present ongoing *spontaneous* pain measures at 2, 3, 4, 6 and 12 months time after SCI, at and below the level of lesion.

Repeated measures ANOVA was performed for ongoing *spontaneous* pain intensity according to at and below the level of SCI in 30 patients and Greenhouse-Geisser test was chosen as indicator of the test, and no significant differences were observed in the 7 day ongoing *spontaneous* pain intensity for

none of the months evaluated, either at the level ($F=2.366$; $df=2.586$, 33.614 ; $p= 0.096$) or below the level of SCI ($F= 0.704$; $df= 3.221$, 41.878 ; $p= 0.565$) (**Fig.2.5 and 2.6** respectively) with an observed power of 0.155 at level and 0.213 below the level. Friedman non parametric analysis neither showed significance below the level of the lesion with $n=14$ (Chi-square = 4.106 ; $df = 4$; $p=0.05$) or at the level (Chi-square = 5.604 ; $df = 4$; $p=0.05$) in the successive measures up to 12 months. However, it may be noticed a rise tendency in pain intensity along the repeated measures, much more pronounced and clear at the level of lesion. Unpleasantness pain intensity were compared either at the level ($F= 1.480$; $df =4$, 38.091 ; $p=0.295$) or below the level of SCI ($F= 0.168$; $df=4$, 4177 ; $p=0.949$) with an observed power of 0.280 at level and 0.071 below the level (see **Fig. 2.7 and 2.8** respectively).

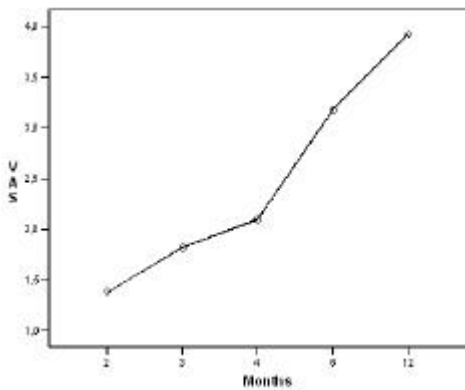


Fig.2.5. 7 day pain intensity in the repeated measures ANOVA at 2, 3, 4, 6 and 12 months after SCI at the level of the lesion.

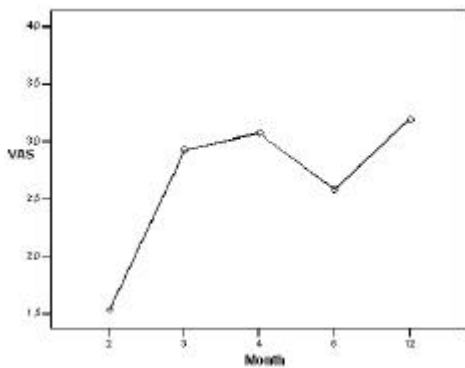


Fig 2.6. 7 day pain intensity in the repeated measures ANOVA at 2, 3, 4, 6 and 12 months after SCI below the level of the lesion.

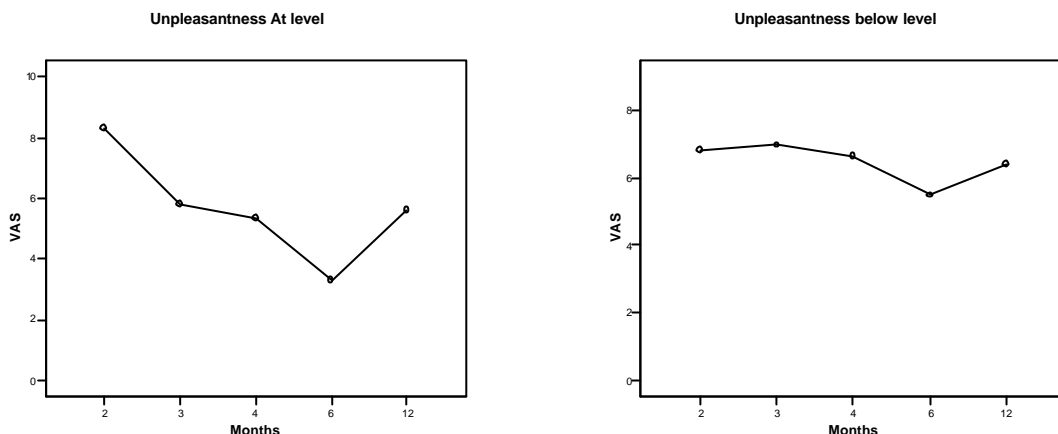


Fig.2.7. and Fig.2.8. Unpleasantness pain intensity in the repeated measures ANOVA at 2, 3, 4, 6 and 12 months after SCI at the level of the lesion.

2.4.4. Effect of SCI Physical Factors on At and Below Lesion Level 7 day Pain Intensity

The data for the mean 7 day ongoing *spontaneous* pain intensity for the following subgroups (complete/incomplete and cervical/thoracic) during the 12 months after SCI is shown in **Figures 2.7-2.12.**, although there were no significant differences between the cervical (n=6) and thoracic (n=8) at the level of the lesion. However, specific comparison between months 2 and 12 in the thoracic SCI subgroup revealed a significant increase ($t=2.54, df=13, p=0.03$) in pain intensity. A progressive and clear rise in pain intensity at the level of the lesion up to 12 months was observed in the thoracic SCI group from 0.8 to 5.1, while a higher constancy of pain in the cervical group. ($2 > VAS > 3$) (**Fig. 2.9**). In complete versus incomplete lesions (see **Table 2.4**) may be observed that up to month 4 after SCI, the patients with complete lesions may suffer more pain than incomplete (**Fig. 2.10**).

Below the level of the lesion, the patients with cervical lesions seemed to be more constant and the thoracic group ends at 12 months time with higher VAS. Incomplete lesions seemed to present more pain, except in month 6, than complete group, and in month 12 the difference was up to 2 points in the 7 day VAS.

Level of lesion	Type of lesion	2m	3m	4m	6m	12m
At level	Cervical	2.4±1.3	2.0±0.6	2.7±1.0	3.0±1.0	2.9±1.1
	Thoracic	0.8±1.3	2.0±0.9	3.2±1.0	3.9±1.3	5.1±0.9*
Below level	Cervical	2.1±1.2	2.5±1.1	2.2±0.9	2.7±0.7	2.7±1.1
	Thoracic	1.7±1.8	0.7±0.6	2.2±0.8	2.7±1.0	2.7±0.9
At level	Complete	1.5±1.2	1.5±1.2	3.1±0.9	4.2±1.1	4.6±1.0#
	Incomplete	1.8±1.5	2.2±1.0	2.7±1.1	2.3±1.1	3.7±1.4
Below level	Complete	2.2±1.4	1.1±0.8	1.9±0.8	2.5±0.9	2.3±0.9
	Incomplete	1.5±1.3	2.4±1.0	3.4±1.1	2.2±1.1	4.7±1.3

Table 2.4. Statistical analysis (Student’s t) between the different measures at 2,3,4,6 and 12 months after SCI, at and below the level of the lesion in cervical and thoracic and complete and incomplete type of lesions (N=30). * $t=2.54, df=13, p=0.03$ compared with 2m; # $t=1.98, df=22, p=0.06$ compared with 3m

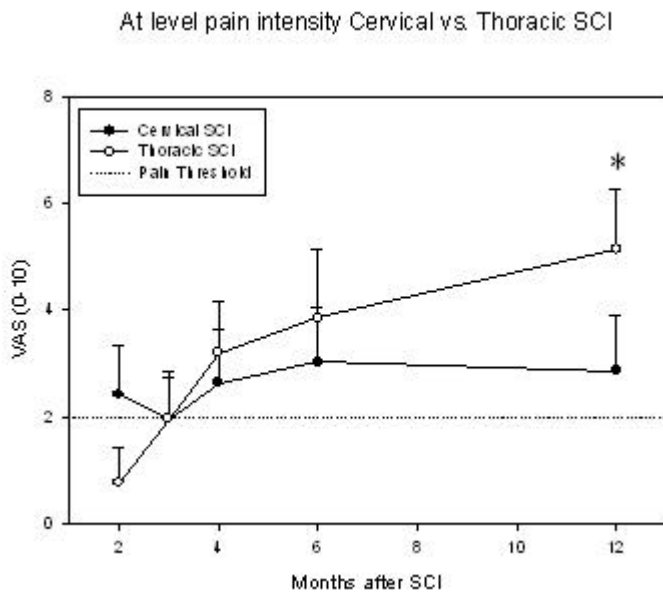


Fig.2.9. 7 day pain intensity at level of the lesion in patients with cervical and thoracic injury at 2, 3, 4, 6 and 12 months after SCI. * $t=2.54$, $df=13$, $p=0.03$ compared with 2m

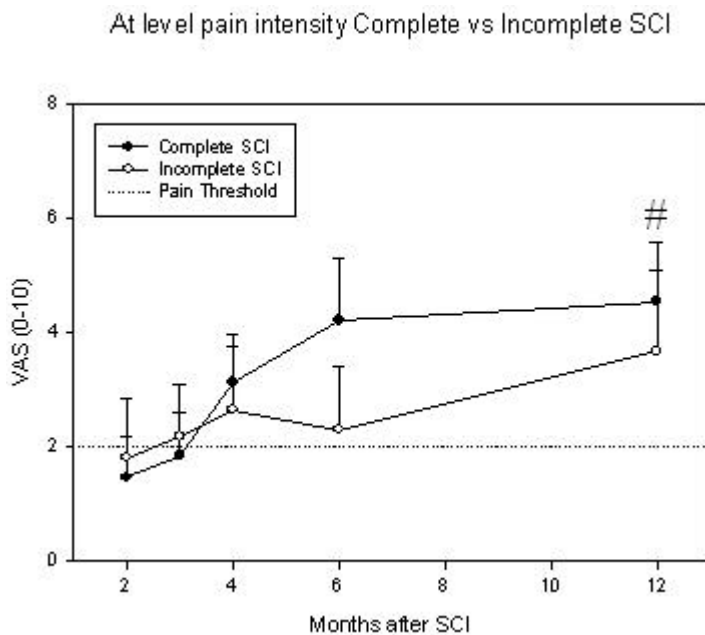


Fig. 2.10. 7 day pain intensity at the level of the lesion in patients with complete and incomplete injury at 2, 3, 4, 6 and 12 months after SCI. # $t=1.98$, $df=22$, $p=0.06$ compared with 3m

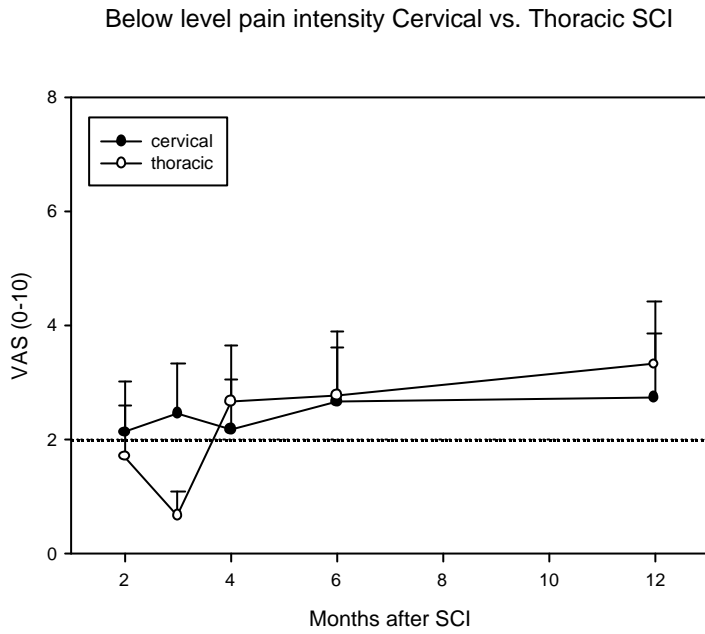


Fig. 2.11. 7 day pain intensity below the level of the lesion in patients with cervical and thoracic injury at 2, 3, 4, 6 and 12 months after SCI

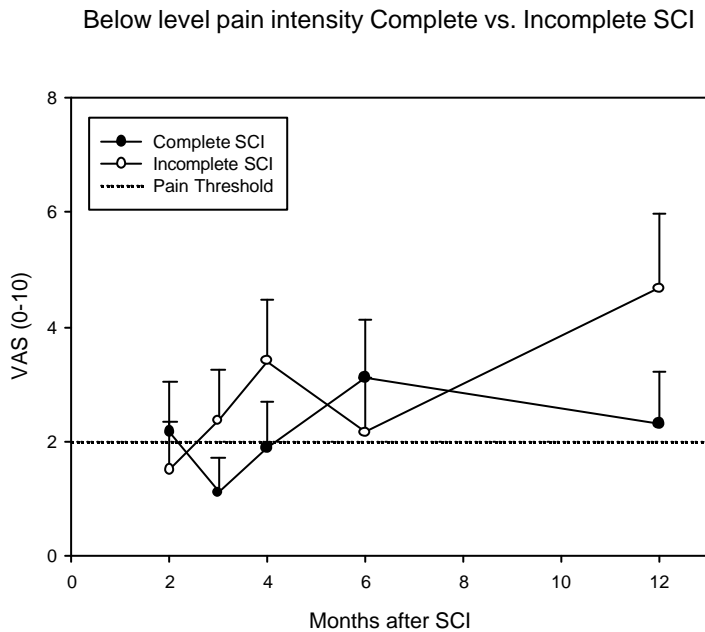


Fig. 2.12. 7 day pain intensity below the level of the lesion in patients with complete and incomplete injury at 2, 3, 4, 6 and 12 months after SCI

2.4.5. Within and Between Subject Interactions for The 7 Day At and Below Level Pain Intensity in the Complete/Incomplete and Cervical/Thoracic SCI Groups.

2.4.5.1. At Level Differences in 7 Day Pain Intensity SCI.

Statistical analysis with repeated ANOVA was also performed for the *complete/incomplete* and *cervical/thoracic* SCI subgroups for each temporal moment, but no significant difference was found within-subject using the Greenhouse-Geisser test for pain intensity at or below SCI (n=30; F= 1.806; df= 2.512, 27.633; p=0.176 with an observed power < 0.080). Although there were no significant differences between-subjects in cervical (n=6) and thoracic (n=8) SCI (F= 0.010; df= 1, 11; p=0.923), as in **Fig 2.7**, a progressive and clear increase in pain intensity from 2 to 12 months was observed in the thoracic SCI group compared to the cervical group (**Fig. 2.11**).

Interaction between SCI subgroups was not observed (F= 0.493; df= 2.1512 , 27.633; p=0.658), neither between complete (n=8) and incomplete (n=6) SCI groups using the Greenhouse-Geisser test (F= 0.020; df= 1, 11 ; p=0.889) (**Fig. 2.12**).

Pain intensity in cervical and thoracic lesions

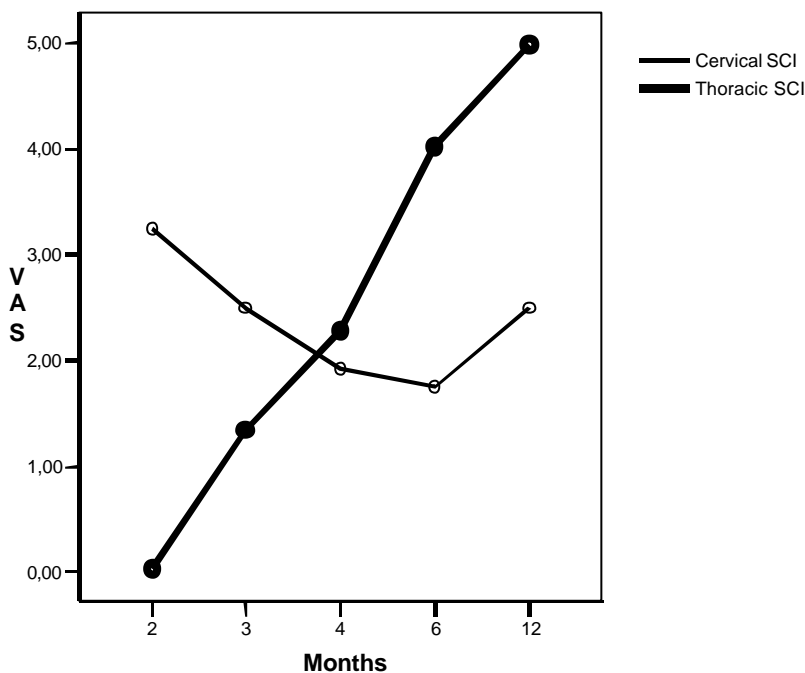


Fig.2.11. At level 7 day Pain intensity of SCI for repeated ANOVA measures at 2, 3, 4, 6 and 12 months after cervical or thoracic SCI.

Pain intensity in complete and incomplete lesions

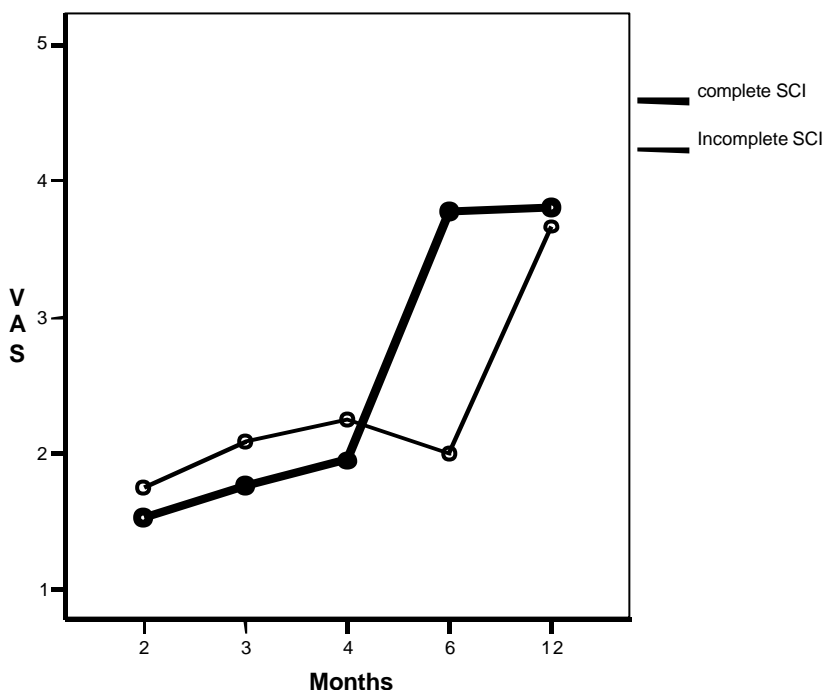


Fig. 2.12. At level 7 day pain intensity with repeated ANOVA measures at 2, 3, 4, 6 and 12 months complete (ASIA A) or incomplete (ASIA B or C) SCI.

2.4.5.2. Below Level Differences in 7 Day Pain Intensity SCI.

Repeated ANOVA testing of below level SCI 7 day ongoing and *spontaneous* pain intensity in the complete/incomplete and cervical/thoracic subgroups for each temporal moment failed to reveal a significant within-subject difference using the Greenhouse Geisser test ($F= 1.168$; $df= 3.034 , 33.379$; $p=0.337$, with an observed power < 0.080). However, we observed different trends between the cervical ($n=6$) and thoracic ($n=8, F= 0.051$; $df= 1, 11$; $p=0.826$) and a significant interaction ($F= 2.916$; $df= 3.034 , 33.379$; $p=0.048$), although large variability of 7 day *spontaneous* pain was observed over time, with a tendency for an increase in the thoracic and decrease in the cervical SCI group, although both groups finally reached a VAS of 3.5. 12 months after injury (**Fig.2.13**).

An interaction was neither identified between cervical ($n=6$) versus thoracic ($n=8$) SCI (Fig 2.13, $F= 1.768$; $df= 3.034, 33.379$; $p=0.172$) nor between complete ($n=8$) and incomplete ($n=6$) subgroups ($F= 1.768$; $df= 3.034, 33.379$; $p=0.172$ (**Fig.2.14**), suggesting a more constant level of ongoing pain intensity following complete SCI.

Pain intensity in cervical and thoracic lesions

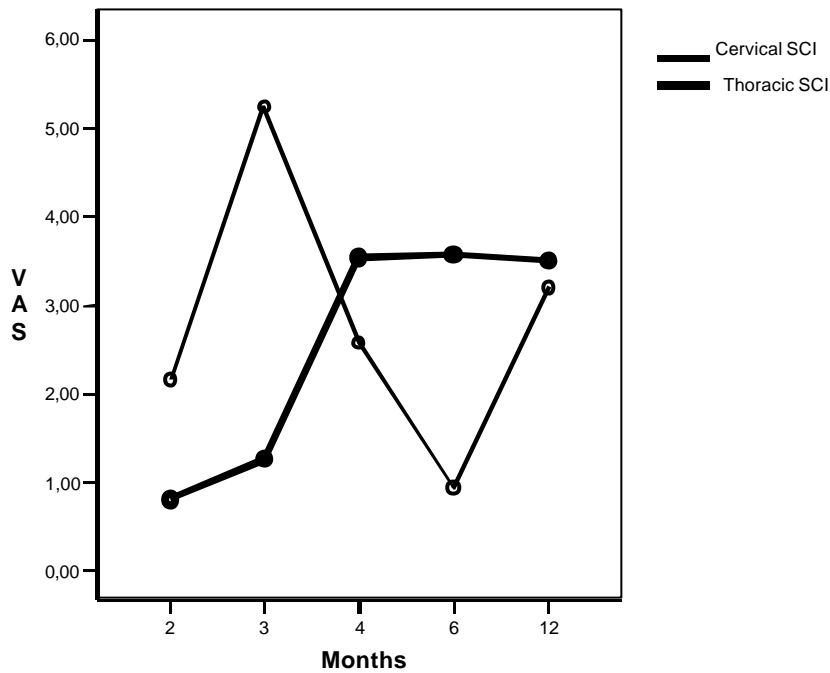


Fig 2.13. Below level 7 day ongoing *spontaneous* pain intensity repeated measures below the injury at 2, 3, 4, 6 and 12 months after cervical or thoracic SCI.

Pain intensity in complete and incomplete lesions

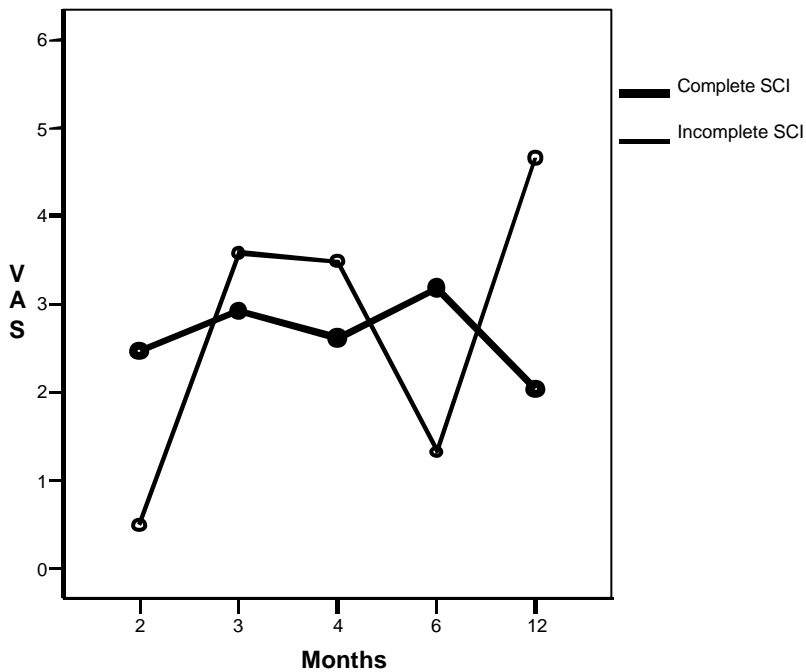


Fig.2.14. Below level 7 day ongoing *spontaneous* pain repeated measures below the injury at at 2, 3, 4, 6 and 12 months after complete (ASIA A) or incomplete (ASIA B or C) SCI.

2.4.6. Longitudinal Analysis of Evoked Pain Signs At and Below the SCI.

A non-parametric Cochran’s analysis was achieved for common *evoked* signs at and below the level of SCI from 2-6 months following the lesion, observing significant differences in temporal summation at the level of the lesion (p=0.029) and also in thermal allodynia below the level of the lesion (p=0.044) (See Table 2.5). In addition Fig 2.15 demonstrates a trend for an increase in *evoked* signs at the level to be constant or increase from 2 to 6 months after SCI, while below the level of SCI pain signs decrease in patients.

	MA At lev	MA Bel lev #	MH At lev	MH Bel lev	TS At lev	TS Bel lev	TA At lev	TA Bel lev
N	6	8	6	6	5	5	6	6
Cochran's Q	3.000	2.000	1.200	1.200	9.000	4.000	6.000	8.077
df	3	2	3	3	3	3	3	3
Sig.	0.392	0.368	0.753	0.753	0.029*	0.261	0.112	0.044*

Table 2.5. Cochran’s analysis for *evoked* signs at 2, 3, 4 and 6 months at and below the SCI level.# Note: MA was analyzed only at 2, 4 and 6 months time. MA = Mechanical Allodynia /Sensibility; MH =Mechanical Hyperalgesia /Sensibility; TS=Temporal Summation; TA=Thermal Allodynia /Sensibility; At lev=at the level of the lesion; Bel lev = below the level of the lesion.

Prevalence of evoked signs at 2 and 6 months after injury

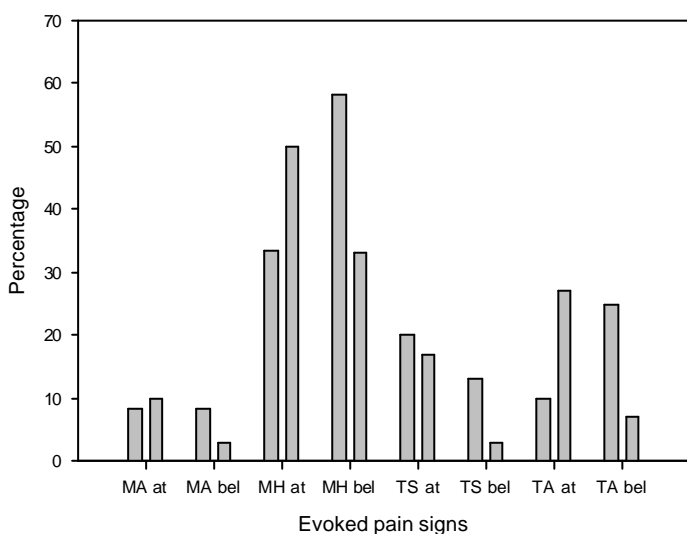


Fig. 2.15. Percentage of patients presenting *evoked* at and below level pain signs 2 (first column) and 6 months (second column) after the SCI. MA= Mechanical Allodynia /Sensitivity; MH=Mechanical Hyperalgesia /Sensitivity; TS=Temporal Summation; TA=Thermal Allodynia /Sensitivity; At lev=at the level of the lesion; Bel lev=below the level of the lesion.

2.4.7. Correlational Analysis Between Spontaneous and Evoked Pain Signs: General SCI

In general, significantly high and positive correlations were obtained both at (Table 2.6) and below (Table 2.7) the level of SCI between all the pain signs at 2 months after injury (Spearman-Rho test, p=0.001, n=28-20). The negative correlations observed between the 7 day ongoing *spontaneous* pain

intensity and *evoked* pain sign intensity (-0.629 < r < -0.960; p=0.001) indicated an inverse relationship suggesting that *evoked* pain sign intensity was high when *spontaneous* pain intensity was low, as expected 2 months after SCI (see Fig. 2.5 and Table 2.4). However mechanical allodynia/sensibility, mechanical hyperalgesia/sensibility, temporal summation and thermal allodynia/sensibility were positively correlated between themselves at 2 months (0.916 < r < 0.960; p=0.001). Although the data is not shown in the tables, post-stimulus sensations were highly and positively correlated with temporal summation either at level (r= 0.879; p=0.001; at 2 months; r= 0.478; p=0.05 at 6 months) or below the level of the lesion (r=0.992; p=0.001; at 2 months; r= 0.491 p=0.05 at 6 months). At 6 months after SCI, only *spontaneous* pain intensity with thermal allodynia/sensibility (r=0.413; p=0.05), and mechanical hyperalgesia/sensibility with thermal allodynia were significantly and positively correlated (r=0.462; p=0.05) at the level of lesion, as was thermal allodynia/sensibility with mechanical allodynia/sensibility below the level (r=0.691; p=0.001). Interestingly the number of involved dermatomes with *spontaneous* or *evoked* pain was positive and significant for at and below level *spontaneous* pain intensity at 2 months, but negatively correlated with *evoked* pain sign intensity at the equivalent time period (-0.629 < r < -0.961; p=0.001). In contrast at 6 months only some correlations at the level of SCI were significantly positive between the number of involved dermatomes and *evoked* pain sign intensity: mechanical allodynia/sensibility with the number of ongoing *spontaneous* pain dermatomes (r=0.427; p=0.05) and number of *evoked* pain dermatomes (r=0.460; p=0.05). Below the level of SCI, the number of *spontaneous* and *evoked* pain dermatomes was correlated with *spontaneous* 7 day pain intensity at 6 months (0.738 and 0.531 respectively; p=0.001). The correlation between the number of at level *spontaneous* and at level *evoked* pain dermatomes was high and positive at 2 and 6 months after SCI (r =0.903 and 0.849 respectively; p=0.001) and below level the level of lesion for the equivalent time periods (r=0.918 and 0.564 respectively; p=0.001).

	7d Sp Pain		MA		MH		TS		TA		Sp Dermat	
MA	-.760**	N=30										
	.402	N=23										
MH	-.731**	N=30	.954**	N=30								
	.372	N=23	.065	N=23								
TS	-.755**	N=29	.949**	N=29	.921**	N=29						
	.081	N=23	.103	N=23	-.098	N=23						
TA	-.636**	N=30	.960**	N=30	.935**	N=30	.916**	N=29				
	.413*	N=23	.407	N=23	.462*	N=23	-.207	N=23				
Sp Dermat	.697**	N=29	-.761**	N=29	-.720**	N=29	-.809**	N=28	-.730**	N=29		
	.349	N=23	.427*	N=23	.179	N=23	.370	N=23	.186	N=23		
Evk Dermat	.657**	N=29	-.699**	N=29	-.629**	N=29	-.772**	N=28	-.714**	N=29	.903**	N=29
	.399	N=23	.460*	N=23	.024	N=23	.379	N=23	.169	N=23	.849**	N=26

Table 2.6. At level SCI correlational analysis between *spontaneous* pain intensity, *evoked* pain sign intensity and number of dermatomes with *spontaneous* or *evoked* pain. Note. 7d Sp Pain = Intensity of spontaneous pain for the previous 7 day; MA= Mechanical Allodynia /Sensitivity; MH = Mechanical Hyperalgesia /Sensitivity; TS = Temporal Summation; TA = Thermal Allodynia /Sensitivity; At lev = at the level of the lesion; Bel lev = below the level of the lesion. Sp Dermat =Dermatomes implicated in spontaneous pain, Evk Dermat = Dermatomes implicated in evoked pain. First row in cells: at 2 months time; Second row in cells: at 6 months time. Bilateral significant correlations (? Spearman) ** ? =0.001 ; * ? =0.05.

	7d Sp Pain	MA	MH	TS	TA	Sp Dermat
MA	-.821** N=30 -.191 N=23					
MH	-.687** N=30 .243 N=23	.955** N=30 -.178 N=23				
TS	-.728** N=29 .180 N=23	.957** N=29 .067 N=23	.948** N=29 -.395 N=23			
TA	-.780** N=30 -.013 N=23	.982** N=30 .691** N=23	.935** N=30 .103 N=23	.944** N=29 .404 N=23		
Sp Dermat	.833** N=29 .738** N=24	-.950** N=29 .097 N=23	-.906** N=29 .260 N=23	-.961** N=28 .054 N=23	-.941** N=29 .117 N=23	
Evk Dermat	.665** N=29 .531** N=24	-.826** N=29 -.232 N=23	-.838** N=29 .184 N=23	-.907** N=28 -.035 N=23	-.834** N=29 -.072 N=23	.918** N=29 .564** N=26

Table 2.7. Below level SCI correlational analysis between *spontaneous* pain intensity, *evoked* pain sign intensity and number of dermatomes with *spontaneous* or *evoked* pain. *Note.* 7d Sp Pain = Intensity of spontaneous pain for the previous 7 day; MA= Mechanical Allodynia /Sensitivity; MH = Mechanical Hyperalgesia /Sensitivity; TS = Temporal Summation; TA = Thermal Allodynia/Sensitivity; At lev = at the level of the lesion; Bel lev = below the level of the lesion. Sp Dermat =Dermatomes implicated in spontaneous pain, Evk Dermat = Dermatomes implicated in evoked pain. First row in cells: at 2 months time; Second row in cells: at 6 months time. Bilateral significant correlations (? Spearman) ** ? =0.001 ; * ? =0.05.

2.4.8. Correlational Analysis Between Spontaneous and Evoked Pain Signs: Effect of Physical Factors

Spearman Rho correlations also permitted specific comparisons physical factors such as complete versus incomplete and cervical versus thoracic SCI. At the level of cervical SCI we observed high positive correlations 2 months after injury and at 6 months only correlations 7 day *spontaneous* pain intensity and number of dermatomes with *evoked* pain ($r=0.615$; $p=0.05$), between the number of dermatomes with *spontaneous* and *evoked* pain ($r=0.955$; $p=0.001$) and lastly thermal allodynia/sensibility and mechanical allodynia/sensibility at level of lesion in month 6 ($r=0.611$; $p=0.05$; **Table 2.8**). In contrast, at level thoracic correlations at 6 months after SCI only revealed a relationship between the number of dermatomes with *spontaneous* and *evoked* pain ($r=.626$; $p=0.05$;) and an original inverse relationship between thermal allodynia/sensibility and temporal summation ($r=-0.739$; $p=0.05$; **Table 2.9**).

In general, correlational analysis of *spontaneous* and *evoked* pain sign intensity below the level of cervical SCI, indicated the same relationships observed in the general analysis (**Table 2.10, see Table 2.7**). Correlational analysis for the below level of thoracic SCI could not be generated because of the small sample given by the analysis ($n=10$) (**Table 2.11**).

	7d Sp Pain		MA		MH		TS		TA		Sp Dermat	
MA	-.811**	N=15										
	.488	N=13										
MH	-.639*	N=15	.923**	N=15								
	.373	N=13	.475	N=13								
TS	-.757**	N=14	.878**	N=14	.848**	N=14						
	.358	N=13	.528	N=13	.113	N=13						
TA	-.631*	N=14	.929**	N=14	.881**	N=14	.850**	N=14				
	.401	N=13	.512	N=13	.611*	N=13	.253	N=13				
Sp Dermat	.558*	N=14	-.635*	N=14	-.554*	N=14	-.662*	N=14	-.702**	N=14		
	.538	N=13	.373	N=13	.367	N=13	.450	N=13	.300	N=13		
Evk Dermat	.578*	N=14	-.655*	N=14	-.515	N=14	-.632*	N=14	-.722**	N=14	.979**	N=14
	.615*	N=13	.384	N=13	.286	N=13	.421	N=13	.192	N=13	.955**	N=14

Table 2.8. Correlational analysis for at level cervical SCI between *spontaneous* pain intensity, *evoked* pain sign intensity and number of dermatomes (*spontaneous* and *evoked* pain). *Note* 7d Sp Pain = Intensity of spontaneous pain for the previous 7 day; MA= Mechanical Allodynia /Sensitivity; MH = Mechanical Hyperalgesia /Sensitivity; TS = Temporal Summation; TA = Thermal Allodynia /Sensitivity; At lev = at the level of the lesion; Bel lev = below the level of the lesion. Sp Dermat =Dermatomes implicated in spontaneous pain, Evk Dermat = Dermatomes implicated in evoked pain. First row in cells: at 2 months time; Second row in cells: at 6 months time. Bilateral significant correlations (? Spearman) ** ? =0.001 ; * ? =0.05.

	7d Sp Pain		MA		MH		TS		TA		Sp Dermat	
MA	-.649**	N=15										
	.265	N=10										
MH	-.722**	N=15	.987**	N=15								
	.394	N=10	-.228	N=10								
TS	-.705**	N=15	.985**	N=15	.963**	N=15						
	-.340	N=10	-.377	N=10	-.351	N=10						
TA	-.520*	N=15	.987**	N=15	.960*	N=15	.954**	N=15				
	.593	N=10	.435	N=10	.376	N=10	-.739*	N=10				
Sp Dermat	.782**	N=15	-.829**	N=15	-.818**	N=15	-.891**	N=15	-.768**	N=15		
	.020	N=10	.559	N=10	-.204	N=10	.211	N=10	.056	N=10		
Evk Dermat	.460	N=15	-.650**	N=15	-.554*	N=15	-.757**	N=15	-.613*	N=15	.784**	N=15
	.077	N=10	.661*	N=10	-.407	N=10	.306	N=10	.150	N=10	.626*	N=12

Table 2.9. Correlational analysis for at level thoracic SCI between *spontaneous* pain intensity, *evoked* pain sign intensity and number of dermatomes (*spontaneous* and *evoked* pain). *Note*. 7d Sp Pain = Intensity of spontaneous pain for the previous 7 day; MA= Mechanical Allodynia /Sensitivity; MH = Mechanical Hyperalgesia /Sensitivity; TS = Temporal Summation; TA = Thermal Allodynia /Sensitivity; At lev = at the level of the lesion; Bel lev = below the level of the lesion. Sp Dermat =Dermatomes implicated in spontaneous pain, Evk Dermat = Dermatomes implicated in evoked pain. First row in cells: at 2 months time; Second row in cells: at 6 months time. Bilateral significant correlations (? Spearman) ** ? =0.001 ; * ? =0.05.

	7d Sp Pain		MA		MH		TS		TA		Sp Dermat	
MA	-.812** -.252	N=15 N=13										
MH	-.602* .272	N=15 N=13	.888** -.320	N=15 N=13								
TS	-.622* .247	N=14 N=13	.885** .133	N=14 N=13	.865** -.343	N=14 N=13						
TA	-.754** .000	N=15 N=13	.960** .677*	N=15 N=13	.822** .000	N=15 N=13	.840** .491	N=14 N=13				
Sp Dermat	.860** .577*	N=14 N=13	-.890** .233	N=14 N=13	-.763** .449	N=14 N=13	-.881** .013	N=13 N=13	-.828** .286	N=14 N=13		
Evk Dermat	.674** .575*	N=14 N=13	-.774** -.352	N=14 N=13	-.743** .471	N=14 N=13	-.911** -.005	N=13 N=13	-.709** -.144	N=14 N=13	.901** .647*	N=14 N=14

Table 2.10. Correlational analysis for below level cervical SCI between *spontaneous* pain intensity, *evoked* pain sign intensity and number of dermatomes (*spontaneous* and *evoked* pain). *Note.* 7d Sp Pain = Intensity of spontaneous pain for the previous 7 day; MA= Mechanical Allodynia /Sensitivity; MH = Mechanical Hyperalgesia /Sensitivity; TS = Temporal Summation; TA = Thermal Allodynia /Sensitivity; At lev = at the level of the lesion; Bel lev = below the level of the lesion. Sp Dermat =Dermatomes implicated in spontaneous pain, Evk Dermat = Dermatomes implicated in evoked pain. First row in cells: at 2 months time; Second row in cells: at 6 months time. Bilateral significant correlations (? Spearman) ** ? =0.001 ; * ? =0.05.

	7d Sp Pain		MA		MH		TS		TA		Sp Dermat	
MA	-.823** --	N=15 N=10										
MH	-.751** .464	N=15 N=10	.988** --	N=15 N=10								
TS	-.778** --	N=15 N=10	.991** --	N=15 N=10	.991** --	N=15 N=10						
TA	-.778** --	N=15 N=10	.991** --	N=15 N=10	.991** --	N=15 N=10	1.000** --	N=15 N=10				
Sp Dermat	.822** .742*	N=15 N=10	-.985** --	N=15 N=10	-.973** .265	N=15 N=10	-.994** --	N=15 N=10	-.994** --	N=15 N=10		
Evk Dermat	.575* .353	N=15 N=10	-.823** --	N=15 N=10	-.849** -.466	N=15 N=10	-.890** --	N=15 N=10	-.890** --	N=15 N=10	.898** .630*	N=15 N=12

Table 2.11. Correlational analysis for below level thoracic SCI between *spontaneous* pain intensity, *evoked* pain sign intensity and number of dermatomes (*spontaneous* and *evoked* pain). *Note.* 7d Sp Pain = Intensity of spontaneous pain for the previous 7 day; MA= Mechanical Allodynia /Sensitivity; MH = Mechanical Hyperalgesia /Sensitivity; TS = Temporal Summation; TA = Thermal Allodynia /Sensitivity; At lev = at the level of the lesion; Bel lev = below the level of the lesion. Sp Dermat =Dermatomes implicated in spontaneous pain, Evk Dermat = Dermatomes implicated in evoked pain. First row in cells: at 2 months time; Second row in cells: at 6 months time. Bilateral significant correlations (? Spearman) ** ? =0.001 ; * ? =0.05.

2.4.9. Correlational Analysis Between At And Below Spontaneous and Evoked Pain Signs

Evidence for the existence of local SCI-NP generating mechanisms during the acute SCI phase may be identified by performing a correlational analysis of *spontaneous* and *evoked* pain signs between at and below the SCI level (c.f. Finnerupp et al., 2003b). The following tables show the correlations at and below the level between pain intensity, *evoked* signs and dermatomes implicated, both groups first (Table 2.12), and then cervical (Table 2.13) and thoracic groups (Table 2.14). Positive and highly significant correlations were observed with *evoked* pain sign intensity between at and below the SCI level 2 months after injury (Table 2.12); at 6 months only thermal allodynia/sensibility at level and mechanical hyperalgesia/sensibility below the level were significantly correlated (r= 0.428; p=0.05). Ongoing *spontaneous* pain intensity at and below level was significantly correlated at 2 (r= 0.525; p=0.001) and 6 months (r= 0.459; p=0.05) after SCI. Although the data was not included in the tables as the correlation analysis was not significant, saying that the number of below level dermatomes with *spontaneous* pain at 6 months after SCI correlated with the level of unpleasantness at level at 6 months. The number of dermatomes with *evoked* pain at and below the level of SCI also correlated at 2 (r= 0.694; p=0.001) and 6 months (r= 0.497; p=0.001) after SCI.

	7d Sp Pain Below	MA Below	MH Below	TS Below	TA Below	Sp Dermat Bel	Evk Dermat Bel
7d Sp Pain At	.525** N=30 .459* N=23						
MA At	-.821** N=30 .237 N=23	1.000** N=30 -.082 N=23					
MH At	-.752** N=29 .058 N=23	.954** N=30 -.249 N=23	.948** N=30 .263 N=23				
TS At	-.687** N=30 .206 N=23	.949** N=29 .000 N=23	.937** N=29 .058 N=23	.976** N=29 .394 N=23			
TA At	-.784** N=29 .230 N=23	.960** N=30 -.152 N=23	.925** N=30 .428* N=23	.944** N=29 -.169 N=23	.977** N=30 .083 N=23		
Sp Dermat At	.500** N=29 .269 N=23	-.761** N=29 .034 N=23	-.716** N=29 .176 N=23	-.753** N=28 .027 N=23	-.732** N=29 .258 N=23	.763** N=29 .198 N=26	
Evk Dermat At	.386* N=29 .371 N=23	-.699** N=29 .087 N=23	-.683** N=29 .165 N=23	-.712** N=28 .091 N=23	-.716** N=29 .303 N=23	.765** N=29 .301 N=26	.694** N=29 .497** N=26

Table 2.12. Correlations between at and below *spontaneous* pain intensity, *evoked* pain sign intensity and number of dermatomes with pain (*spontaneous* and *evoked*) 2 and 4 months after SCI. *Note.* 7d Sp Pain = Intensity of spontaneous pain for the previous 7 day; MA= Mechanical Allodynia /Sensitivity; MH = Mechanical Hyperalgesia /Sensitivity; TS = Temporal Summation; TA = Thermal Allodynia /Sensitivity; At lev = at the level of the lesion; Bel lev = below the level of the lesion. Sp Dermat =Dermatomes implicated in spontaneous pain, Evk Dermat = Dermatomes implicated in evoked pain. First row in cells: at 2 months time; Second row in cells: at 6 months time. Bilateral significant correlations (? Spearman) ** ? =0.001 ; * ? =0.05.

In general the cervical SCI group (Table 2.13) revealed correlations similar to those identified in the general analysis (Tables 2.12); and the correlations for the thoracic SCI group could not be generated because of the small sample given by the analysis (n=10, Table 2.14). Nevertheless the correlation between the number of dermatomes with *spontaneous* and *evoked* pain at the level of cervical SCI with below level mechanical hyperalgesia/sensibility at 6 months revealed a distinct change in relationship compared to the constant and negative relationship with thoracic SCI at 2 and 6 months.

	7d Sp Pain Below	MA Below	MH Below	TS Below	TA Below	Sp Dermat Bel	Evk Dermat Bel
7d Sp Pain At	.719** N=15 .576* N=13						
MA At	-.812** N=15 .335 N=13	1.000** N=15 -.083 N=13					
MH At	-.670** N=15 .436 N=13	.923** N=15 -.357 N=13	.948** N=15 .450 N=13				
TS At	-.649* N=14 .392 N=13	.878** N=14 .044 N=13	.869** N=14 .282 N=13	.985** N=14 .536 N=13			
TA At	-.685** N=15 .287 N=13	.929** N=15 -.256 N=13	.854** N=15 .648* N=13	.885** N=14 -.136 N=13	.977** N=15 .031 N=13		
Sp Dermat At	.329 N=14 .369 N=13	-.635* N=14 .083 N=13	-.630* N=14 .539 N=13	-.685** N=13 -.036 N=13	-.631* N=14 .337 N=13	.715** N=14 .359 N=14	
Evk Dermat At	.379 N=14 .436 N=13	-.655* N=14 .128 N=13	-.608* N=14 .463 N=13	-.640* N=13 .079 N=13	-.661* N=14 .378 N=13	.711** N=14 .469 N=14	.569* N=14 .310 N=14

Table 2.13. Correlations between at and below cervical lesion *spontaneous* pain intensity, *evoked* pain sign intensity and number of dermatomes with pain (*spontaneous* and *evoked*) 2 and 4 months after SCI. *Note.* 7d Sp Pain = Intensity of spontaneous pain for the previous 7 day; MA= Mechanical Allodynia /Sensitivity; MH = Mechanical Hyperalgesia /Sensitivity; TS = Temporal Summation; TA = Thermal Allodynia /Sensitivity; At lev = at the level of the lesion; Bel lev = below the level of the lesion. Sp Dermat =Dermatomes implicated in spontaneous pain, Evk Dermat = Dermatomes implicated in evoked pain. First row in cells: at 2 months time; Second row in cells: at 6 months time. Bilateral significant correlations (? Spearman) ** ? =0.001 ; * ? =0.05.

	7d Sp Pain Below		MA Below		MH Below		TS Below		TA Below		Sp Dermat Bel		Evk Dermat Bel	
7d Sp Pain At	.319	N=15												
	.355	N=10												
MA At	-.823**	N=15	1.000**	N=15										
	.186	N=10	-	N=10										
MH At	-.822**	N=15	.987**	N=15	.975**	N=15								
	-.210	N=10	-	N=10	.091	N=10								
TS At	-.744**	N=14	.985**	N=15	.973**	N=15	.982**	N=15						
	-.021	N=10	-	N=10	-.094	N=10	-	N=10						
TA At	-.876**	N=15	.987**	N=15	.969**	N=15	.984**	N=15	.984**	N=15				
	.249	N=10	-	N=10	-.248	N=10	-	N=10	-	N=10				
Sp Dermat At	.634*	N=15	-.829**	N=15	-.770**	N=15	-.797**	N=15	-.797**	N=15	.792**	N=15		
	.083	N=10	-	N=10	-.559	N=10	-	N=10	-	N=10	.107	N=12		
Evk Dermat At	.292	N=15	-.650**	N=15	-.643**	N=15	-.703**	N=15	-.703**	N=15	.699**	N=15	.779*	N=15
	.281	N=10	-	N=10	-.472	N=10	-	N=10	-	N=10	.334	N=12	.647*	N=12

Table 2.14. Correlations between at and below thoracic lesion *spontaneous* pain intensity, *evoked* pain sign intensity and number of dermatomes with pain (*spontaneous* and *evoked*) 2 and 4 months after SCI. *Note.* 7d Sp Pain = Intensity of spontaneous pain for the previous 7 day; MA= Mechanical Allodynia /Sensitivity; MH = Mechanical Hyperalgesia /Sensitivity; TS = Temporal Summation; TA = Thermal Allodynia /Sensitivity; At lev = at the level of the lesion; Bel lev = below the level of the lesion. Sp Dermat =Dermatomes implicated in spontaneous pain, Evk Dermat = Dermatomes implicated in evoked pain. First row in cells: at 2 months time; Second row in cells: at 6 months time. Bilateral significant correlations (? Spearman) ** ? =0.001 ; * ? =0.05.

Lastly, in order to identify common pathophysiological mechanisms active shortly after at level SCI which may in turn activate later below level NP mechanisms, a temporal correlation was made between the pain signs at 2 months and 6 months. The number of painful dermatomes (*spontaneous* and *evoked*) at and below the level of the SCI in patients with thoracic/generalized lesions were not significant except for *spontaneous* dermatomes at the level of the lesion at 2 months and *evoked* below the lesion at 6 months (Table 2.15).

	Sp Dermat At 2m		Evk Dermat At 2m	
Sp Dermat sp Below 6m	.278	N=25	.384	N=25
Evk Dermat Below 6m	.425*	N=25	.206	N=25

Table 2.15. Correlation between number of painful dermatomes (*spontaneous* and *evoked*) at and below the level of the SCI at 2 and 6 months after thoracic SCI. *Note.* Sp Dermat =Dermatomes implicated in spontaneous pain, Evk Dermat = Dermatomes implicated in evoked pain; Below= below the level of the lesion; At= at the level of the lesion. Bilateral significant correlations (? Spearman) *: ? =0.05.

2.4.10. Neuropathic Pain Based on Mechanisms Interview Analysis

Five questions from the NP Mechanism Interview with sufficient n for being analyzed (**Table 2.16**) were chosen, using the Student's t-test for each temporal moment compared two by two for the following temporal moments: 2, 3, 4, 6 and 12 months, at and below the level of the SCI. The questions were: static mechanical *evoked* pain intensity (0-10), dynamic mechanical *evoked* pain intensity (0-10), thermal *evoked* pain intensity (0-10), continuous *spontaneous* pain (0-10), and number of descriptors (0-10, burning, pulsing, pricking, stinging, stabbing, cutting, cramping, pressuring, tingling, itching).

Month	BELOW LEVEL	N	Mean	SD
2	static mechanical evoked pain	12	2,250	3,9341
2	dynamic mechanical evoked pain	12	,333	,8876
2	thermal evoked pain	12	,00	,000
2	continuous pain	12	1,7	,389
2	number of descriptors	12	3,58	2,906
3	static mechanical evoked pain	20	2,300	4,1308
3	dynamic mechanical evoked pain	20	,600	2,0876
3	thermal evoked pain	20	,60	2,257
3	continuous pain	21	2,9	,463
3	number of descriptors	20	2,30	1,490
4	static mechanical evoked pain	27	,778	2,2589
4	dynamic mechanical evoked pain	27	,593	1,7598
4	thermal evoked pain	27	,00	,000
4	continuous pain	22	3,2	,477
4	number of descriptors	27	1,96	2,361
6	static mechanical evoked pain	24	1,250	3,0963
6	dynamic mechanical evoked pain	24	,458	1,6146
6	thermal evoked pain	24	,00	,000
6	continuous pain	24	4,2	,504
6	number of descriptors	24	2,25	1,871
12	static mechanical evoked pain	18	2,722	4,1275
12	dynamic mechanical evoked pain	18	2,167	3,8079
12	thermal evoked pain	18	1,28	2,986
12	continuous pain	19	3,7	,496
12	number of descriptors	18	1,89	1,937

Table 2.16. Descriptive statistics of the NP Based on Mechanisms Interview at the level of injury.

Month	BELOW LEVEL	N	Mean	SD
2	static mechanical evoked pain	12	,083	,2887
2	dynamic mechanical evoked pain	12	,500	1,4460
2	thermal evoked pain	10	1,00	3,162
2	continuous pain	12	,42	,515
2	number of descriptors	12	1,75	1,658
3	static mechanical evoked pain	20	1,475	3,2666
3	dynamic mechanical evoked pain	20	1,550	3,3003
3	thermal evoked pain	16	,75	2,517
3	continuous pain	20	,45	,510
3	number of descriptors	20	2,20	1,704
4	static mechanical evoked pain	27	1,500	3,1348
4	dynamic mechanical evoked pain	27	1,315	2,7913
4	thermal evoked pain	27	,26	1,347
4	continuous pain	27	,30	,465
4	number of descriptors	27	1,59	1,803
6	static mechanical evoked pain	24	,583	2,1653
6	dynamic mechanical evoked pain	24	1,375	2,6220
6	thermal evoked pain	23	,43	2,085
6	continuous pain	23	,22	,422
6	number of descriptors	24	2,04	2,368
12	static mechanical evoked pain	18	3,000	4,1016
12	dynamic mechanical evoked pain	18	3,222	4,3731
12	thermal evoked pain	17	2,71	3,917
12	continuous pain	20	,35	,489
12	number of descriptors	18	1,72	1,776

Table 2.17. Descriptive statistics of the Neuropathic Pain Based on Mechanisms Interview at the level of injury.

Figures 2.16-2.22 show the pattern followed by the patients in the questions at and below the level of the lesion: they usually reported higher scores in month 2 after SCI and then decreased to month 6, then the scores tended to rise again to a similar point where they started. However, at the level of the injury the patients reported higher scores than below the level and higher number of descriptors were seen up to month 6. Nevertheless, at 12 months after the injury the pain intensity levels were similar for all questions.

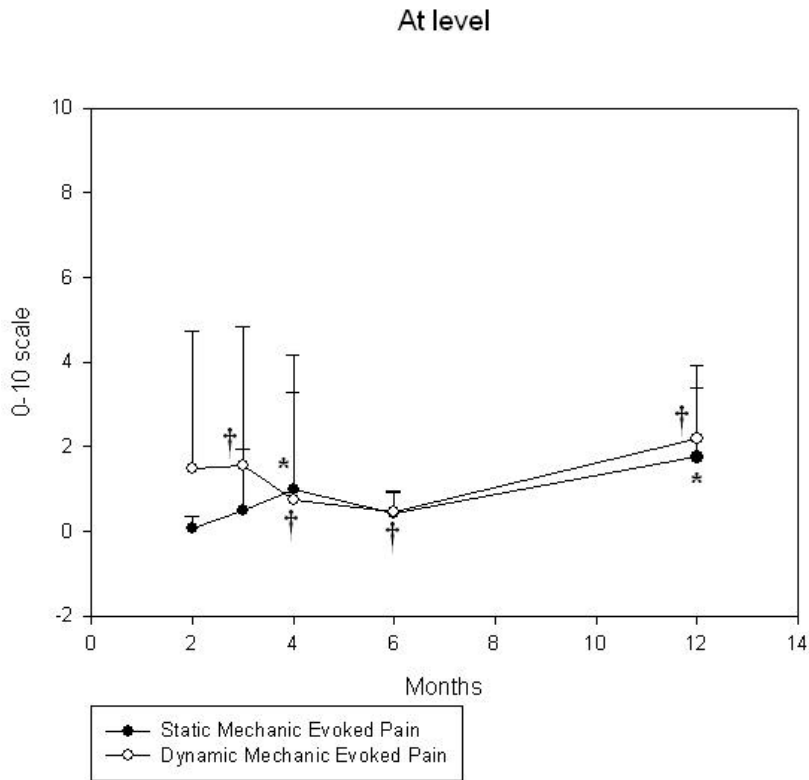


Fig.2.16. Questions “Static Mechanic *Evoked Pain*” and “Dynamic Mechanic *Evoked Pain*” of the Neuropathic Pain Based on Mechanisms Interview at the level of SCI at 2, 3, 4, 6 and 12 months after injury.

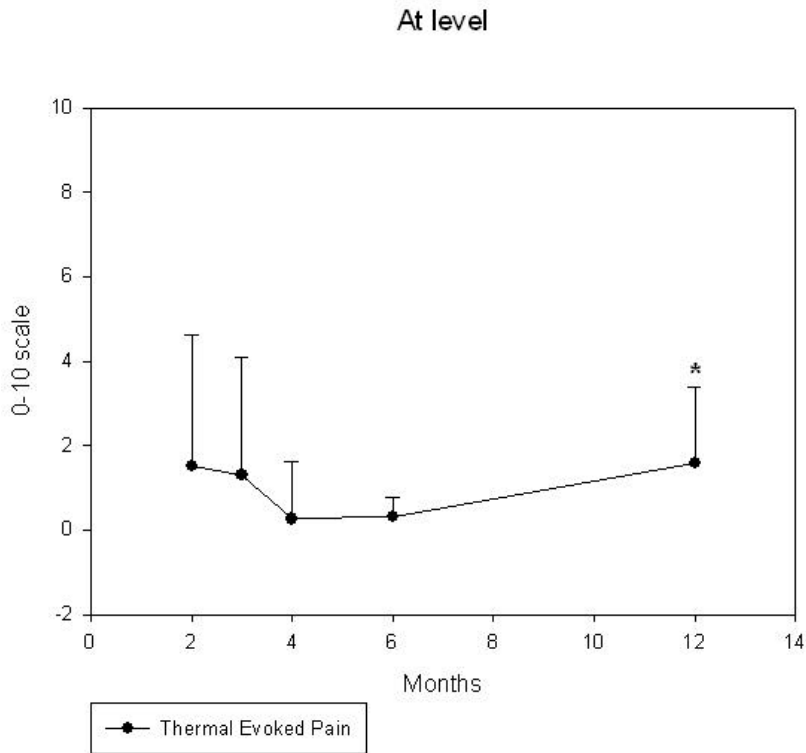


Fig.2.17. Question “*Thermal Evoked Pain*” of the Neuropathic Pain Based on Mechanisms Interview at the level of SCI at 2, 3, 4, 6 and 12 months after injury.

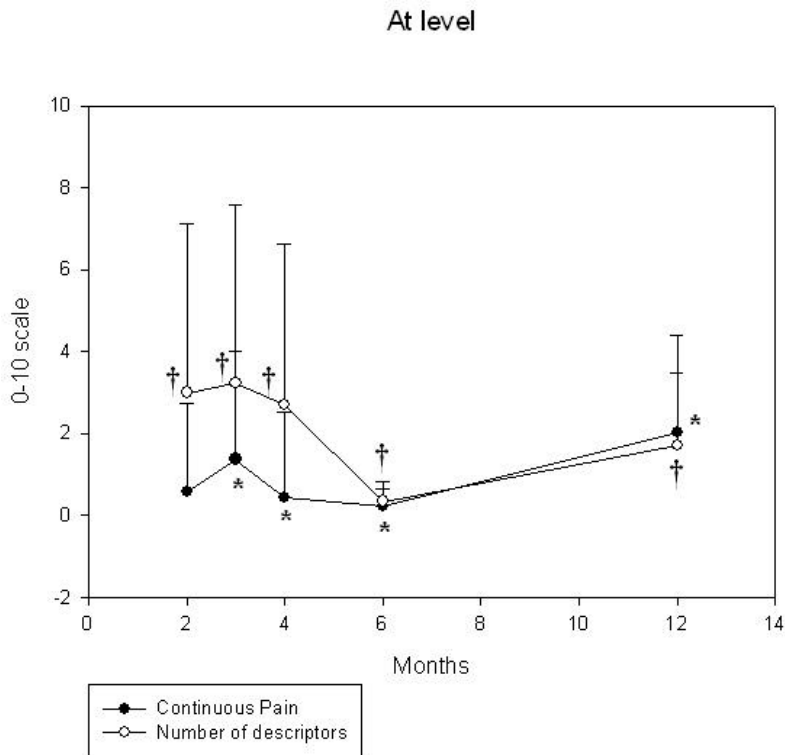


Fig 2.18. Questions “*Continuous Pain*” and “*Number of descriptors*” of the Neuropathic Pain Based on Mechanisms Interview at the level of SCI at 2, 3, 4, 6 and 12 months after injury.

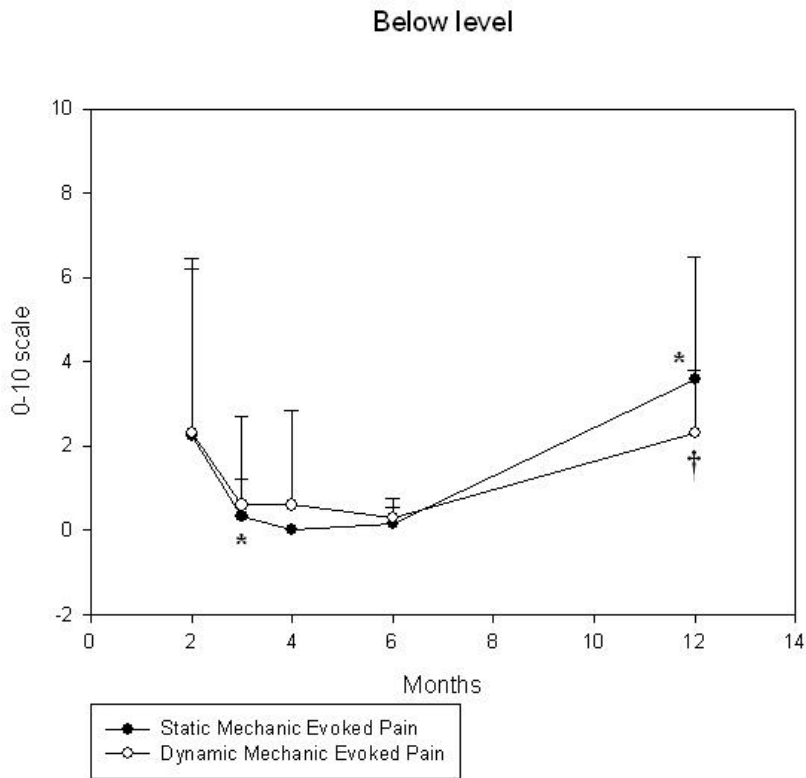


Fig.2.19. Questions “Static Mechanic *Evoked Pain*” and “Dynamic Mechanic *Evoked Pain*” of the Neuropathic Pain Based on Mechanisms Interview below the level of SCI at 2, 3, 4, 6 and 12 months after injury.

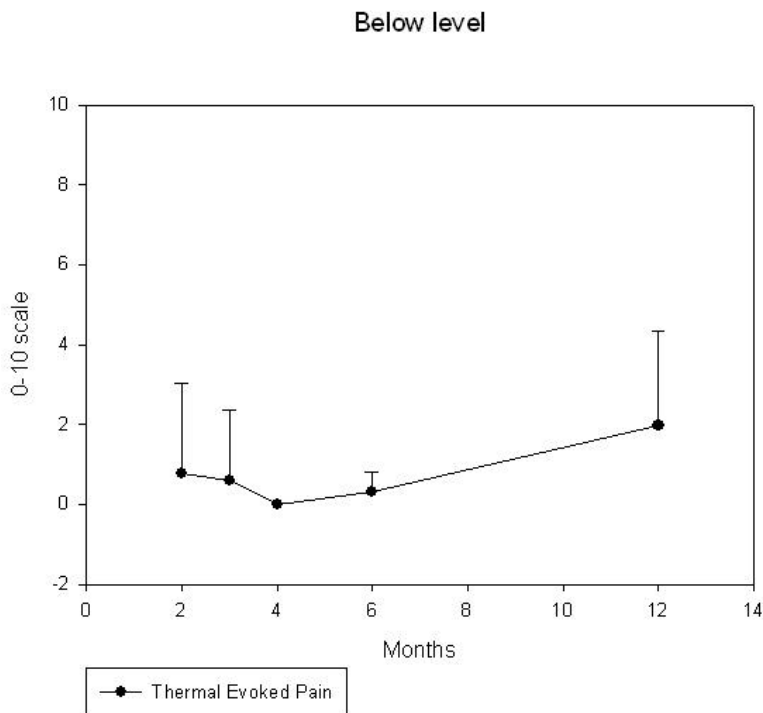


Fig.2.20. Question “Thermal *Evoked Pain*” of the Neuropathic Pain Based on Mechanisms Interview below the level of SCI at 2, 3, 4, 6 and 12 months after injury.

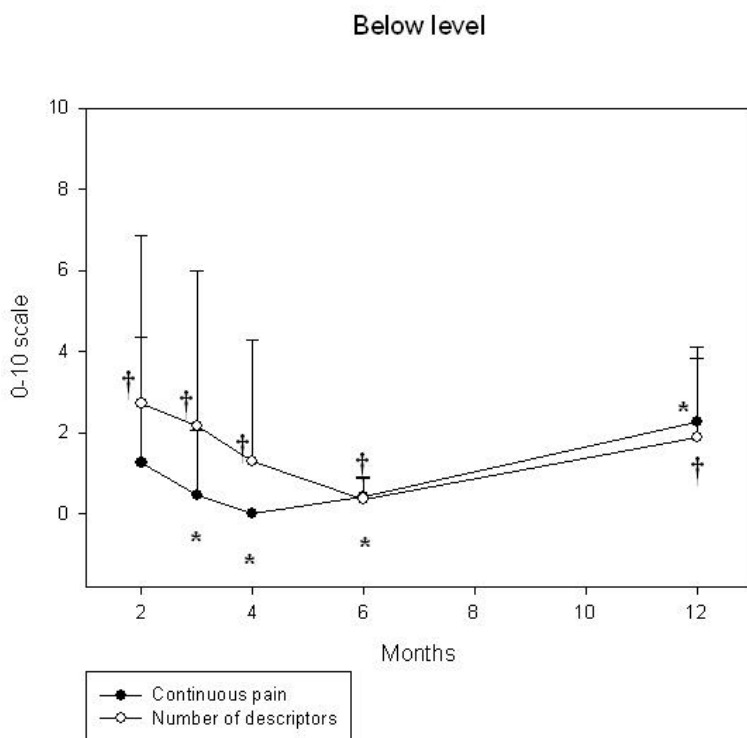


Fig 2.21. Questions “Continuous Pain” and “Number of descriptors” of the Neuropathic Pain Based on Mechanisms Interview below the level of SCI at 2, 3, 4, 6 and 12 months after injury.

Independent samples Student’s t test analysis revealed that were mainly significant, and therefore different from the other time points in each question, those related to continuous pain and number of descriptors, either at or below the level of lesion, and dynamic mechanical *evoked* pain at level for the 12 months. At the level of injury (**Table 2.18**), the following differences were significant: static mechanic *evoked* pain intensity at 4 and 12 months ($p=0.020$ and 0.006 respectively); dynamic mechanic *evoked* pain intensity at 3, 4, 6 and 12 months ($p=0.049$, 0.021 , 0.017 and 0.006 respectively); thermal *evoked* pain intensity only at 12 months ($p=0.012$); continuous *spontaneous* pain at 3, 4, 6 and 12 months ($p=0.010$, 0.005 , 0.0001 and 0.005 respectively); number of descriptors were significantly different for all the time measures ($p=0.010$, 0.001 , 0.003 , 0.022 and 0.005 respectively). Below the level of lesion (**Table 2.19**), the following differences were significant: static mechanic *evoked* pain intensity at 3 and 12 months ($p=0.022$ and 0.012 respectively); dynamic mechanic *evoked* pain intensity only at 12 months ($p=0.027$); continuous *spontaneous* pain at 3, 4, 6 and 12 months ($p=0.010$, 0.005 , 0.0001 and 0.005 respectively); number of descriptors were significantly different for all the time measures ($p=0.001$, 0.0001 , 0.0001 , 0.0001 and 0.001 respectively).

	Stat Mech Evk Pain			Dyn Mech Evk Pain			Thermal Evk Pain			Continuous Pain			Number of pain descriptors		
	t	df	Sig	t	df	Sig	t	df	Sig	t	df	Sig	t	df	Sig
2m	1.00	11.00	0.339	1.20	11.00	0.256	1.00	9.00	0.343	1.48	11.00	0.166	2.80	11.00	0.017*
3m	2.02	19.00	0.058	2.10	19.00	0.049*	1.19	15.00	0.252	2.83	20.00	0.010*	3.94	19.00	0.001*
4m	2.49	26.00	0.020*	2.45	26.00	0.021*	1.00	26.00	0.327	3.13	21.00	0.005*	3.31	26.00	0.003*
6m	1.32	23.00	0.200	2.57	23.00	0.017*	1.00	22.00	0.328	4.05	23.00	0.0001*	2.47	22.00	0.022*
12m	3.10	17.00	0.006*	3.13	17.00	0.006*	2.85	16.00	0.012*	3.24	18.00	0.005*	3.20	19.00	0.005*

Table 2.18. Student’s t significant differences at the level of the lesion between five questions of the Neuropathic Pain Based on Mechanisms Interview analysis.

	Stat Mech Evk Pain			Dyn Mech Evk Pain			Thermal Evk Pain			Continuous Pain			Number of pain descriptors		
	t	df	Sig	t	df	Sig	t	df	Sig	t	df	Sig	t	df	Sig
2m	1.98	11.00	0.073	1.30	11.00	0.220	-	-	-	1.48	11.00	0.166	4.27	11.00	0.001*
3m	2.49	19.00	0.022*	1.29	19.00	0.214	1.19	19.00	0.249	2.83	20.00	0.010*	6.90	19.00	0.0001*
4m	1.79	26.00	0.085	1.75	26.00	0.092	-	-	-	3.13	21.00	0.005*	4.32	26.00	0.0001*
6m	1.98	23.00	0.060	1.39	23.00	0.178	-	-	-	4.05	23.00	0.0001*	5.89	23.00	0.0001*
12m	2.80	17.00	0.012*	2.41	17.00	0.027*	1.82	17.00	0.087	3.24	18.00	0.005*	4.14	17.00	0.001*

Table 2.19. Student’s t significant differences below the level of the lesion between five questions of the Neuropathic Pain Based on Mechanisms Interview analysis. Note: some analysis (-) could not be done since the SD=0.

2.4.11. Dermatome Analysis

Independent samples Student’s t test analysis were achieved in each temporal moment (2, 3, 4, 6 and 12 months after injury), both at and below the level of the SCI (**Figures 2.22-2.25**). Difference in dermatomes implicated in *spontaneous* pain at the level of the injury were found significant between months 4 and 12 (p=0.055) in the cervical group. Significant differences were seen between months 3 and 6 (p=0.044) and between 4 and 12 (p=0.022) in dermatomes implicated in *evoked* pain. Also were seen differences in dermatomes implicated in *spontaneous* pain between months 2 and 4 (p=0.044) and between 2 and 6 (p=0.025) in thoracic lesions; and differences in dermatomes implicated in *evoked* pain between months 2 and 3 (p=0.044) and between 2 and 4 (p=0.016) also in the thoracic group.

A tendency may be observed in cervical group below the level along the months and was a diminishing number of dermatomes implicated either in *spontaneous* and *evoked* pain, while thoracic group tended to increase the number of dermatomes in *spontaneous* and *evoked* pain in time. At the level of the injury, cervical group tended to be more constant and thoracic more heterogeneous along the different temporal measures. **Pictures 2.2 and 2.3** (below) show examples of Maps of dermatomes of two NP patients with cervical and thoracic lesions respectively.

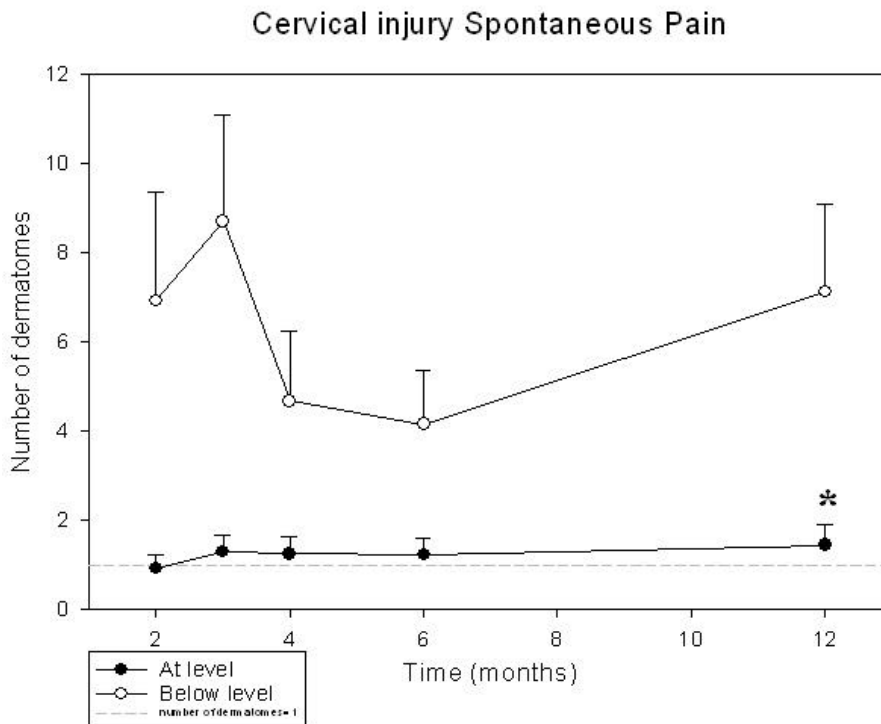


Fig.2.22. Means and SD of dermatomes implicated in *spontaneous* pain in cervical lesions. Significant differences were seen between months 4 and 12 (p=0.055)

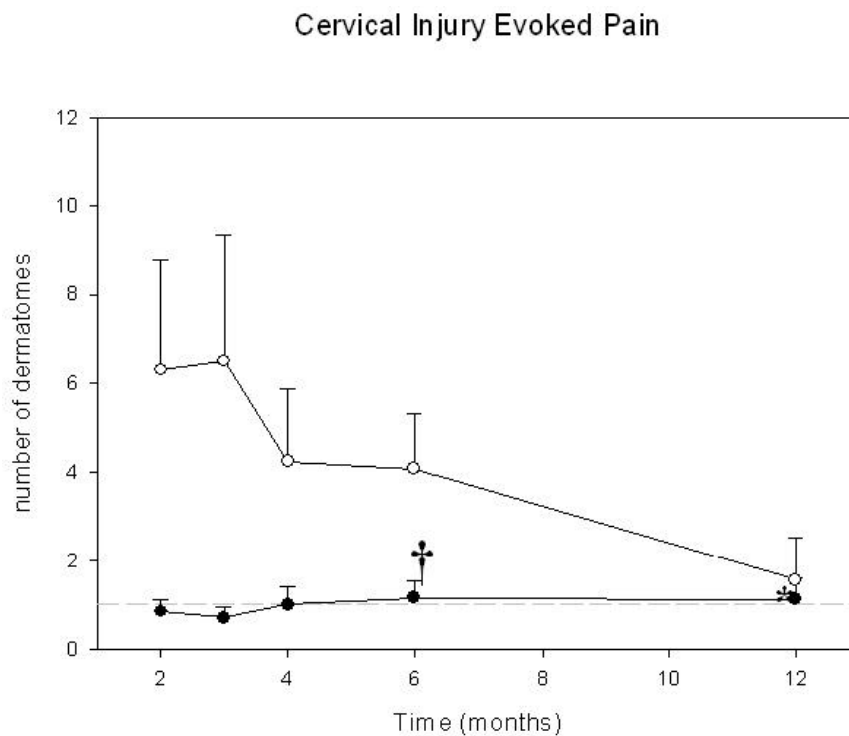


Fig.2.23. Means and SD of dermatomes implicated in *evoked* pain in cervical lesions. Significant differences were seen between months 3 and 6 (p=0.044, †) and between 4 and 12 (p=0.022, *).

Thoracic Injury Spontaneous Pain

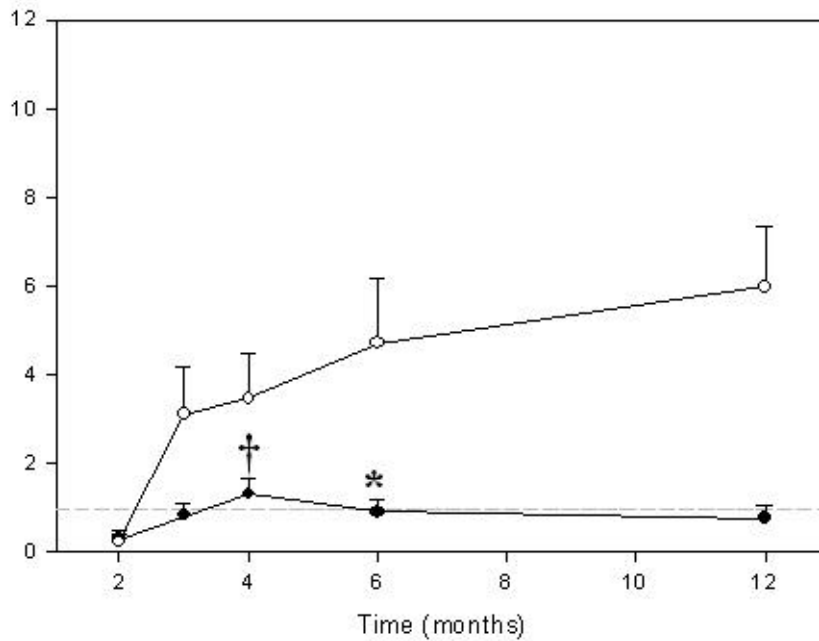


Fig.2.24. Means and SD of dermatomes implicated in *evoked* pain in thoracic lesions. Significant differences were seen between months 2 and 4 ($p=0.044$) (symbol †) and between 2 and 6 ($p=0.025$) (symbol *)

Thoracic Injury Evoked Pain

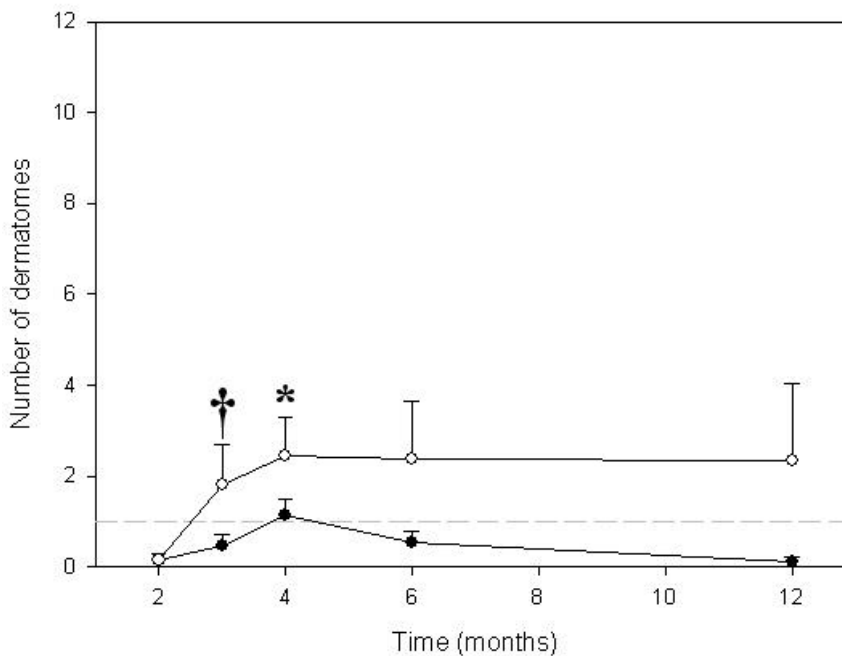
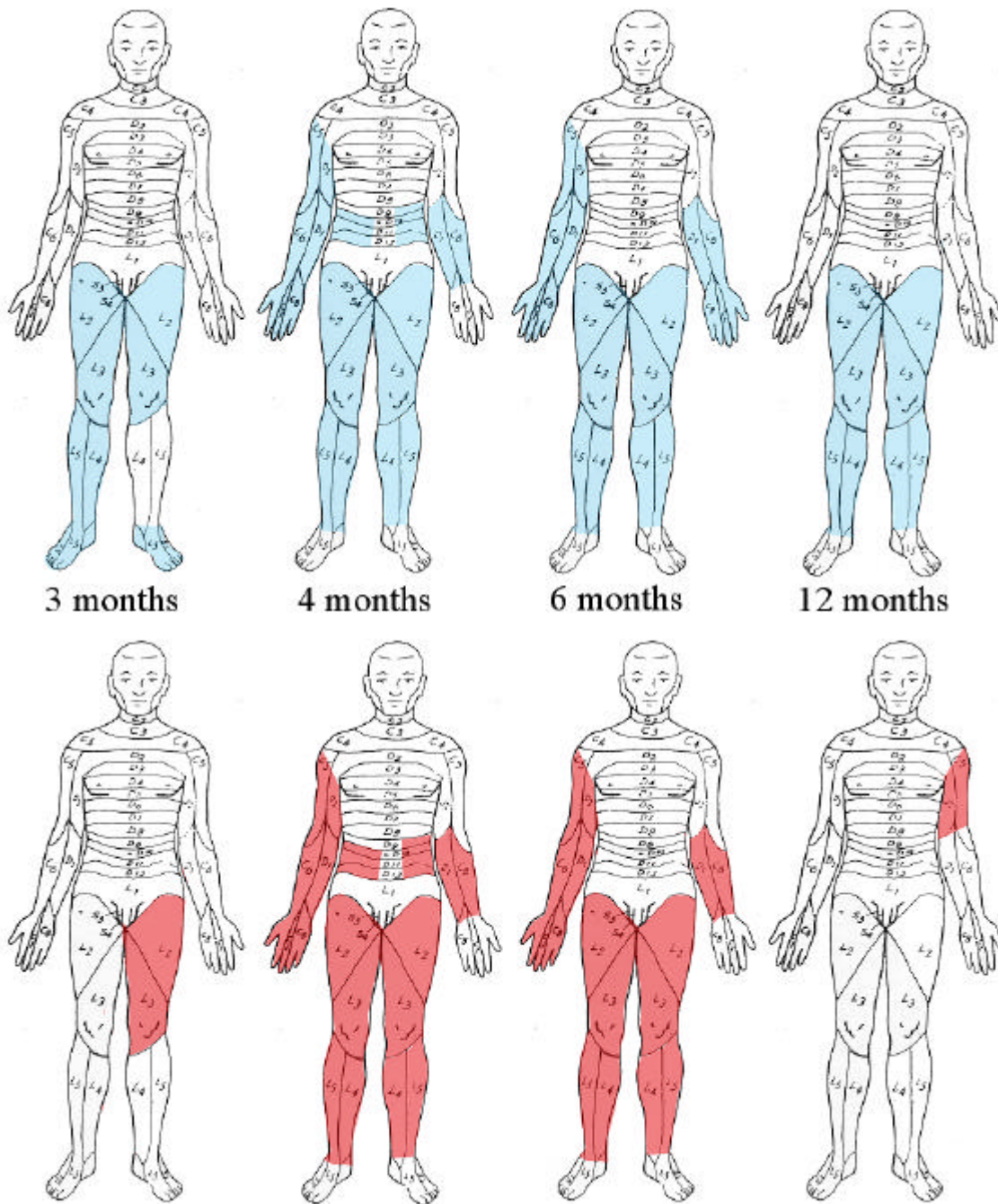
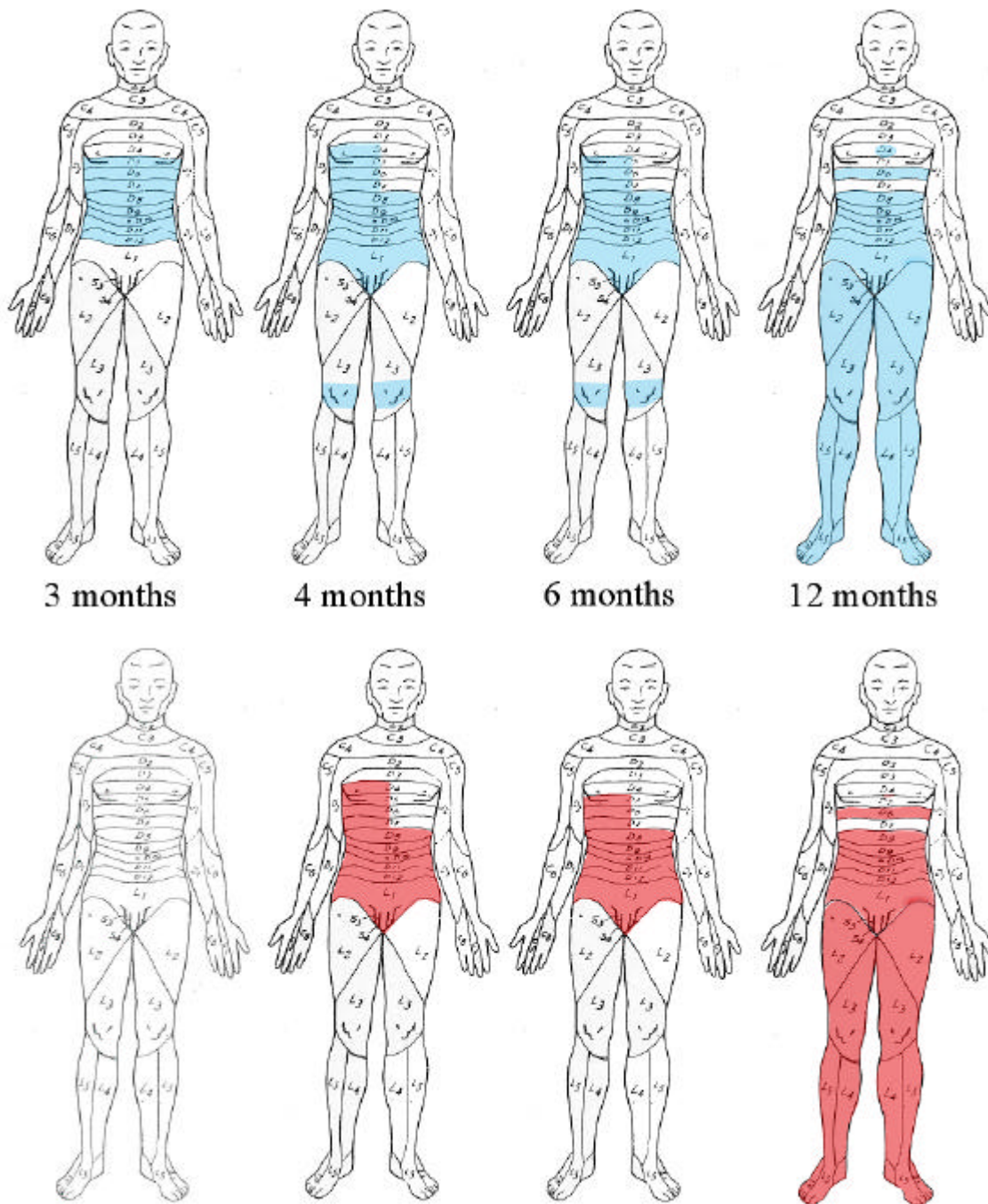


Fig.2.25. Means and SD of dermatomes implicated in *evoked* pain in thoracic lesions. Significant differences were seen between months 2 and 3 ($p=0.044$) (symbol †) and between 2 and 4 ($p=0.016$) (symbol *)



Picture 2.2. Dermatomal map of a NP patient with cervical SCI. First row of figures represent the evolution of dermatomes with *spontaneous* pain at month 3, 4, 6 and 12 after SCI (C4 level). The second row represents the evolution of dermatomes with *evoked* pain at month 3, 4, 6 and 12 after the SCI.



Picture 2.3. Dermatomal map of a NP patient with thoracic SCI. First row of figures represent the evolution of dermatomes with *spontaneous* pain at 3, 4, 6 and 12 months after the SCI (D5 level). The second row represents the evolution of dermatomes with *evoked* pain at month 3, 4, 6 and 12 after the SCI.

2.5. Discussion

This is the first descriptive study assessing the longitudinal evolution of NP from the acute (from 2 to 6 months) up to the chronic phase (12 months after SCI), analysing the relationship between *spontaneous* pain intensity and *evoked* pain signs, with the objective of analysing the implicated mechanisms and its impact on the patient. We especially focussed on the diagnostic utility of *spontaneous* and *evoked* pain measures involved in NP. The patient characteristics in our study sample have an extensive range of age, male and female subjects, aetiology and level of lesion; which favours considerably the inclusion of a large number of different physical factors in the study group.

The vast majority of studied patients began their NP between 2 and 3 months after SCI, and presented more pain *at level* than *below the level* of lesion. Since the observed power in the analysis is rather low, most probably because of the low number of patients included in the analysis, the significant results presented here must be interpreted cautiously. However, parametrical analysis are the ones that permit a longitudinal analysis of our data. We observed a tendency for an increase in *spontaneous* pain intensity up to 12 months, which was more considerable *at level* than below the level of SCI. Patients with thoracic lesion presented a progressive increase in pain *at level* during all the temporal measures in contrast to a constant pain intensity following cervical SCI. *Below the level* of SCI, patients with cervical and thoracic lesions eventually developed the same *spontaneous* pain intensity, but with a large degree of temporal variability. The most common *evoked* pain signs observed either at 3 or at 6 months after the lesion, were thermal allodynia and temporal summation to punctate mechanical stimulation *at level*, and mechanical hyperalgesia *at and below the level*. Interestingly only thermal allodynia correlated with *spontaneous* pain intensity at 6 months after SCI.

2.5.1. *Spontaneous Pain During the 12 Months After SCI*

After a qualitative examination and comparison of the three measures of *spontaneous* pain intensity and in agreement with other pain studies (**Finnerup et al. 2003b**), we adopted the “7 day” intensity measure and not “Present” or “Maximum” intensity because it was judged that more informative and reliable data could be obtained from the of the referred pain in the patient’s report of pain intensity, compared to the “Present” pain intensity measure associated with extensive temporal variation that depended on different factors (the moment of the day, atmospheric changes, etc.). In the first stage (months 2 and 3 after SCI), 86.7% of our patients began to experience “burning” and “pressing” sensations of NP, in agreement with other studies identifying early ongoing pain symptoms in NP-SCI patients (**Siddall et al. 2003**). In addition, the higher prevalence of NP *at level* with respect to NP *below the level* of injury also agrees with the work of authors such as **Siddall et al. (2003)** and **Finnerup et al. (2003b)**. The use of prescription medication is associated with having pain with neuropathic features, high pain intensity and multiple pain sites, and descriptors also indicate that the presence of multiple types of pain is predictive of use of prescription medication (**Widerström-Noga and Turk, 2003**). *Spontaneous* pain intensity was associated with a tendency to increase up to 12 months after SCI, which was more accentuated at rather than below the level of lesion, in agreement with other studies (**Finnerup et al., 2003b; Jensen et al., 2003**) where the results indicated that patients with SCI and *central* pain more frequently presented hypersensitivity in the dermatomes corresponding to the level of SCI, than those without pain.

Focussing on the development of *spontaneous* pain intensity at the level of the lesion we identified a clear and progressive rise in pain intensity during all the temporal measures in the in thoracic SCI group (from 0 to 5 on the VAS), in contrast to a more constant pain intensity in the cervical SCI group, which may reflect the development of important physiopathological characteristics not present with at higher level injuries. The observed tendency therefore means a worsening in the thoracic SCI group and a relative stability in patients with cervical SCI. Although the longitudinal study performed by **Siddall et al. (1999)** distinguished a difference during the thoracic and cervical SCI during their first temporal measure (2 weeks after SCI), the following measures identified a higher *spontaneous* pain intensity in patients with cervical lesions, at a similar level to that observed in our patients. An

examination of the development of *spontaneous* pain intensity below the level of the lesion failed to reveal significant difference between the cervical and thoracic group, with a large variability observed over all time points for the former, and a trend for an increase in pain intensity following thoracic SCI. Indeed the same pain intensity was observed one year after SCI for both groups. After thoracic injury, ongoing pain intensity seemed to be installed early in time and that remained in constant way in the chronic phase. **Siddall et al. (1999)** also found the same trend 2 weeks after injury as we found at 2 months after SCI with our data.

The influence of the lesion grade (complete versus incomplete injury) on the development of at level *spontaneous* pain intensity was less clear at the level reaching about the same 12 months after SCI (VAS=4). However although the increase in *spontaneous* pain intensity following complete SCI was significant ($p=0.06$, 12 months versus 3 month data), pain intensity increased to the same intensity level at 4 months after complete SCI compared to 6 months after incomplete lesion. Like **Siddall et al. (1999)**, these patients presented slightly more pain at the level of the lesion than complete patients (either at 2 weeks and 2 months) though in our sample the same pain intensity is shown for both groups at 12 months.

Spontaneous pain intensity below the SCI after complete lesion was associated as relatively constant up to 12 months whilst patients with incomplete lesions revealed an overall increase in intensity level. At 2 months after injury our patients with complete SCI presented more pain intensity below their level than incomplete injury, again in accordance with **Siddall et al. (1999)**.

Taken together these data, though without statistical significance, represents a profile whereby the patients with cervical lesion revealed a constant pain intensity at the level of SCI but much more variable below level, whereas in patients with thoracic lesion *spontaneous* pain intensity showed a progressive increase at level while below the level pain increased and stabilized at 4 months after lesion.

Patients were medicated in the successive follow-ups after the first measure (baseline), so a reduced VAS score was found in intensity of pain at the end of their evaluations for the complete group only below the level of the lesion, assessed with the 7days VAS (**Fig 2.13**).

The maximum pain perceived was very intense in the majority of cases (e.g. Max VAS =6.3 below the level at 2 months after SCI and Max VAS =5.4 at the level at 12 months); besides the specific comparison between months 2 and 12 in the thoracic SCI subgroup revealed a significant increase to 5.1 in pain intensity ($p=0.03$) at level; and also the number of *spontaneous* pain dermatomes showed significant increase of them in the thoracic group at level after 4 and 6 months and cervical at 12 months following SCI. All this facts could explain why many studies indicate that a third of the total number of SCI patients with chronic pain suffer intense or severe pain (**Bonica, 1991; Finnerup et al., 2001; Siddall et al., 2001**).

Whilst patients with cervical SCI saw their pain intensity and involved dermatomes diminish with time, pain intensity and dermatomes increased at the level of injury over time following thoracic injury. These significant but small increases in dermatomes at level are very important, since in general we may suggest that the number of dermatomes implicated in pain corresponds to the pain intensity experienced by the patient up to one year after SCI. In general a trend for a decrease in the dermatomes involved with *spontaneous* and *evoked* pain was observed below cervical SCI, while the thoracic lesion group revealed a general increase in the number of dermatomes with both *spontaneous* and *evoked* pain types.

2.5.2. Central Pain Generator (CPG) Hypothesis

2.5.2.1. CPG Background

Research groups studying central pain after SCI in animals (**Vierck, 2000**) and in patients (**Finnerup and Jensen, 2004; Melzack and Loeser, 1978**) have supported the hypothesis that an area of neuronal

hyperexcitability at the level of injury may generate and alter nociceptive remote from the injury area; below (**Vierck, 2000**) and above the level (**Finnerup and Jensen, 2004**), possibly through the activation of a diffuse transmission system such as the propriospinal system. The results obtained in this thesis may generally follow this line concerning neuronal hyperexcitability at the level of SCI. The *spontaneous* pain intensity gradually presented at level during the first six months of SCI, presumably when the *CPG* is activate, and the high correlations between the *evoked* pain signs either at level (thermal allodynia/sensibility and *spontaneous* pain intensity at 6 months post-SCI) in addition to correlations between at and below level *evoked* pain signs is in consonance with this theory. The combination of ascendant tract deafferentation and the activation of rostral pain targets (thalamus, etc.) by an enhanced activity in other spinal pathways (propriospinal system, **Vierck et al., 2000**), may be a responsible mechanism of NP that affects so many SCI patients, with no distinction between the spinal level affected or the grade of completeness of the lesion.

Melzack and Loeser's results (**1978**) already suggested the existence of a *Central Pain Generator (CPG)* in the spinal cord in patients with SCI, which supposed the existence of *central modulatory mechanisms* and is a hypothesis derived from the *Gate Control Theory (Melzack and Wall, 1965)*. Briefly, this theory proposed that damage to those fibres which normally inhibit pain transmission in the spinal cord is the reason for the existence of continuous pain; dysfunction in those fibres that normally close/inhibit the gate would be unable to modulate spinal sensory transmission, with the end result being perception of pain (**Melzack and Wall, 1965**). Although this theory has been criticized, evidence suggests a role for A fibres in the inhibition of C fibres induced responses in human experimental pain (**Yarnitsky et al., 1992; Wasner et al., 2004**).

2.5.2.2. Evidence for the CPG in Acute SCI NP?

A network of hyperexcitable neurons at the level of the lesion in the spinal cord may behave as a *pain generator*. These cells are normally activated following spatiotemporal signalling systems involved in the precise localization and intensity coding for non-nociceptive and painful sensory input that constitute the normal spinal nociception (**Melzack and Loeser, 1978**). These authors suggested that the *central pain generator* may be located rostral to the SCI level, because a subsequent cordectomy performed immediately above the level of lesion failed to eradicate pain below lesion level. In addition, NMDA receptor and sodium channel antagonists are effective in reducing pain at and below the level of SCI (**Finnerup et al., 2001; Eide et al., 1995; Gonzalez-Valdizan et al., 2004**). Moreover, there is evidence to suggest that central pain following SCI may be the result of supraspinal neuroplasticity in response to ascending tract deafferentation and abnormal input from a spinal generator (**Finnerup et al., 2004**).

Thus, suprathreshold stimuli is required in deafferentation pathologies, like when the number of nerve impulses per unit time from the somatic projection systems to the brain areas that subserve to pain exceed a critical level and results in pain, is produced by a nociceptive input. Other studies like **Crue et al. (1976)** support a similar idea to activate directly or secondarily spinal or supraspinal pain processing areas, as a direct result of altered sensory input. It has been published recently about the myelinated fibres in the inhibition of painful responses with menthol in healthy volunteers (**Wasner et al., 2004**), supporting the hypothesis that NP may unleash certain physiopathologies of A fibres.

Finnerup and Jensen (2004) have proposed that sensory input from the primary afferents may be distorted by two mechanisms: 1) spinothalamic tract projection neurons below the SCI may be injured and may increase rostral sites of neuronal hyperexcitability, including the thalamus, following deafferentation 2) second order dorsal horn neurons within the rostral end of the spinal lesion may become hyperexcitable as a consequence of local excitotoxic changes and disinhibition of GABAergic inhibitory neurons at the level of injury. Abnormal sensory input into these neurons at the rostral end of the spinal lesion may be transmitted via the propriospinal system to the deafferented neurons of the thalamus, resulting in "referred pain" sensation below the level of the lesion (See **Appendix Picture 2.3.**)

In contrast another possibility is that the descending inhibitory pain system originated from the brainstem (**Finnerup and Jensen, 2004**) in patients with thoracic SCI may be more altered, with a higher degree of axonal dieback, particularly as we have observed higher levels of *spontaneous* pain (7 day intensity) compared with patients with cervical lesions, implicating a greater role of central neuronal hyperexcitability at the thoracic level. However, correlational analysis indicated that hyperexcitable neurons may be present either at the cervical or thoracic level at 2 and 6 months after the injury, suggesting an early activation of a potential CPG mechanism after SCI.

2.5.2.3. *Local neuronal hyperexcitability induced by “Enhancing Factors”.*

Physical conditions which undermine the state of health of the patient with SCI, such as urinary sepsis or infected pressure sores, are known to magnify the patient’s reaction to pain. Specific conditions which are common to the enhancement of pain is of particular interest, like bladder distension by an excessive volume of residual urine, bladder spasms resulting from an uncontrolled infection or calculi and constipation (**Botterell et al., 1954**). In addition many patients report that their pain becomes worse with damp cold weather (14%) and some patients find relief when they are transferred to a drier climate (**Damirel et al., 1998**); and some (10%) also complain that smoking cigarettes aggravate their pain (**Botterell et al., 1954**). These conditions are known to medical consultants as pain “*enhancing factors*”, and also include other factors such as anxiety, tiredness and depressive states of the patient.

Therefore, the abnormal activity generated by a group of deafferented central neurons as in SCI, may be open to additional modulation by somatic, visceral and autonomic sources of information activated by external “*enhancing factors*” and also by neural mechanisms activated in different emotional and personality states. An alteration in sensory input or indeed in its modulation at the segmental or higher level would lead to generalized neuronal excitation in the sensory transmission, which would greatly facilitate abnormal nociceptive processing. Moreover, the previous pain neuronal states, at the spinal and supraspinal levels may become further exaggerated with significant changes in spatiotemporal pain processing (**Melzack and Loeser, 1978**).

2.5.2.4. *Deafferentation and reorganization of cortical sensory input after SCI.*

The majority of patients with SCI do not suffer from phantom limb pain, which suggests that abnormal neuronal activity may cease or be blocked by an additional inhibitory control exerted by other descending inhibitory pathways or segmental pathways like the propioespinal system (the excitation of SRT neurons may reflect activity in spino-bulbo-spinal loops that produce a prolonged action in inhibitory circuits, such as the diffuse noxious inhibitory control (DNIC) system (**Cervero and Wolstencroft, 1984; Bouhassira et al., 2000**)). As we will explain in Chapter 3, the two point discrimination has been used as a clinical measure of the cortical representation of the skin, and reduced thresholds have been related to increased cortical representation (**Song et al., 1993**) only found in chronic patients with central pain and an extensive lesion, as no difference was found with NP acute patients (See **3.4.Results from Chapter 3**).

However this does not preclude the fact that a year after SCI the “neuronal circuitry” and sensory fields are significantly reorganized. A gradual development of a local NP generator aggravated by external “*enhancing factors*” and accompanied by long-term deafferentation would lead to chronic reorganization in sensory processing systems.

2.5.3. *Evoked Pain Signs and Correlations*

2.5.3.1. *Evoked Pain Signs*

Cochran’s analysis revealed a significant decrement in number of patients presenting temporal summation to mechanical punctate stimulation at the level of SCI and also in thermal allodynia/sensibility below the level of lesion from 2 to 6 months. As we have seen in the majority of

evoked pain signs, a higher number of patients presented *evoked* signs at 6 months after the SCI at the level of lesion than at 2 months (with the exception of temporal summation) in contrast to the lower prevalence of *evoked* pain signs at 6 months below the SCI. Taking into account the significant *decrease* in temporal summation at level and thermal allodynia below level over time we may suggest that the CPG centre is already operating in the early stage of SCI (2-3 months post-SCI), and becomes less predominant once the patients reach the 6 month post-injury period accompanied by a gradual increase in *spontaneous* pain during the same time period in the majority of the patients studied. We cannot exclude additional changes in higher level structures such as the spinothalamic system from 6 months after injury onwards. The data obtained indicating a decrease in temporal summation after SCI has not been described elsewhere in the literature, and as such may represent an important diagnostic for the identification of the CPG at the earliest time point after SCI.

As in the **Siddall et al. (2003)** study, mechanical allodynia/sensibility to brush was present only in a relatively small percentage of patients (mainly at the very early 2 month post-SCI stage). In contrast to the results obtained from the previous **Siddall et al. (1999)** study, that examined pain in the first 6 months following injury, we failed to identify a relationship between mechanical allodynia/sensibility and central cord injury or incomplete SCI, but thermal allodynia/sensibility was related to the presence of at-level *spontaneous* neuropathic pain. This suggests that allodynia/sensibility to mechanical stimuli that persist up to six months may be due to different mechanisms associated with early allodynia onset originally identified by **Siddall et al. (2003; 1999)** in the very early phase following SCI. This is consistent with our results, because the percentage of patients affected by mechanical allodynia changed later. A possible explanation will be widely explained in **Chapter 3**, it could be related to the posterior changes occurring in the spinothalamic pathways and dorsal column system, and the possibility that the CPG may suppose different importance after the first 6 months of injury.

2.5.3.2 Temporal summation to nociceptive input after SCI

The presence of central sensitivity to nociceptive stimuli at the level of SCI using the temporal summation testing procedure has been suggested to be a key pain sign for the presence of NP (**Eide et al., 1995**), although it is not always observed in all patients (**Finnerup et al., 2003b**). The fact that authors like **Finnerup et al. (2003b)** did not detect temporal summation to repeated punctate mechanical stimulation at the level of the SCI may probably reflect that their actual SCI were chronic (several years of evolution), although the involvement of peripheral pathologies cannot be excluded. The level of temporal summation observed during the acute and chronic injury stage may also be different. The lack of temporal summation may also reflect methodological problems associated with the testing procedures (**See Chapter 3**). Besides, other factors like the temporal summation of the stimulus may be critical in the diagnose of central sensitivity, due to it may also play a role related to the hyperalgesia where the neurons of the dorsal horn expand their receptive fields and therefore more temporal summation of the afferent/efferent information may occur (**Cook et al. 1987**), and high correlations below the level seems to indicate so. **Arendt-Nielsen et al. (1996)** recently demonstrated an increase in central sensitization in hyperalgesic pain areas (which occurs in our case with temporal summation 2 months after SCI) and therefore suggests a way in which temporal summation may be present and indeed modulated. NMDA mediated modulation of temporal and spatial summation of pain processing, indicates that similar common neural mechanisms may govern hyperalgesia and temporal summation.

2.5.5. Longitudinal analysis of dermatomes with neuropathic pain

In general longitudinal dermatomal analysis suggests that the higher the number of dermatomes with *spontaneous* or *evoked* pain, the higher the pain intensity reported by the patient, at least during the acute SCI phase up to one year after the SCI. At the level of the cervical SCI, the number of dermatomes tended to be more constant over time while the number of dermatomes at the level of thoracic SCI was significantly more variable along the different temporal measures. A tendency for a

reduction in the number of dermatomes involved with *spontaneous* or *evoked* pain below cervical SCI was observed up to 12 months. In contrast the number of dermatomes with *evoked* pain increased significantly below level after thoracic SCI.

2.5.3.3. Correlations

As alluded to above the results from our study indicate that evidence for mechanical hyperalgesia/sensibility and thermal allodynia/sensibility at both levels and temporal summation to repeated mechanical punctate stimulation at level (using standard “Bedside Sensory Testing” methods) may in fact be useful diagnostic tools for detecting NP at 2 months after SCI. However we included the *evoked* NP signs as being present when the intensity VAS score was more than 0, particularly as some of these signs were described by several patients as being associated as being unpleasant or irritating (VAS<2) but not painful (VAS>2, **see Discussion in Chapter 3**). Whether the presence of these pain signs with an intensity of between 2 and 3 is open to question.

Importantly our results reached a high level of significant correlation using the Spearman’s Rho statistical test for every pain sign analyzed at or below the level of the lesion at 2 months post-SCI. The presence of negative correlations between *spontaneous* and *evoked* pain sign intensity suggests that the latter was higher when pain intensity of *spontaneous* pain was lower at the very early (2 month) phase after SCI. A possible explanation for this inverse relationship may be due to the gradual development of NP, firstly because the patient did not greatly feel *spontaneous* pain, but as time progressed, sensations such as paraesthesias converted into dysesthesias. Another possibility is that the presence of local neuronal hyperexcitability may facilitate the development of *spontaneous* pain at 2 and 6 months after the lesion. Furthermore, mechanical allodynia/sensibility, mechanical hyperalgesia/sensibility, temporal summation to repeated punctate mechanical stimulation and thermal allodynia/sensibility were positively correlated between them at the early 2 month period. This may be interpreted as a generalized and common facilitation of *evoked* pain signs and their associated mechanisms, which may be the Central Pain Generator (CPG), already active at the very early phase of NP (2-3 months post-SCI), which in turn would modulate the abnormal sensations and increased pain intensity associated with later *spontaneous* pain. Once this generalized mechanism has been initiated, it would be more difficult to control the pain at a later date. It is interesting to speculate that the anecdotal clinical evidence suggesting that early treatment with anticominals and other pharmacological treatments may be decisive in the effective control of pain in the later chronic phase (6-12 months post-SCI).

In direct contrast with the measures obtained at 2 months post-SCI, at 6 months after SCI a relationship developed between thermal allodynia/sensibility and the 7 day *spontaneous* pain intensity at the level of lesion, meanwhile any correlation between *evoked* and *spontaneous* pain signs disappeared. The only exception is temporal summation and thermal allodynia at level and patients with thoracic lesions, highly and negative correlated, which could be due to the medication taken by the patients, as lesser patients than at 2 months presented thermal allodynia. At 6 months after injury at the level of SCI the only positive and significant correlations observed between pain signs were between temporal summation to repeated mechanical punctate stimulation and post-stimulus sensations, and a relationship between thermal allodynia/sensibility and mechanical hyperalgesia/sensibility. Below the lesion, positive and significant relationships between temporal summation and post-stimulus sensations, and between mechanical and thermal allodynia were maintained.

The loss of relationship between *evoked* pain sign intensity at and below the level of SCI after six months, indicated that other pathophysiological mechanisms may already be present, including the

possible implications of more extensive damage to grey matter and possibly white matter tracts. Nevertheless, temporal summation and thermal allodynia/sensibility as *evoked pain* signs were remained 6 months after injury, presumably mediated by a higher degree of C fibre activity, associated with central sensitivity in turn perhaps mediated by a loss of A β and A δ fibres inhibition over small fibre activity (Wasner et al., 2004), and the presence of local neuronal hyperexcitability (Finnerup et al., 2003b).

The number of dermatomes with *spontaneous* or *evoked* pain at any level found a relation between *spontaneous* pain intensity, as well with a correlation between *spontaneous* and *evoked* pain intensity identified previously exemplified for example by the significant correlation between 7 day pain intensity and the number of dermatomes at 6 months after SCI. In patients with thoracic lesions, the correlations at the level of the injury at 6 months indicated that the number of dermatomes involved with *evoked* pain correlate highly with mechanical allodynia/sensibility and appears to be the most important *evoked* pain sign at this time period, as no other significant correlations were observed. In contrast in the cervical patient group, the number of *evoked* dermatomes are related to the *spontaneous* 7 day pain intensity rather than other *evoked* pain signs.

2.5.4 Utility of self-report pain questionnaires

Data from the *Neuropathic Pain Based on Mechanisms Interview*, revealed that the intensity of “continuous” pain and the number of descriptors, either at or below the level of lesion, and “dynamic” mechanical *evoked* pain at the level of injury were important measures over time. The scores (0-10) did not presented high rates in general, and only the number of descriptors seemed to show higher levels (mean = 4.2) specially in the early stages. In addition, we observed that all patients answered our questions with higher scores at the beginning (2 months after SCI), possibly due to a worsening in the interpretation of NP, and the fact that the increase in their scores from 6 months may be due to the end of the process of their rehabilitation in the hospital and a return to daily activity, with all the emotional implications (see Chapter 4). Therefore, we may state that the patients did not distinguish clearly between the areas of the body affected (at and below the level of injury) and between *spontaneous* and *evoked* pain. The interview revealed that *evoked* pain tests like Bedside Sensory Testing are very useful for the study of NP development and that this information could not be obtained by the patients themselves or even with the help of such a semi-directive interview.

2.5.4. The role of spinal grey and white matter lesion.

Naturally spinal cord injury may be associated with different levels and grades of lesion including various degrees of pathological damage to white and grey matter (Catalaa et al. 1999). For instance, in Finnerup's et al. (2003b) sample of patients with below level SCI pain it was observed, using neuroimaging techniques, that patients with at level hypersensitivity and pain compared to patients without pain presented a higher degree of grey matter injury at the rostral end of the lesion (Finnerup et al., 2004).

Although this present study does not contribute magnetic resonance imaging data (see Chapter 3), a gradual change in at level *spontaneous* pain intensity was observed up to one year after SCI and in both complete or incomplete SCI patients assessed (Fig. 2.12 and 2.14) accompanied by a generalized increase in the prevalence of at level mechanical hyperalgesia/sensibility, thermal allodynia/sensibility and temporal summation to repeated mechanical punctate stimulation, reflecting a generalized increase in neuronal hyperexcitability following incomplete and complete SCI and therefore a combination of white and grey matter injury.

Vierck et al. (2002) described traumatic spinal cord injury following vertebral displacement (the most common case of injury according to medical practitioners) to initiate a process of ischemia in the spinal grey matter which would progress in time to finally involve the white matter. Thus, the excitotoxic destruction of the grey matter maybe a preliminary and prominent characteristic of clinical spinal cord injury. Because of this process, early treatments aimed at modulating spinal ischemia,

inflammation and excitotoxicity may indeed reduce the progression of grey matter damage (**Yeziarski, 2000**), and therefore ensuing chronic pain symptoms and perhaps the “spasticity” syndrome (spasms and co-activation of antagonists: **Dietz et al., 1994**) might be also eliminated. Depending on the initial pattern of the lesion, the impairment to the white matter also maybe reduced, since this process may also develop quistic cavities (**Yeziarski, 2000**).

In primates who received anterolateral cordotomies which extended medially into the grey matter , enhanced escape responses to noxious stimuli were noted when applied below the lesion, in contrast to more superficial white matter lesions (confirmed by histology) which did not present them (**Vierck et al. 1990**). This suggests that, whilst the white matter tracts play a role in the development of central pain after the SCI, the combination of trauma in both grey and white matter is responsible for the onset of NP below the level of the lesion (**González-Valdizán et al., 2004**).

Neuropathic SCI pain below the level of the lesion has been observed either in patients with incomplete spinal section (**Beric et al., 1988**) or complete/incomplete (**Finnerup et al., 2003b**). In experimental spinal lesions with the application of excitatory amino acid EEA (**Yeziarski, 2000**), data suggests that not only the involvement of glutamate and the NMDA receptor (see **Chapter 1**) contributes to tissue damage, but also the involvement of non-NMDA receptors; which would offer an interesting future for new treatments. One viable option in the future is the implantation of a viable grey-white bridge in the injured area to be utilized efficiently as a "neural tissue bridge" for incomplete spinal cord injuries (**Krishnan, 2003, See Appendix Picture 2.2.**)

2.5.5. Study Benefits

We could determine the role of physiopathological processes during the development of NP both at and below the level of the lesion, at different measure times 2, 3, 4, 6 and 12 months after the injury. The simple but useful VAS is able to guide studies like this one to focus on a subjective assessment of *spontaneous* pain and compare to *evoked* pain measurements, even to correlate both measures as we have seen previously. The evolutionary trends showed here may be very useful as future basis for other pain studies, since this longitudinal analysis have shown that different neural mechanisms are operating in acute and chronic phases of the SCI. In fact, a *Central Pain Generator* system (CPG) may be the responsible in the development of NP at and below the level of injury in the majority of patients in the early stages, which suppose an important factor to pay attention with in order to search for new treatments in the pain process. Also interestingly, the Neuropathic Pain Based on Mechanisms Interview have shown different and novel results from the BST in the subjective point of view of the patients that began to know better their pain since month 4 after the SCI.

2.5.6. Study Limitations

The main limitation of this study was the degree of missing data mainly during month 12 after the injury, probably because of the difficulty in patients to complete the assessment forms. For this reason, the desired number was low making the statistical analysis practically impossible in some occasions and in others sufficient to suggest a trend of what may happen in our NP patients. Another limitation was the pharmacological medication which may lower the *evoked* pain sign intensity, although the pharmacological treatment appeared not to affect the *spontaneous* pain intensity reported by the patients using any of the four *spontaneous* pain measures adopted. As the intensity was in general very low for *evoked* signs, we cannot exclude the possibility that some pain sign intensities such as thermal allodynia or mechanical hyperalgesia would reach higher pain scores in untreated patients.

2.5.7. New research lines in SCI-CPG research.

The CPG hypothesis provides a general mechanistic explanation to the development of NP at the very early SCI phase, and opens new directions in simple diagnostic research, and directs the analysis of NP

mechanisms at the level of SCI based on new psychophysical assessment techniques that incorporate measures of central sensitization to tonic thermal stimuli using the new TSAR system (Peltier type, **Vierck et al., 1997**) and the subsequent identification of neuronal hyperexcitation (**see Chapter 3**). In Chapter 3 the TSAR technique studies utilizing the system either alone or together with other stimuli, may be able to more fully activate processes of central hyperexcitability in acute SCI patients, particularly as this technique appears to be a more powerful technique than other existing technologies, which may explain why key evidence for the presence of NP (such as temporal summation) is not always observed after SCI patients. In **Chapter 3** we will identify and analyse the temporal characteristics of the CPG at different levels of the lesion at 4-5 months post- SCI, using an electronic psychophysical analysis system that identifies the stimulus-response function using long duration thermal nociceptive stimuli (c.f. **Morin et al. 1998; Koyama et al., 2004**) and an additional examination of temporal summation (**Vierck et al., 2002**). In the future, the results of this project would be to improve the diagnosis and prognosis of NP associated with SCI, specifically creating a new useful methodology for Pain Clinics and experimental pain research studies.

2.5.8. Conclusions

In this chapter the presence of *spontaneous* and *evoked* pain, and their inter-relationship, during the gradual development of NP both at and below the level of the lesion from 2 to 12 months after SCI has been examined. The use of simple but clinically useful VAS ratio scales for the measurement of pain intensity is able to guide studies like this one to focus on subjective assessment of *spontaneous* pain and compare and correlate these responses to *evoked* pain measurements. The description of the development of SCI-NP showed here may be very useful as a future basis for other pain studies, since this longitudinal analysis has shown that different neural mechanisms are present and operating in both the acute and chronic phases of the SCI. In fact, a *Central Pain Generator* system (CPG) may be responsible for the development of NP at and below the level of injury in the majority of patients in the very early stage, and represents an important pathological process which could be used to assess and search for new treatments. Also interestingly, the self-report Neuropathic Pain Based on Mechanisms Interview have shown different and novel results compared to the results obtained with repeated bedside sensory testing highlights the subjectivity of the patients in reliably assessing the presence of pain symptoms and intensity from 4 months onwards after SCI.

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CHAPTER 2 APPENDIX

1--EVALUACIÓN CUALITATIVA DE MECANISMOS/CARACTERÍSTICAS FISIOPATOLÓGICAS DE DOLOR POR DEBAJO DE LA LM BASADA EN ENTREVISTAS (Basada en Woolf, C.J. 1999).

1.- *Localización /distribución del dolor*
A) Espontáneo
 Dermatomas implicados:.....

B) Evocado
 Dermatomas implicados:.....

el dolor aumenta por otros dermatomas después de un estímulo mecánico puntual

2.- *Evaluación clínica*

Presenta hipersensibilidad dolor espontáneo dolor evocado

Presenta hiposensibilidad dolor espontáneo (anestesia dolorosa) sensibilidad disminuida

Presenta sensibilidad normal el dolor se produce sólo si es evocado

3.- *Dolor espontáneo o dolor evocado por debajo de la LM*
 Descripción del dolor por el paciente (se produce dolor al contacto con la ropa?, por presión con el corsé? etc).....

Hay correlación entre dolor espontáneo y evocado por debajo de la LM

Hay correlación entre dolor espontáneo y evocado en el nivel de LM

4.- *Dolor evocado*
 Naturaleza e intensidad de los estímulos

a) ¿se produce por estímulos mecánicos estáticos? Intensidad del 1-10 :.....
 Con tipo de Estímulo: Presión mecánica suave Puntual Difuminado en un área concreta Impreciso
 ¿qué sensaciones produce?

b) ¿se produce por estímulos mecánicos dinámicos? Intensidad del 1-10 :.....
 Frotamiento, cepilladura Leve toque difuso Pinchazo de alfiler Movimientos imprecisos
 ¿qué sensaciones produce?

c) ¿se produce por estímulos térmicos? Intensidad del 1-10 :.....
 Frío incrementa el dolor Calor incrementa el dolor
 ¿qué sensaciones produce?

d) ¿se produce por movimientos corporales? ¿Cuáles?.....
 Intensidad del 1-10 :.....
 Sensación de quemazón en la piel Presión fuerte en la piel
 ¿qué sensaciones produce?

5.- *Cualidad del dolor espontáneo /evocado.¿Cómo se definiría? (Marcar con ES/EV)*

Ardiente..... pulsátil..... punzante..... pinchazo..... apuñala..... cortante.....
 calambreado..... te aplasta..... hormigueo..... picazón.....

6.- *Duración*
A) Espontáneo
 es continua es intermitente

B) Evocado
 El dolor aumenta con un estímulo repetitivo de frotamiento o pinchazo de alfiler
 Intensidad del 1-10 :.....
 Hay sensación dolorosa tras el estímulo ¿Con qué estímulo?.....
 Intensidad del 1-10 :.....

7.- *Intensidad medida con VAS: (Marcar con ES/EV)*
 VAS actual.....(/ /)VAS máx:.....VAS mín:.....VAS usual:.....

Protocol 2.1. Spanish version of the Neuropathic Pain Based on Mechanisms Interview below the level of the SCI.

2--EVALUACIÓN CUALITATIVA DE MECANISMOS/CARACTERÍSTICAS FISIOPATOLÓGICAS DE DOLOR AL NIVEL DE LA LM BASADA EN ENTREVISTAS sin contacto físico al paciente (Basada en Woolf, C.J. 1999).

1.- *Localización /distribución del dolor*
 A) Espontáneo
 Dermatomas implicados:.....

B) Evocado
 Dermatomas implicados:.....

2.- *Evaluación clínica*

Presenta hipersensibilidad dolor espontáneo dolor evocado

Presenta hiposensibilidad dolor espontáneo (anestesia dolorosa) sensibilidad disminuida

Presenta sensibilidad normal el dolor se produce sólo si es evocado

3.- *Dolor espontáneo o dolor evocado por debajo de la LM*
 Descripción del dolor por el paciente (se produce dolor al contacto con la ropa?, por presión con el corsé? etc).....

 Hay correlación entre dolor espontáneo y evocado por debajo de la LM

Hay correlación entre dolor espontáneo y evocado en el nivel de LM

4.- *Dolor evocado*
 Naturaleza e intensidad de los estímulos

a) ¿se produce por estímulos mecánicos estáticos? Intensidad del 1 -10 :.....
 Con tipo de Estímulo: Presión mecánica suave Puntual Difuminado en un área concreta Impreciso
 ¿qué sensaciones produce?

b) ¿se produce por estímulos mecánicos dinámicos? Intensidad del 1 -10 :.....
 Frotamiento, cepilladura Leve toque difuso Pinchazo de alfiler Movimientos imprecisos
 ¿qué sensaciones produce?

c) ¿se produce por estímulos térmicos? Intensidad del 1 -10 :.....
 Frío incrementa el dolor Calor incrementa el dolor
 ¿qué sensaciones produce?

d) ¿se produce por movimientos corporales? ¿Cuáles?.....
 Intensidad del 1 -10 :.....
 Sensación de quemazón en la piel Presión fuerte en la piel
 ¿qué sensaciones produce?

5.- *Cualidad del dolor espontáneo /evocado.¿Cómo se definiría? (Marcar con ES/EV)*

Ardiente..... pulsátil..... punzante..... pinchazo..... apuñala..... cortante.....
 calambreante..... te aplasta..... hormigueo..... picazón.....

6.- *Duración*
 A) Espontáneo
 es continua es intermitente

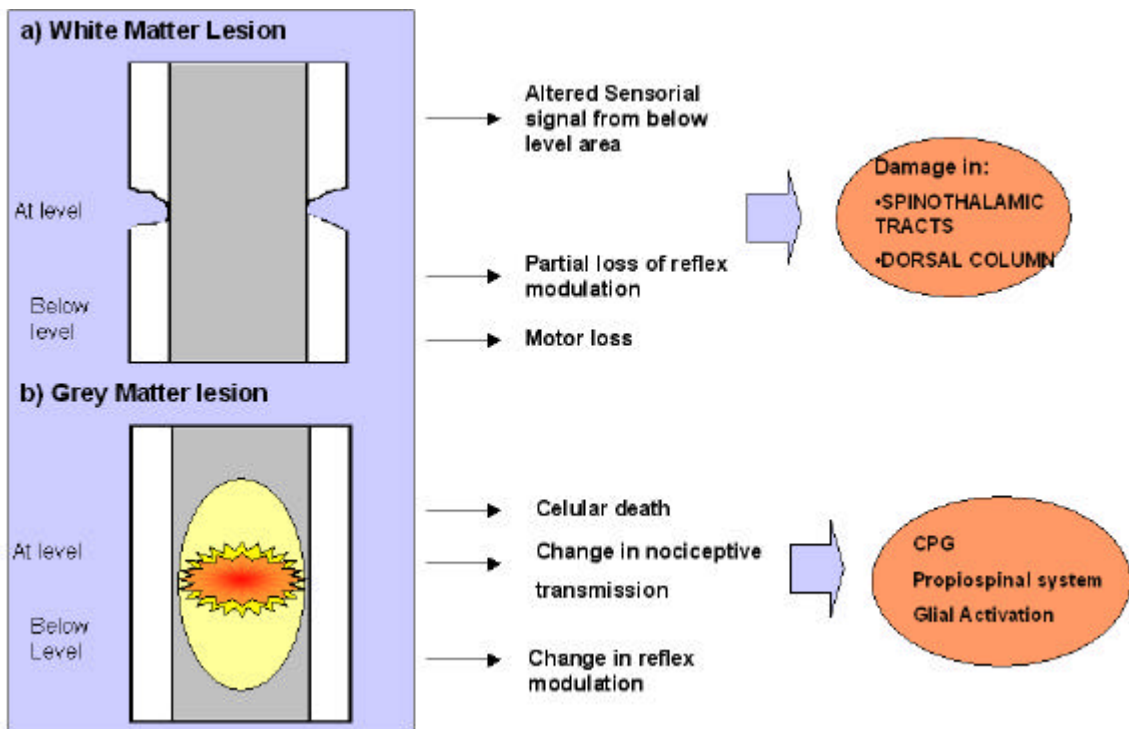
B) Evocado
 El dolor aumenta con un estímulo repetitivo de frotamiento o pinchazo de alfiler
 Intensidad del 1 -10 :.....
 Hay sensación dolorosa tras el estímulo ¿Con qué estímulo?.....
 Intensidad del 1 -10 :.....

7.- *Intensidad medida con VAS: (Marcar con ES/EV)*
 VAS actual.....(/ /) VAS máx:..... VAS mín:..... VAS usual:.....

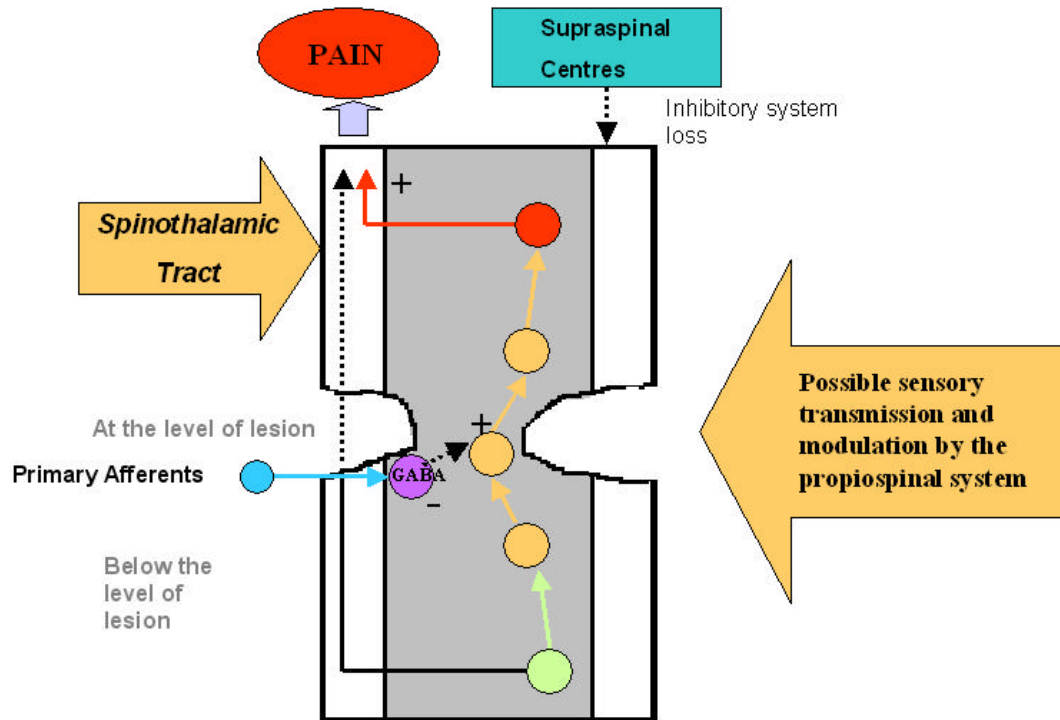
Protocol 2.2. Spanish version of the Neuropathic Pain Based on Mechanisms Interview at the level of the SCI



Appendix Picture 2.1. Standard “Bedside Sensory Testing” instruments used in the study: VAS scale, brush, pin and acetone.



Appendix Picture 2.2. Schematic illustrating the functional consequences of white and grey matter SCI and the involvement of different spinal sensory processing systems.



Appendix Picture 2.3. Schematic illustrating the alternative sensory nociceptive transmission after SCI with damage to the spinothalamic tract and disinhibition of local propriospinal gaba-ergic interneurons, constituting a possible physiological basis for Central Pain Generator “CPG” hypothesis.

--VERSIÓN RESUMIDA EN ESPAÑOL--**CAPÍTULO 2.****DIAGNÓSTICO DE DOLOR NEUROPÁTICO DESPUÉS DE LA LESIÓN MEDULAR:
ANÁLISIS LONGITUDINAL DE LOS MECANISMOS FISIOPATOLÓGICOS PRESENTES
AL NIVEL Y POR DEBAJO DEL NIVEL DE LESIÓN.****2.1. Introducción***2.1.1. Características y Mecanismos del DN Al Nivel y Por Debajo del Nivel de Lesión Tras la LM.*

El dolor neuropático (DN) *por debajo* del nivel (y otras condiciones de dolor central) supone una función espinotalámica anormal con sensibilidad alterada a la temperatura y al pinchazo de alfiler (**Bowsher, 1996**), aunque la lesión espinotalámica es condición necesaria, no suficiente (**Finnerup et al, 2003b**). Otra característica es que los componentes periféricos tienen menos implicación por debajo del nivel de lesión que al nivel (**Finnerup et al, 2003b**).

Existen pruebas neurológicas (**Jensen et al., 2003**) que permiten una aproximación a los mecanismos centrales presentes después de la LM y que incluyen signos como alodinia dinámica, hiperalgesia mecánica e hiperalgesia al frío presentes al nivel de la LM (**Finnerup et al., 2003b**) aunque la sumación temporal no estaba presente. Según las investigaciones de **Jensen et al., 2003**, pacientes LM con Dolor Central presentaban más frecuentemente hipersensibilidad en los dermatomas correspondientes *al nivel* de LM que aquellos pacientes sin dolor y existe una correlación significativa entre la intensidad de disestesia evocada por cepilladura al nivel de la LM y el dolor *espontáneo* por debajo del nivel de LM.

Se cree que el *tálamo* juega un papel crítico en el dolor central (**Dostrovsky, 2000**), indicada por una representación incrementada de la zona límite del tálamo y campos proyectados referidos a áreas anestésicas del cuerpo. Los mecanismos no son claros, pero pueden ser causados por una reducida inhibición GABAérgica, un equilibrio perturbado entre el tálamo medial y lateral, desinhibición de las vías espinoreticulotalámicas, o cambios en la conducción aferente excitatoria de la transección del tracto espinotalámico (**Jensen y Lenz, 1995**); la proyección hacia la corteza puede explicar la representación somatotópica y consciente del dolor.

2.1.2. Correlación entre Al Nivel y Debajo del Nivel de Lesión. La hipótesis del “Central Pain Generator CPG” (Generador de Dolor Central)

Siddall et al., (2003) ha identificado el componente del dolor neuropático más debilitante para los pacientes tras la LM: el desarrollo de la disestesia por debajo de la LM con más de un año del trauma inicial está asociada con una intensidad severa del DN. Pero la localización exacta de la hiperexcitabilidad neuronal responsable del dolor *evocado* o disestesia después de la LM no es aún conocida.

La presencia de la excitabilidad neuronal en la medula espinal ha sido identificada en pacientes con LM, (**Loeser et al., 1968**), y existe una correlación entre el dolor *evocado* al nivel y la intensidad de la disestesia por debajo del trauma (**Finnerup et al., 2003b**). En el estudio de **Melzack y Loeser (1978)**, realizando una cordectomía arriba de la LM inicial no obtuvieron resultados en la eliminación del dolor por debajo de la lesión, sugiriendo que el centro generador de dolor estará ubicado a un nivel rostral a la LM. Sin embargo varios autores describen un alivio de dolor mediante bloqueos de anestésicos locales. Específicamente **Pollock (1951)** describió que el dolor neuropático por debajo de una lesión medular se puede eliminar con la aplicación de “anestésicos locales” arriba de la LM, pero no cuando había un “bloqueo del líquido espinal”; indicando que un centro medular era clave en el mantenimiento del dolor neuropático por debajo de la LM. Esto apoya el papel de una *hiperactividad al nivel* y una *hiperexcitabilidad por debajo del nivel de lesión*. Además, un estudio con lidocaína alivió el dolor al nivel y por debajo, sugiriendo un *generador de dolor espinal o central* (“*Central Pain Generator CPG*”), en algunos pacientes debido más a un mecanismo rostral (**Loubser y Donovan, 1991**). Recientemente **Loubser and Clearman (1993)** indicaron que la lidocaína aplicada al nivel de la LM produjo eliminación de dolor y espasticidad. Asimismo, el fracaso en el alivio de dolor en las intervenciones DREZ parece ser debido a un inadecuado emplazamiento de la lesión.

Pacientes con y sin dolor tenían similares reducciones de detección termal u mecánica y umbrales de dolor y potenciales sensoriales evocados, pero los pacientes con dolor por debajo tuvieron significativamente *más hipersensibilidad sensorial al nivel* que los pacientes sin dolor (Finnerup et al., 2004), y estos presentaban mayores lesiones de sustancia gris en el extremo rostral de la lesión, visto con resonancia magnética (Finnerup et al., 2003a).

Estos datos junto con los de Vierck y Light (1999, 2000) sugieren que la lesión de la vía espinotalámica por sí misma no explica el dolor central en los pacientes, y que la *hiperexcitabilidad neuronal* causada por cambios excitotóxicos y lesión de neuronas inhibitorias del *extremo rostral* de la lesión, puede ser un mecanismo importante adicional para el dolor por debajo del nivel. Así, el dolor central en la LM puede ser el resultado de cambios neuroplásticos supraespinales en respuesta a la desaferentación y estímulo anormal desde un generador espinal. (Finnerup et al., 2004)

Sin embargo, no todos los pacientes con LM presentan señales de hiperexcitabilidad (Finnerup et al., 2003b y 2004), indicando que otros mecanismos están presentes. El dolor neuropático en la LM representa condiciones de dolor heterogéneas que dependen de diferentes mecanismos. (Finnerup et al., 2004).

Otra posibilidad es que las medidas clínicas no son suficientemente sensibles para la detección de hiperexcitación neuronal, o que la hiperexcitación estaba presente en un tiempo anterior, durante la fase aguda /sub-aguda (0-6 meses) después de la LM (como la presencia de alodinia (Siddall et al., 1999))

2.1.3. Estudios Longitudinales de los Mecanismos de DN en LM al Nivel Local.

Es claro que la información útil relativa al desarrollo de los signos de dolor y por tanto a los mecanismos fisiopatológicos podrían ser identificados al nivel espinal utilizando estudios longitudinales de los pacientes agudos LM hasta un año después de la lesión. Una aproximación hacia el entendimiento de los mecanismos de dolor involucraría un progreso sustancial en la caracterización de la fisiopatología del DN y el desarrollo de más precisas herramientas para descubrir qué mecanismos contribuyen al síndrome doloroso (Woolf and Decosterd, 1999). De hecho, Finnerup and Jensen (2004) ha sugerido la utilidad de relajar evaluaciones repetidas de los signos de LM-DN y síntomas cuando el dolor significativo comienza a desarrollarse dentro del área de pérdida de sensibilidad.

En uno de los pocos estudios de desarrollo longitudinal del DN en LM, Siddall et al. (1999; 2003) estudió una amplia muestra de pacientes con LM traumática para determinar el tiempo de comienzo, prevalencia y severidad de diferentes tipos de dolor, incluido el DN al y por debajo del nivel hasta 5 años después de la lesión. Concluyeron que hasta los 6 meses la alodinia experimentada estuvo presente predominantemente en pacientes con lesiones incompletas a nivel cervical más que a nivel dorsal, y también con síndrome espinal central. Los pacientes con LM presentaron tanto DN al nivel (36%) como dolor por debajo (19%) a un tiempo temprano (2 semanas) que duró hasta el tiempo de estudio (5 años). La media de tiempo de comienzo para el DN al nivel fue la más corta (media de 1.2 años), mientras que por debajo del nivel tuvo generalmente comienzo más tardío (1.8 years) para pacientes crónicos, y a las dos semanas para los agudos. Los pacientes con DN al nivel fueron menos del 40% durante la fase aguda (0-6 meses) y crónica de la LM (6 meses a 5 años), mientras por debajo del nivel el DN fue observado en pacientes con lesión cervical y toraco-lumbar, por debajo del nivel el DN fue identificado en el 50% de los pacientes con lesión cervical comparado con sólo el 20% de los pacientes con lesiones toraco-lumbares. Los pacientes con lesiones incompletas presentaron ligeramente más intensidad de dolor que las completas, en el mismo momento temporal (Siddall et al., 1999). En general, el DN fue más probablemente descrito como “severo” o “excruciante” que el dolor musculoesquelético, y se identificó una correlación significativa entre la presencia de DN al nivel a los 5 años y momentos temporales más tempranos. La gravedad, el comienzo temprano y la prevalencia del DN en LM en general, 5 años después de la lesión y su alta correlación con la intensidad de dolor en momentos tempranos parecen indicar un tipo de DN con LM que ocurre tempranamente, es difícil de tolerar y persiste de modo continuo a pesar de los intentos para manejarlo. Se deduce que si un paciente presenta DN poco después de la LM es probable que éste sea tanto severo como persistente al nivel y por debajo de la lesión. En contraste, por debajo del nivel está presente en ligeramente menos proporción de pacientes a tiempos de comienzo posteriores (1, 2, 3 y 6 meses) pero con similares niveles de intensidad. Esto es consistente con informes previos sugiriendo que el DN al nivel ocurre a los pocos días o semanas tras la lesión y que el DN por debajo, en las primeras semanas o años después (Beric et al., 1988).

Similarmente que con el DN al nivel, el dolor por debajo del nivel es severo y persistente con correlaciones altas entre momentos tempranos e intensidad de dolor a los 5 años de la lesión. El comienzo tardío del DN por debajo del nivel puede reflejar una diferencia en los mecanismos subyacentes responsables de la generación de dolor p

quizá un proceso relativamente lento de degeneración neuronal, quizá del sistema espinotalámico, que finalmente conduce a la desaferentación e hiperactividad neuronal de estructuras supraespinales (Vierck et al., 2000).

Los exámenes neurológicos estándar de signos de dolor (Jensen et al., 2003) permiten una aproximación de los mecanismos centrales presentes después de la LM e incluye signos como la alodinia dinámica, la hiperalgesia mecánica y al frío presente al nivel de la lesión aunque la sumación temporal no estuvo presente (Finnerup et al., 2003b, Eide et al., 1996). Es evidente que la mayoría de pacientes de DN incluidos en el estudio de Finnerup et al. (2003b) presentaron lesiones completas y por tanto los procesos fisiopatológicos que provocan la sensibilización central no estaban tan intactos que en pacientes con lesión incompleta. Basado en esta investigación, los pacientes LM con dolor *central* presentaron hipersensibilidad más frecuentemente en los dermatomas correspondientes al nivel de lesión que aquellos sin dolor y encontraron una correlación significativa entre la intensidad de disestesia evocada por cepilladura al nivel de LM y el dolor continuo por debajo del nivel de lesión. En el estudio de Siddall et al. (2003), la alodinia estuvo presente en un porcentaje relativamente pequeño de pacientes, más en aquellos con lesiones cervicales. Sin embargo, Siddall (1999; 2003b) no proporcionó ninguna información entre los meses 2 y 6, y después hasta los 5 años, por lo que no dio información de la evolución del dolor del paciente en tiempo (sólo la prevalencia), y no es suficiente para seguir un mecanismo cambiante como el CPG. Además, sólo se midió la alodinia mecánica pero no otros signos de dolor como la hiperalgesia o la alodinia térmica.

En este estudio las medidas de la función sensorial después de la LM fueron periódicamente evaluadas al nivel y por debajo del nivel de lesión durante la fase aguda de la LM para identificar los mecanismos centrales del DN. En particular las técnicas de medida neuropsicológica como la escala psicofísica de ratios (escala analógica visual o VAS) (Price et al., 1983; Woolf et al., 1999) que ha sido usada con éxito en pacientes con LM (Widerström-Noga et al., 2001; Defrin et al., 2001; Finnerup et al., 2003) fue empleada en los pacientes con LM para evaluar 5 medidas del dolor espontáneo y continuo usando BST estándar de la función sensorial después de LM completa o incompleta. Para conseguir esto, se realizaron ANOVA de medidas repetidas para dolor espontáneo respecto al nivel de LM (al y por debajo del nivel); tests no paramétricos de chi-cuadrado fueron realizados en la prevalencia de signos evocados al nivel y por debajo del nivel de lesión, y se consiguieron análisis correlacionales de signos espontáneos y evocados al nivel y por debajo a los 2 y 6 meses después de la LM utilizando el test Rho de Spearman.

2.2. Objetivos

2.2.1. El papel del Generador de Dolor Central al nivel de la LM y su efecto en el desarrollo de DN por Debajo del Nivel de Lesión.

El objeto de estudio fue determinar el papel de los procesos fisiopatológicos espinales locales durante el desarrollo de dolor neuropático al nivel y por debajo del nivel, hasta un año después de la LM completa o incompleta. Para ello se recogieron medidas de signos de dolor usando un cuestionario de dolor global y semi-directivo y un examen neurológico a los 2, 3, 4, 6 y 12 meses, para identificar cambios en los mecanismos de sensibilidad con evidencia específica para la disestesia, alodinia mecánica y térmica, hiperalgesia mecánica y sumación temporal al pinchazo repetido de alfiler. Se realizaron análisis longitudinales para estudiar la relación entre dolor espontáneo y evocado al nivel y debajo del nivel de lesión, seguido de análisis específicos en pacientes con lesiones cervicales y dorsales.

2.2.2. Hipótesis de Estudio

El CPG es responsable del desarrollo de DN al nivel y por debajo del nivel de LM en la mayoría de los pacientes, y la escala VAS y el examen de sensibilidad son instrumentos válidos para su evaluación.

2.3. Métodos

2.3.1. Criterios de Selección

2.3.1.1. Criterios de Inclusión

Los pacientes fueron reclutados en el Hospital Nacional de Parapléjicos de Toledo (España), y cubren toda la población del territorio español. Revisamos un total de 258 historias clínicas y 30 de ellos fueron apropiados para el estudio longitudinal BST de signos de dolor después de la LM. Pacientes con dolor neuropático (sensación de

quemazón y/o presión principalmente, a cualquier nivel dermatómico) y lesión medular completa o incompleta sensitivo-motora (según la escala ASIA A-C) con un nivel por encima del cono medular (D10) evaluado a partir de los 2 meses después del trauma, es decir, en su fase aguda (según la estabilidad neurológica). La etiología de la LM fue traumática o atraumática (enfermedad). Las edades estaban comprendidas entre los 18 y los 75 años. Comprenden y hablan Español. Los espasmos relativos al dolor neuropático se permitieron, independientemente del nivel de LM. Todos los pacientes fueron voluntarios y firmaron un informe de consentimiento. Manifestaron una intensidad mayor que 3 en la Escala Analógica Visual VAS (EVA) equivalente a “moderado” en la escala descriptiva de PPI de McGill (Ligero, Moderado, Angustioso, Horrible, Insoportable), a los dos meses después de la LM. Los pacientes pudieron manifestar cualquier otro dolor no Neuropático (nociceptivo, mecánico, osteomuscular, oncológico, etc) en cualquier estadio de la recogida de medidas.

2.3.1.2. Criterios de Exclusión

Se excluyeron los pacientes con dolor psicógeno, esclerosis múltiple, neuropatías periféricas, “síndrome de dolor complejo regional (CRPS)”, daño cerebral, incapacidad para la comunicación verbal, hipoacusia severa o demencia, así como los pacientes que no pudieron ser examinados en la primera evaluación (antes del tratamiento farmacológico). Los pacientes con espasmos no relativos al dolor neuropático también se excluyeron del estudio.

2.3.1.3. Grupos Experimentales

Los pacientes con DN se seleccionaron de acuerdo a tres características físicas definidas por: localización, descripción y origen (Siddall et al., 2003). Se realizaron comparaciones entre la presencia de dolor al nivel o por debajo de la LM en pacientes con DN: a) DN al nivel y b) DN por debajo del nivel de lesión. El dolor se describió como agudo y quemante y/o opresivo en un área mayor a 4 dermatomas por debajo del nivel de lesión. También se realizaron comparaciones de acuerdo a sus niveles vertebrales de lesión: a) lesiones cervicales y b) lesiones dorsales; y grado de lesión: a) lesiones completas y b) lesiones incompletas.

2.3.1.4. Diseño General de Estudios con Pacientes.

Todos los procedimientos fueron aprobados por el Comité Ético de Investigación Clínica del “Complejo Hospitalario de Toledo-SESCAM” y se informó al paciente de la naturaleza del estudio, permitiéndole abandonar a voluntad.

2.3.2. Instrumentos

2.3.2.1. Evaluación ASIA

Se realizaron exámenes neurológicos a todos los pacientes según la evaluación estándar ASIA (“ASIA A” representa una LM completa sensitivo-motora; “ASIA B y C”, incompleta sensitiva o motora) (Ditunno, JF et al, 1994), por los médicos de rehabilitación especializados de nuestro hospital, con experiencia de varios años en el tratamiento de pacientes con lesión de la médula espinal.

2.3.2.2. Escala Analógica Visual (VAS)

La escala analógica visual es una herramienta psicofísica estándar que facilita al paciente la identificación de la intensidad de su dolor. El paciente elige un valor actual entre un mínimo “0” (“ninguna sensación de dolor”) a un máximo “10” (“el peor dolor imaginable”). Las palabras “sin sensación” y “máximo dolor” se situaron en los extremos de la escala, y una marca en el punto 2 indicó el umbral de sensaciones no nociceptivas y el paciente comenzó a sentir dolor (“casi dolor”). En este estudio se aplicaron tres valores de VAS: el máximo (el valor más alto de dolor dado por el paciente en algún momento), mínimo (el valor más bajo de dolor dado por el paciente en algún momento) actual (el que presenta el paciente en el momento de la medición), 7 días (la media de todos los valores VAS obtenidos durante la última semana) y de desagradabilidad (grado de molestia que le produce el dolor en la última semana) facilitando así un seguimiento periódico y objetivo.

2.3.2.3. Entrevista Basada en Mecanismos de Dolor Neuropático

Con la finalidad de desarrollar una entrevista semi-directiva para la identificación de las características fisiopatológicas del dolor después de la LM, construimos dos completos cuestionarios para el dolor por debajo de la LM y otro similar para el dolor al nivel de la LM. Está basada en los mecanismos fisiopatológicos de **Woolf (1999)**.

Contiene preguntas sobre localización del dolor, dibujando en un mapa de dermatomas las zonas de disestesias y parestesias; zonas de sensibilidad normal o alterada, definición del dolor por el propio paciente, naturaleza e intensidad de los estímulos que provocan dolor (estímulos mecánicos estáticos, dinámicos o térmicos); definición del dolor *espontáneo /evocado* por descriptores; y continuidad o intermitencia del dolor. (**Ver Protocolos 2.1 y 2.2 en Appendix de este capítulo**). Se utilizaron líneas de 10 cm para describir el dolor al y por debajo del nivel de LM en los VAS de 7 días, máximo, mínimo, actual y de desagradabilidad.

2.3.2.4. Pruebas Semi-Cuantitativas de Sensibilidad (BST)

Los pacientes usaron la escala de VAS para cuantificar de 0 a 10, donde 2 era el umbral de dolor, (**Ver sección 2.3.2.2**) la magnitud de la intensidad *evocadas* con pruebas diseñadas para evaluar la presencia de signos y características fisiopatológicas tanto para el dolor nociceptivo como neuropático. Para la intensidad del dolor no *evocado* utilizamos la escala de VAS (con un VAS=2 como umbral de dolor) para sensaciones de parestesias (VAS < 2; sensaciones anormales, pero que no son consideradas desagradables) y disestesias (VAS>2; sensaciones anormales desagradables).

Medimos varias características de dolor neuropático como alodinia mecánica y térmica, hiperalgesia al pinchazo de alfiler y sumación temporal al pinchazo de alfiler repetido. Para ello se utilizó un pincel fino suave, presión manual estática, un pinchazo de alfiler en una aplicación y en cuatro aplicaciones del estímulo a intervalos de menos de un segundo, y una gota de acetona que se dejó caer sobre la piel con un cuentagotas (**Ver Appendix Picture 2.1**).

2.3.3. Procedimiento Clínico

Antes de llevar a cabo las mediciones relevantes para el proyecto se realizó un estudio piloto de n=10 pacientes, de similares características al definitivo en el que se comprobó que la medida pre-tratamiento era necesaria para nuestros objetivos y en el que se determinó que el cambio del dolor en las diferentes medidas temporales podía ser de gran importancia. Este pequeño estudio, con medida pre y post-tratamiento (a las 6 semanas) se llevó a cabo entre junio y noviembre de 2003. En tres de estos pacientes se pudieron seguir las medidas post-tratamiento y por tanto se incluyeron en el estudio definitivo.

Un total de 30 pacientes con LM de entre 258 historias revisadas participaron en el estudio, recogiendo datos de ellos desde el 1 de julio de 2003 hasta 1 de marzo de 2005. Los pacientes incluidos en nuestro estudio fueron seleccionados de entre las seis plantas del Hospital Nacional de Paraplégicos de Toledo que habitualmente tienen ingresados a pacientes cervicales y dorsales en rehabilitación, según disponibilidad y voluntariedad de éstos, siendo excluidos aquellos a los que no se pudo realizar la primera medida pre-tratamiento.

Todos los pacientes estudiados recibieron el tratamiento estándar del hospital que precisaron en cada caso. La primera medida del dolor del paciente y demás pruebas de sensibilidad se tomaron antes de que se prescribieran fármacos analgésicos, pudiendo estar expuestos o no a ellos en los sucesivos exámenes, según modificaciones de la pauta farmacológica por los facultativos. El seguimiento de las medidas a cada paciente se realizó a los 2, 3, 4, 6, y 12 meses del inicio de la lesión medular. El número de seguimientos dependió así del inicio del dolor con respecto al inicio de su lesión.

En cada sesión, en primer lugar se le preguntaba al paciente por la intensidad de dolor actual que presentaba, con el VAS máximo, mínimo, 7 días y de desagradabilidad, al nivel y por debajo del nivel. A continuación, la cualidad de su dolor era recogida en las cuestiones de la *Entrevista Basada en Mecanismos de Dolor*. Después en las *“Pruebas semi-cuantitativas de sensibilidad”* se le practicaron al paciente las distintas medidas en contacto con la piel de sensibilidad/ dolor a los estímulos de: cepilladura, presión manual, pinchazo/ s de alfiler y gota de acetona. La duración de cada sesión de recogida de datos al paciente fue variable en cada caso, aproximadamente 30 minutos.

2.4. Resultados

2.4.1. Datos Demográficos y Diagnósticos

Un total de 30 pacientes fueron reclutados. La media de edad fue de 39 años (DE +/- 13) con edades comprendidas entre los 21 y 71 años. Un tercio de ellos fueron mujeres (33,3 %) y dos tercios hombres (66,7 %). La etiología más común fue traumática por accidente de tráfico en un 40 % seguido de cerca por lesión atraumática (causas médicas y tumores óseos) con un 36,7 %; traumatismo por caída en un 13,3 %; zambullida 6,7 % y arma de fuego en un 3,3%. Según el nivel vertebral afectado valorado mediante el diagnóstico, la mitad de los pacientes tenían lesiones cervicales y la otra mitad dorsales. Más específicamente, el 26,7 % presentaba lesión cervical alta (C2-C4), el 23,3 % lesión cervical baja (C5-C8), el 16,7 % lesión dorsal alta (D1-D4) y el 33,3 % lesión dorsal baja (D5-D10). Esta última, con 10 pacientes fue la más prevalente de entre todas en nuestro estudio. Incluimos tanto lesiones completas (ASIA A) como incompletas (ASIA B y C), siendo dos tercios del primer tipo (63,3%) y un 10 % y 36,7 % del segundo, respectivamente.

2.4.2. Tiempo de Comienzo del DN Espontáneo

Aunque el DN en la fase aguda presenta un comienzo variable, la gran mayoría de los 30 pacientes empezó a percibir síntomas disestésicos (VAS ≥ 3) entre el segundo (40.0%) y tercer mes (46.7%). Tan sólo un paciente comenzó al cuarto mes, y tres de ellos en el sexto mes (3.3 y 10.0 % respectivamente) (**Ver Fig .2.1**)

La prevalencia del DN *espontáneo* al nivel y por debajo de nivel de LM en cada mes evaluado para los 30 pacientes se presenta en la **Fig.2.2**. En ella se puede apreciar que en el mes 2 de LM el DN por debajo se sitúa en el 30 %, para después aumentar a más del doble en posteriores meses. El DN al nivel de LM sobrepasa el 50 % en todos los meses, y va en consonancia con la subida que experimentan los pacientes a lo largo del tiempo.

La prevalencia del DN *evocado* al nivel y por debajo del nivel de LM evaluado en dos momentos temporales, al tercer y sexto mes de LM indican que en ambos tiempos, la hiperalgesia mecánica es la más prevalente tanto al nivel como por debajo, y llega a estar presente en el 50 % de los pacientes al nivel a los 6 meses. En general se observan más signos presentes de dolor *evocado* al nivel que por debajo a los 6 meses (n=30, **Fig.2.3 y 2.4**); mientras que la alodinia térmica por debajo disminuye a la mitad a los 6 meses, la alodinia térmica al nivel aumenta el doble a los 6 meses.

2.4.3. Intensidad del Dolor Espontáneo

El análisis de medidas repetidas de las diferentes intensidades de dolor espontáneo al nivel de LM indicó un aumento general de los 2 a los 12 meses después de la LM. La **Tabla 2.3** muestra un incremento progresivo de DN a lo largo de las medidas repetidas al nivel, mayor con el VAS de Desagradabilidad. La intensidad de dolor máximo también incrementa su intensidad con las medidas y el actual muestra similar intensidad en el comienzo y fin. Por debajo del nivel de lesión, la intensidad de 7 días y máxima también incrementan su intensidad. La desagradabilidad se mantiene muy alta y la intensidad actual disminuye de los 2 a los 12 meses. Usamos el VAS de 7 días para el resto de los análisis estadísticos ya que fue considerado más homogéneo (ver DS), informativo y fiable como informe de la intensidad del dolor por el paciente. Además, el análisis no fue significativo o no se pudo realizar por la falta de medidas en la mayoría de los momentos temporales (y la potencia observada fue cercana a 1.00).

Se realizó un ANOVA de medidas repetidas para el dolor espontáneo y continuo en los niveles de lesión estudiados, al nivel y por debajo en los 30 pacientes y se utilizó como indicador la prueba de Greenhouse-Geisser, no observándose diferencias significativas en intensidad de dolor de 7 días para ninguno de los meses evaluados, tanto al nivel de LM (F=2,366; gl=2,586 ,33,614 ; p=0,096) como por debajo del nivel (F= 0,704; gl= 3,221 ,41,878 ; p=0,565) (**Fig.2.5 and 2.6** respectivamente). Con una potencia observada de 0,155 al nivel y 0,213 por debajo. Con análisis no paramétricos como en la prueba de Friedman tampoco vemos significación estadística por debajo de LM con n=14 (Chi-cuadrado =4,106; gl=4) ni tampoco al nivel (Chi-cuadrado =5,604; gl=4) en las sucesivas medidas hasta los 12 meses. No obstante, se aprecia una tendencia al aumento de la intensidad del dolor a lo largo de las medidas repetidas, mucho más acusado y claro al nivel de la LM. El mismo ANOVA se realizó para el VAS de Desagradabilidad pero ninguna de las diferencias fue significativa, tanto al nivel (F= 1,480; gl = 4 , 38,091; p= 0,295) como por debajo (F= 0,168; gl= 4 ,4177 ; p= 0,949) (**Fig.2.7 and 2.8** respectivamente) con una potencia observada de 0,280 al nivel y 0,071 por debajo.

2.4.4. Efecto en los Factores Físicos de la intensidad de dolor de 7 días Al Nivel y Por Debajo del nivel de lesión.

Las **Figuras 2.7-2.12** muestran las medias en intensidad de dolor espontáneo 7 días para los grupos (completo/incompleto y cervical/dorsal) a lo largo de los 12 meses tras la LM en intensidad de dolor (VAS de 7 días). Aunque no se vieron diferencias significativas al nivel de lesión inter-sujetos en cervical (n=6) versus dorsal (n=8) (**Ver Tabla 2.4**), excepto para los meses 2 y 12 en lesiones dorsales, podemos observar un incremento progresivo y claro en la intensidad de dolor ($t=2.54$, $df=13$, $p=0.03$) sobre todas las medidas temporales en el grupo dorsal desde 0.8 a 5.1 frente a una mayor constancia del dolor en el grupo cervical ($2 > \text{VAS} > 3$) (**Fig. 2.9**). En lesiones completas versus incompletas (**Ver Tabla 2.4**), se puede observar que hasta el mes 4 después de la LM, los pacientes con lesiones completas pueden sufrir más dolor que los incompletos (**Fig. 2.10**). Por debajo del nivel de lesión, los pacientes con lesiones cervicales parecen ser más constantes y el grupo dorsal termina a los 12 meses con un mayor VAS. Las lesiones incompletas parecen presentar más dolor, excepto en el mes 6º, que el grupo de completos, y en el mes 12 la diferencia fue de más de 2 puntos en el VAS de 7 días.

2.4.5. *Diferencias intra-sujetos e interacciones inter-sujetos entre grupos lesionados completos-incompletos y cervicales-dorsales medidos al nivel y por debajo del nivel de LM en intensidad de dolor en los grupos completo/incompleto y cervical/dorsal.*

2.4.5.1. Diferencias Al Nivel de lesion en Intensidad de Dolor de 7 días.

Se realizó así mismo un ANOVA de medidas repetidas para los subgrupos de *lesiones completas-incompletas y cervicales-dorsales* en cada momento temporal, sin encontrar diferencias significativas generales intrasujeto mediante la prueba de Greenhouse-Geisser ($F= 1,806$; $gl= 2,512$, $27,633$; $p=0,176$; con una potencia observada de < 0.080). Aunque no se aprecian diferencias significativas intersujeto entre el subgrupo de cervicales (n=6) frente a dorsales (n=8) ($F= 0,010$; $gl= 1, 11$; $p=0,923$) como en la **Fig 2.7**, se puede observar un claro y progresivo incremento en intensidad de dolor de los 2 a los 12 meses observado en el grupo de LM dorsal comparado con el cervical (**Fig. 2.11**). No se observó interacción inter-grupos ($F= 0,493$; $gl= 2,1512$, $27,633$; $p=0,658$) entre completos (n=8) e incompletos (n=6) mediante la misma prueba de Greenhouse-Geisser, ya que no observamos significación estadística ($F= 0,020$; $gl= 1, 11$; $p=0,889$) (**Fig. 2.12**).

2.4.5.2. Diferencias Por Debajo del Nivel de lesion en Intensidad de Dolor de 7 días.

Se realizó el mismo tipo de análisis por debajo del nivel de LM que al nivel, un ANOVA de medidas repetidas para *lesiones completas-incompletas y cervicales-dorsales* para la intensidad de dolor espontáneo de 7 días en cada momento temporal, sin encontrar significación estadística mediante la prueba de Greenhouse-Geisser para diferencias intrasujeto ($F= 1,168$; $gl= 3,034$, $33,379$; $p=0,337$; con una potencia observada de < 0.080). Sin embargo, se aprecian diferencias significativas entre el grupo de cervicales (n=6) frente a dorsales (n=8) ($F= 0,051$; $gl= 1, 11$; $p=0,826$), pudiéndose observar en la interacción significativa ($F= 2,916$; $gl= 3,034$, $33,379$; $p=0,048$) aunque gran variabilidad longitudinal del dolor espontáneo, tendiendo a aumentar en los dorsales y a disminuir en los cervicales, aunque en la última medida a los 12 meses de LM ambos grupos muestran un VAS de 3.5 a los 12 meses tras la LM (**Fig.2.13**).

No se aprecia interacción ($F= 1,768$; $gl= 3,034$, $33,379$; $p=0,172$) ni diferencias intergrupales entre completos (n=8) frente a incompletos (n=6) con la misma prueba de Greenhouse-Geisser ya que no observamos significación estadística ($F= 1,768$; $gl= 3,034$, $33,379$; $p=0,172$). (**Fig.2.14**), indicando una tendencia más constante del dolor en los completos.

2.4.6. Signos de Dolor Evocados.

Análisis Cochran no paramétricos fueron realizados para los niveles de lesión estudiados al y por debajo del nivel de LM en las medidas desde 2-6 meses después de la lesión, observando diferencias significativas en sumación temporal al nivel de la lesión ($p=0,029$) y también en la alodinia térmica por debajo del nivel de lesión ($p=0,044$) (**Ver Tabla 2.5**). Como vemos en la **Fig 2.15**, demuestra una tendencia para el incremento en signos evocados al nivel que es constante o aumenta de los 2 a los 6 meses después de la LM, mientras que por debajo de la LM los signos de dolor disminuyen en los pacientes.

2.4.7. Análisis de Correlaciones entre Dolor Espontáneo y Signos de Dolor Evocado: LM en general.

En general se obtuvieron correlaciones altas y positivas con el estadístico Rho de Spearman en todos los signos de dolor al nivel de la LM y por debajo del nivel en la medida a los 2 meses ($28 < n < 30$), con $p=0,001$ (**Tablas 2.6 y 2.7**). Las correlaciones negativas entre el VAS 7 días y los signos ($-0.629 < r < 0.960$; $p=0.001$) indican una relación inversa sugiriendo que la intensidad de los signos de dolor evocado era alta cuando la intensidad del dolor espontáneo era baja, como se esperaba a los 2 meses de LM (**Fig. 2.5 y Tabla 2.4**). Por otra parte, tanto la alodinia mecánica/ sensibilidad, hiperalgesia mecánica/sensibilidad, sumación temporal y alodinia térmica/sensibilidad se hallaron correlacionadas positivamente a los 2 meses ($0.916 < r < 0.960$; $p=0.001$). Aunque no se muestra en las tablas, las sensaciones post-estímulo estuvieron correlacionadas alta y positivamente con la sumación temporal al nivel de la lesión ($r=0.879$; $p=0.001$; a 2 meses; $r=0.478$; $p=0.05$ a 6 meses) o por debajo del nivel ($r=0.992$; $p=0.001$; a 2 meses; $r=0.491$ $p=0.05$ a 6 meses). A los 6 meses de la LM, sólo la intensidad de dolor espontáneo y alodinia térmica/sensibilidad ($r=0.413$; $p=0.05$) e hiperalgesia mecánica/sensibilidad y alodinia térmica/sensibilidad ($r=0.462$; $p=0.05$) al nivel de lesión, y alodinia mecánica/sensibilidad y térmica/sensibilidad por debajo del nivel ($r=0.691$; $p=0.001$). También el número de dermatomas afectados es significativo y positivo a ambos niveles con la intensidad de dolor en el mes 2, pero negativamente correlacionada con los signos de dolor evocados para ese periodo ($-0.629 < r < -0.961$; $p=0.001$). Por otra parte, en el mes 6 algunas correlaciones son positivas y significativas al nivel entre el número de dermatomas y signos: alodinia mecánica y número de dermatomas de dolor espontáneo ($r=0.427$; $p=0.05$) y evocado ($r=0.460$; $p=0.05$). Por debajo del nivel de lesión, el número de dermatomas de dolor espontáneo de 7 días y evocado correlacionó con la intensidad también a los 6 meses (0.738 y 0.531 respectivamente; $p=0.001$). La correlación entre el número de dermatomas al nivel fue alta y positiva tanto a los 2 como a los 6 meses después de la lesión ($r=0.903$ and 0.849 respectivamente; $p=0.001$) al nivel y por debajo del nivel de lesión ($r=0.918$ y 0.564 respectivamente; $p=0.001$) y por debajo del nivel de lesión por periodos de tiempo equivalentes ($r=0.918$ y 0.564 respectivamente; $p=0.001$).

2.4.8. Análisis de Correlaciones entre Dolor Espontáneo y Signos De Dolor Evocado: efecto de los Factores Físicos.

Las correlaciones con el estadístico Spearman Rho también permitió las subsiguientes comparaciones entre grupos cervicales y dorsales (**Tablas 2.8 and 2.9**). Al nivel de LM en el grupo cervical observamos correlaciones altas y positivas en el 2º mes después de la lesión y a los 6 meses sólo correlaciones de intensidad de dolor de 7 días y número de dermatomas con dolor evocado ($r=0.615$; $p=0.05$) entre el número de dermatomas con dolor espontáneo y evocado ($r=0.626$; $p=0.05$) y una relación original e inversa entre alodinia térmica/ sensibilidad y sumación temporal ($r=-0.739$; $p=0.05$; **Tabla 2.9**).

En general, los análisis de correlaciones de intensidad de dolor evocado y espontáneo por debajo del nivel de lesión cervical indicaron las mismas relaciones observadas en el análisis general conjunto (**Tabla 2.7 and 2.10**). Los análisis de correlaciones por debajo del nivel de lesión para lesiones dorsales no pudieron generarse por la pequeña muestra dada por el análisis ($n=10$) (**Tabla 2.11**).

2.4.9. Análisis de Correlaciones entre Dolor Espontáneo y signos de Dolor Evocado Al Nivel y Por Debajo del Nivel de LM.

Se puede identificar una evidencia de la existencia de mecanismos generadores de DN locales durante la fase aguda de la LM que pueden identificarse por el análisis correlacional de los signos de dolor espontáneos y evocados entre al nivel y por debajo del nivel de lesión (c.f. **Finnerupp et al., 2003b**). Las siguientes tablas muestran las correlaciones al nivel y por debajo del nivel entre intensidad de dolor, signos evocados y dermatomas implicados, primero ambos grupos (**Tabla 2.12**), y después cervicales (**Tabla 2.13**) y dorsales (**Tabla 2.14**). Correlaciones positivas y altamente significativas se observaron con la intensidad de los signos de dolor evocado entre al nivel y por debajo del nivel a los 2 meses después de la LM (**Table 2.12**); a los 6 meses sólo la alodinia térmica /sensibilidad al nivel e hiperalgesia mecánica/ sensibilidad por debajo del nivel estaban correlacionadas significativamente ($r=0.428$; $p=0.05$). La intensidad de dolor espontáneo al y por debajo del nivel fue correlacionada significativamente a los 2 ($r=0.525$; $p=0.001$) y a los 6 meses ($r=0.459$; $p=0.05$) después de la LM. Aunque los datos no estaban incluidos en las tablas ya que el análisis correlacional no era significativo, decir que el número de dermatomas por debajo con el dolor espontáneo a los 6 meses después de la LM correlacionó con el nivel de desagradabilidad al nivel a los 6 meses. El número de dermatomas con dolor evocado al y por debajo del nivel de lesión también correlacionó a los 2 ($r=0.694$; $p=0.001$) y a los 6 meses ($r=0.497$; $p=0.001$) después de la LM.

En general el grupo cervical de LM (**Table 2.13**) reveló correlaciones similares a aquellas identificadas en el análisis general (**Tables 2.12**); y las correlaciones para el grupo dorsal no pudieron ser generadas por la pequeña muestra del análisis (n=10, **Table 2.14**). No obstante, la correlación entre el número de dermatomas con dolor espontáneo y evocado al nivel de la LM cervical con hiperalgesia mecánica /sensibilidad a los 6 meses demostró un cambio distinto en la relación comparada con la relación negativa de la LM dorsal a los 2 y 6 meses.

Por último, para identificar mecanismos comunes fisiopatológicos activos después de poco tiempo después de la LM al nivel que pueden cambiar y activar más tarde mecanismos de DN por debajo del nivel, se realizó una correlación temporal entre los signos de dolor a los 2 y 6 meses. El número de dermatomas dolorosos (espontáneos y evocados) al y por debajo del nivel de la LM en pacientes con lesiones dorsales/ generalizadas no fueron significativas excepto para los dermatomas espontáneos al nivel de lesión a los 2 meses y evocados debajo de la lesión a los 6 meses (**Table 2.15**).

2.4.10. Análisis de la Entrevista Basada en Mecanismos de Dolor Neuropático

Cinco preguntas de la Entrevista Basada en Mecanismos de DN con n suficiente (**Tabla 2.16**) fueron analizadas mediante t de Student en cada momento temporal comparadas dos a dos para los siguientes momentos temporales: 2, 3, 4, 6 y 12 meses tras la LM al y por debajo del nivel de lesión: intensidad de dolor evocado mecánico estático (0-10), intensidad de dolor evocado mecánico dinámico (0-10), intensidad de dolor evocado térmico (0-10), dolor espontáneo continuo (0-10), y número de descriptores (0-10) (ardiente, pulsátil, punzante, pinchazo, apuñala, cortante, calambreante, te aplasta, hormigueo, picazón).

Las figuras **2.16-2.22** muestran el patrón seguido por los pacientes en las preguntas relativas al dolor por debajo de la lesión: informan de más altas puntuaciones en el mes 2 tras la LM y después bajan hasta el mes 6, más tarde tienden a subir de nuevo a un punto similar a donde empezaron. Sin embargo, al nivel de la lesión los pacientes informaron de más altas puntuaciones que por debajo del nivel y se vio un número más alto de descriptores hasta el mes 6°. Sin embargo, a los 12 meses tras la LM los niveles de intensidad de dolor fueron similares en todas las preguntas.

El análisis t de Student para muestras independientes reveló que fueron principalmente significativos, y por tanto diferentes de otros momentos temporales, aquellos relacionados con el dolor continuo y el número de descriptores, tanto al nivel como por debajo del nivel de lesión, y dolor evocado mecánico dinámico al nivel a lo largo de los 12 meses. Al nivel de la lesión (**Table 2.18**), las siguientes diferencias fueron significativas: intensidad de dolor evocada mecánica estática a los 4 y 12 meses (p=0.020 y 0.006 respectivamente); intensidad de dolor evocada mecánica dinámica a 3, 4, 6 y 12 meses (p=0.049, 0.021, 0.017 y 0.006 respectivamente); intensidad de dolor evocado térmico sólo a 12 meses (p=0.012); dolor espontáneo continuo a 3, 4, 6 y 12 meses (p=0.010, 0.005, 0.0001 y 0.005 respectivamente); el número de descriptores fue significativamente diferente para todas las medidas (p=0.010, 0.001, 0.003, 0.022 y 0.005 respectivamente). Por debajo del nivel de lesión (**Table 2.19**), las siguientes diferencias fueron significativas: intensidad de dolor evocada mecánica estática a 3 y 12 meses (p=0.022 y 0.012 respectivamente); intensidad de dolor evocada mecánica dinámica sólo a 12 months (p=0.027); dolor espontáneo continuo a 3, 4, 6 y 12 meses (p=0.010, 0.005, 0.0001 y 0.005 respectivamente); el número de descriptores fue significativamente diferente para todas las medidas (p=0.001, 0.0001, 0.0001, 0.0001 y 0.001 respectivamente).

2.4.11. Análisis de Dermatomas.

Se realizaron análisis t de Student para muestras independientes en cada momento temporal (2, 3, 4, 6 y 12 meses tras la LM), ambos al nivel y por debajo del nivel de LM (**Figuras 2.22-2.25**). Se encontró diferencia significativa entre los dermatomas implicados en dolor espontáneo al nivel de la lesión entre los meses 4 y 12 (p=0,055) en el grupo cervical. También significativas entre los meses 3 y 6 (p=0,044) y entre 4 y 12 (p=0,022) en los dermatomas implicados en el dolor evocado. Además, en dolor espontáneo en los meses 2 y 4 (p=0,044) y 2 y 6 (p=0,025) en lesiones dorsales; y diferencias en dolor evocado entre los meses 2 y 3 (p=0,044) y entre 2 y 4 (p=0,016) también en el grupo de dorsales.

La tendencia en el grupo cervical que se puede observar por debajo del nivel a lo largo de los meses es un disminuido número de dermatomas implicados tanto en dolor espontáneo como evocado, mientras que en el grupo dorsal el número tendió a incrementarse en el tiempo. Al nivel, el grupo cervical tendió a ser más constante y el dorsal más heterogéneo a lo largo de las medidas temporales.

En **Pictures 2.2 y 2.3** se muestran ejemplos de mapas de dermatomas de DN en dos pacientes con lesión cervical y dorsal respectivamente.

2.5. Discusión

Nuestro estudio es el primero que recoge la evolución longitudinal del DN desde la fase aguda de la LM (antes de 6 meses) hasta su fase crónica (un año después de la lesión), analizando la relación entre intensidad de dolor espontáneo y signos de dolor evocado, con el objetivo de analizar los mecanismos implicados y su impacto sobre el paciente. Especialmente nos hemos centrado en la utilidad de las medidas del dolor *espontáneo* y *evocado* al nivel y por debajo de la LM para identificar los mecanismos implicados en el DN. Las características clínicas de los pacientes de nuestra muestra poseen amplio espectro en cuanto a edad, género, etiología y nivel de lesión; lo cual favorece la inclusión de gran cantidad de factores en los grupos de estudio.

La gran mayoría de los pacientes estudiados comenzaron su DN entre los meses 2 y 3 después de la LM, y presentan más dolor al nivel que por debajo del nivel de lesión. Dado que la potencia observada en el análisis es más bien baja probablemente por el bajo número de pacientes, los resultados significativos deben ser tomados con cautela, sin embargo podemos observar las tendencias proporcionadas, ya que el único análisis que permite medidas longitudinales con nuestros datos es un ANOVA de medidas repetidas. En intensidad del dolor *espontáneo* observamos una tendencia al aumento del dolor hasta los 12 meses, mucho más considerable al nivel de la LM que por debajo de ésta. Los pacientes con lesiones dorsales al nivel de lesión presentaron un aumento progresivo del dolor en todas las medidas temporales frente a una mayor constancia del dolor en lesiones cervicales. Por debajo del nivel de lesión, pacientes con lesiones cervicales y dorsales llegaron al mismo nivel de dolor, pero con gran variabilidad en todas las medidas. Los signos de dolor *evocado* más comunes fueron, tanto en los 3 meses como 6 meses posteriores a la lesión, la hiperalgesia mecánica al nivel y por debajo, y la alodinia térmica y la sumación temporal ambos al nivel. Tan sólo la alodinia térmica correlacionó con la intensidad de dolor *espontáneo* a los 6 meses después de la LM.

2.5.1. El Dolor Espontáneo en los 12 meses después de la LM.

Después de un examen cualitativo y comparación de las 3 medidas de intensidad de dolor y de acuerdo con otros estudios (**Finnerup et al. (2003b)**), elegimos el VAS de “7 días” y no el “Actual” o “Máximo” porque parecía una medida más estable y fiable del dolor referido por el paciente, ya que el VAS actual presentaba amplia variabilidad, dependiendo del momento del día, cambios atmosféricos, etc.

En el primer estadio (meses 2-3 tras la LM), un 86,7% de los pacientes comenzaron a experimentar sensaciones de DN como “quemazón” y “opresión”, que siguió los resultados de comienzo eminentemente temprano de los síntomas del DN en la LM en otros estudios (**Siddall et al. 2003**). El mayor porcentaje de prevalencia del DN al nivel con respecto al DN por debajo del nivel de lesión concuerda con autores como **Siddall et al. (2003)** y **Finnerup et al. (2003b)**. El uso de prescripción médica se asocia con más características de dolor, alta intensidad de dolor y múltiples sitios de dolor, y los descriptores también indican que la presencia de múltiples tipos de dolor es predictivo del uso de prescripción médica (**Widerström-Noga and Turk, 2003**).

La intensidad del dolor *espontáneo* fue asociada con una tendencia al aumento de la intensidad del dolor a nivel longitudinal hasta los 12 meses de LM, mucho más acusado y claro al nivel de la LM que por debajo de ésta, como ya se ha visto en estudios anteriores, (**Finnerup et al., 2003b** y **Jensen et al., 2003**) donde los resultados mostraron que los pacientes LM con *Dolor Central* presentaban más frecuentemente hipersensibilidad en los dermatomas correspondientes *al nivel* de LM que aquellos pacientes sin dolor.

Focalizando los resultados en el nivel de lesión, podemos apreciar un claro aumento progresivo de la intensidad de dolor en todas las medidas temporales en el grupo de dorsales (desde 0 hasta 5 en el VAS), frente a una mayor constancia del dolor en los cervicales, que puede estar dando una importante clave en cuanto a características fisiopatológicas del nivel de lesión, y así parece que la tendencia observada aquí es de empeoramiento en los dorsales y de más estabilidad en los cervicales. Aunque **Siddall et al. (1999)** realizó un estudio longitudinal distinguiendo entre esta clasificación de dorsales y cervicales sólo en su primera medida temporal (2 semanas), encontrando más incidencia de dolor en los cervicales al nivel, al igual que en nuestro caso ocurría a los 2 meses.

Mirando ahora los resultados obtenidos por debajo del nivel de lesión, se aprecia un progresivo y claro incremento en la intensidad de dolor en todas las medidas temporales en el grupo dorsal (from 0 to 5 in VAS), frente a mayor constancia en el grupo cervical, el cual puede estar dando una importante clave de las características fisiopatológicas del nivel de lesión, y así parece que la tendencia que se observa aquí es a un

empeoramiento en los pacientes con lesión dorsal y más estabilidad en lesión cervical. Aunque **Siddall et al. (1999)** realizó un estudio longitudinal distinguiendo entre esta clasificación de lesión cervical y dorsal sólo en la primera medida temporal (a las 2 semanas después de la LM) encontró más incidencia de dolor en pacientes con lesiones cervicales, concordante con nuestros pacientes sólo a los 2 meses de la lesión.

Un examen del desarrollo de la intensidad de dolor espontáneo por debajo del nivel no reveló diferencias significativas entre el grupo cervical y dorsal, con una variabilidad observada en todos los momentos temporales, y una tendencia al incremento en intensidad de dolor tras la lesión dorsal; y la misma intensidad de dolor se observó un año después para ambos grupos. Después de una lesión dorsal, la intensidad de dolor continuo pareció estar instalada temprano y permaneció constante en la fase crónica, **Siddall et al. (1999)** también encontró la misma tendencia 2 semanas después de la LM, como nosotros a los 2 meses.

La influencia del grado de lesión (completa o incompleta) fue menos claro al nivel en intensidad alcanzada a los 12 meses (VAS=4). Sin embargo, aunque el incremento en dolor espontáneo tras lesiones completas fue significativo ($p=0.06$, 12 meses vs 3 meses) el dolor aumentó a la misma intensidad comparado con los incompletos que lo hacen a los 6 meses. Como **Siddall et al. (1999)**, los incompletos presentan ligeramente más dolor al nivel de LM que los completos (tanto a las 2 semanas como a los 2 meses) aunque en nuestra muestra la intensidad de dolor es mostrada para ambos grupos a los 12 meses.

La tendencia más constante del dolor en el grupo de lesiones completas por debajo del nivel de LM parece terminar a los 12 meses de LM en una tendencia a la baja mientras que en los incompletos es al alza en intensidad de dolor. En la primera medida (2 meses) nuestros pacientes con lesión completa presentaron más dolor por debajo, signo que concuerda otra vez con los resultados de **Siddall et al. (1999)**.

Estos datos, aunque sin significación estadística, pueden trazar una tendencia de perfil de los pacientes con lesión cervical como aquellos que muestran una intensidad de dolor más estable al nivel y mucho más variable por debajo del nivel, mientras que en los dorsales la intensidad va en aumento progresivo al nivel y se estabiliza a los 4 meses por debajo del nivel de LM.

Los pacientes fueron medicados en los sucesivos seguimientos después de la medida de base, y se encontró un VAS reducido en intensidad de dolor al final de las evaluaciones para el grupo completo sólo por debajo del nivel de lesión, evaluado con el VAS 7 días (**Fig 2.13**).

El dolor máximo percibido fue muy intenso en la mayoría de los casos, además la comparación específica entre los meses 2 y 12 en el subgrupo dorsal reveló un significativo incremento del dolor al nivel, lo que podría explicar que en la mayoría de los estudios indiquen que un tercio de los pacientes con dolor crónico padecen dolor intenso o severo (**Bonica 1991; Finnerup et al. 2001a; Siddall et al. 2001**).

Mientras que los pacientes con lesiones cervicales vieron disminuida la intensidad de dolor y dermatomas en su evolución, los pacientes con lesiones dorsales vieron cómo su dolor e intensidad se incrementaron en el tiempo. Estos cambios pequeños pero significativos son muy importantes, ya que sugieren en general que el número de dermatomas implicados corresponde con la intensidad de dolor experimentada por el paciente hasta un año después de la LM. En general se observó una tendencia de decremento de dermatomas de dolor *espontáneo* y *evocado* por debajo de la LM cervical, mientras que la dorsal reveló un incremento general en el número de dermatomas con ambos tipos de dolor.

2.5.2. Hipótesis del Generador de Dolor Central (CPG)

2.5.2.1. Las bases del CPG

Grupos de investigación en el estudio de animales (**Vierck 2000**) y pacientes (**Finnerup y Jensen 2004, Melzack y Loeser 1978**) han apoyado la hipótesis de que la hiperexcitabilidad neuronal al nivel de la lesión puede influenciar vías nociceptivas por debajo del nivel de lesión (**Vierck 2000**) y por encima del nivel (**Finnerup y Jensen 2004**), posiblemente a través del sistema propioespinal. Nuestros resultados parecen seguir esta línea explicativa sobre la hiperexcitabilidad neuronal al nivel de la LM por un mecanismo central. La mayor intensidad de dolor *espontáneo* al nivel a lo largo del tiempo de lesión, cuando queda activado el mecanismo *Generador de Dolor Central (CPG)*, y las altas correlaciones entre signos de dolor *evocado* tanto al nivel (alodinia térmica/ sensibilidad e intensidad del dolor espontáneo a los 6 meses) como por debajo parece estar en consonancia con esta teoría; la desaferentación de los tractos ascendentes y una activación de dianas rostrales por otras fuentes de la actividad espinal (sistema propioespinal) (**Vierck et al., 2000**), pueden ser los responsables

del dolor neuropático que afecta a tantos lesionados medulares, sin distinción del nivel medular afectado o grado de lesión completa/incompleta que presenten.

Los resultados de **Melzack y Loeser (1978)** sugirieron ya la existencia de un *Generador de Dolor Central (CPG)* en la médula espinal de pacientes con LM, lo que supone *mecanismos de modulación central*, y es una hipótesis derivada de la *Teoría de la Puerta de Control (Melzack y Wall, 1965)*. Brevemente, esta última propone que el daño producido a aquellas fibras que inhiben la transmisión del dolor en la médula espinal es la razón de la existencia de dolor continuo; aquellas fibras que normalmente cierran la puerta no podrán funcionar y las señales llegarán hasta el cerebro sin modulación alguna, donde se percibirán como dolor (**Melzack y Wall, 1965**). Aunque esta teoría ha sido posteriormente criticada, existen evidencias que sugieren el papel de fibras A en la inhibición de respuestas después de la activación de fibras C en humanos (**Yarnitsky et al., 1992; Wasner et al., 2004**).

2.5.2.2. Mecanismo Posible del CPG.

Una red de neuronas con hiperexcitabilidad al nivel de la lesión en la médula espinal puede actuar como *mecanismo de generación de patrones de dolor*. Estas células están normalmente por debajo del control sensorial. En parapléjicos, puede estar localizado por encima del nivel de sección o cordotomía. Estas regiones pueden proyectar a las del cerebro involucradas en la localización precisa de entradas sensoriales y dolorosas. (**Melzack y Loeser, 1978**). Estos autores fueron los que sugirieron que el centro generador de dolor puede estar ubicado a un nivel rostral a la LM, ya que realizando una cordotomía por arriba de la LM inicial no obtuvieron resultados en la eliminación del dolor por debajo de la lesión. Además antagonistas de receptores de NMDA son eficaces para disminuir el dolor al nivel y por debajo del nivel de la LM (**Finnerup et al., 2001; Eide et al., 1995; González-Valdizán et al., 2004**). Pero también hay evidencias de que el dolor central en la LM puede ser el resultado de cambios neuroplásticos supraespinales en respuesta a la desaferentación y estímulo anormal desde un generador espinal. (**Finnerup et al., 2004**).

Así, el dolor ocurre cuando el número de impulsos nerviosos por unidad de tiempo desde los sistemas de proyección somáticos a las áreas cerebrales que subyacen al dolor exceden un nivel crítico, producido éste por una lesión o estimulación nociceptiva. Otros estudios como **Crue et al. (1976)** et al. apoyaron que similar nivel supraumbral puede ocurrir directa o secundariamente como resultado de la pérdida de entrada de información. Recientemente se ha publicado sobre el papel de las fibras mielínicas en la inhibición de respuestas dolorosas con mentol en voluntarios sanos (**Wasner et al., 2004**), apoyando la hipótesis de que el DN pueda desencadenar ciertas fisiopatologías de las fibras A.

Finnerup y Jensen (2004) proponen que la entrada proveniente de los aferentes primarios puede ser distorsionada por dos mecanismos: 1) las neuronas de proyección del tracto espinotalámico por debajo de la lesión medular pueden estar lesionadas e incrementar la hiperexcitabilidad de las neuronas desaferentadas, incluidas las del tálamo, 2) las neuronas de segundo orden en el asta dorsal en el extremo rostral de la lesión medular pueden volverse hiperexcitables como consecuencia de cambios excitotóxicos y desinhibición de neuronas GABAérgicas al nivel. Una entrada anormal de estas neuronas de segundo orden en el extremo rostral de la lesión medular puede propagarse por el sistema propioespinal a las neuronas desaferentadas del tálamo, dando como resultado dolor referido a áreas por debajo del nivel de lesión medular. (**Ver Appendix Picture 2.3.**)

Por otra parte, otra posibilidad es que el sistema descendente inhibitorio de dolor (**Finnerup and Jensen, 2004**) en pacientes con lesiones dorsales puede encontrarse más alterado, como se observó en los altos niveles de dolor espontáneo (VAS 7 días) comparado con los de lesiones cervicales, y podrían estar implicados mecanismos centrales. Sin embargo, nuestras correlaciones mostraron que un posible núcleo puede activarse tanto en lesiones cervicales como dorsales a los 2 y 6 meses después de la lesión medular, sugiriendo un potencial mecanismo CPG después de la LM.

2.5.2.3. Hiperexcitabilidad Neuronal inducida por “Espinass Irritativas”.

Se conoce que las condiciones físicas que deterioran la salud del paciente LM, como las sepsis urinarias o las heridas por presión infectadas magnifican la reacción de dolor del paciente. Son de interés la distensión vesical, los espasmos vesicales resultado de una infección incontrolada o cálculos y estreñimiento (**Botterell et al., 1954**). Muchos pacientes informan de que su dolor empeora con el tiempo frío y húmedo y algunos mejoran al trasladarse a un clima más seco (**Damirel et al., 1998**); y algunos se quejan de que los cigarrillos lo agravan (**Botterell et al., 1954**). Estas condiciones toman el nombre de “*espinass irritativas*” del proceso doloroso y pueden ser activados externamente o por mecanismos neurales que recaen en variables emocionales y de

personalidad. La modulación, o pérdida de entrada de información, sensitiva desde vías segmentales o descendientes conduciría a una entrada disminuida a los mecanismos del tronco cerebral que normalmente ejercen una influencia inhibitoria (de arriba a abajo en la transmisión sensorial), y ésta facilitaría el desencadenamiento de patrones anormales por medio de entradas de información nociva. La liberación de esta inhibición y más en conjunto con la desaferentación sensorial, permitiría una actividad anormal sin control, y el dolor persistiría en el tiempo. La inhibición disminuida permitiría el reclutamiento de neuronas adicionales al grupo de neuronas anormales y de ese modo, subyacería la intensificación y extendería el dolor. (**Melzack y Loeser, 1978**)

2.5.2.4. *Desaferentación y Reorganización del Input Sensorial Cortical después de la LM.*

Como la mayoría de los parapléjicos no sufren de dolor de miembro fantasma, es razonable asumir que en ellos, tanto la actividad anormal puede cesar espontáneamente como ser bloqueada por control inhibitorio ejercido por estructuras cerebrales descendientes o vías segmentales como el sistema propioespinal. Como se explica en el Capítulo 3, la discriminación de dos puntos se utiliza para la representación cortical de la piel, y reducidos umbrales se relacionan con una representación cortical aumentada (**Song et al., 1993**) sólo encontrados en pacientes crónicos con dolor central y lesión extensa, ya que no se encontró con pacientes agudos con DN (Ver **3.4. Resultados del Capítulo 3**).

Sin embargo, el hecho de que algunos pacientes no presentan dolor en la fase aguda de la LM no significa que pasado un año (cuando se sabe que se reorganiza la “circuitería neuronal”) o incluso muchos años después, aparezca el dolor de las mismas características que las que sufren los pacientes agudos. Esto podría deberse a que, si en un primer momento hubo buen control inhibitorio, podría perderse por incidencia de cualquiera de los múltiples factores que desencadenan o agravan un dolor neuropático (“espinas irritativas”) lo que puede llevar a la reorganización crónica en los sistemas de procesamiento sensoriales.

2.5.3. *Signos de Dolor Evocados y Correlaciones.*

2.5.3.1. *Signos de Dolor Evocados*

El análisis Cochran reveló una disminución del número de pacientes que presentan sumación temporal a la estimulación mecánica al pinchazo al nivel de la LM y también a la alodinia térmica/ sensibilidad por debajo del nivel de lesión desde los 2 a los 6 meses. Como hemos visto en los resultados, un mayor número de pacientes presentó signos de dolor evocado a los 6 meses después de la LM al nivel de lesión que a los 2 meses (excepto en sumación temporal) en contraste con un menor porcentaje de pacientes a los 6 meses después por debajo de la lesión. Teniendo en cuenta que la sumación temporal al nivel resultó significativa, y también lo fue la alodinia térmica por debajo del nivel, podemos sugerir que si el sistema CPG está operando ya en el primer estadio de la LM (2-3 meses después), y parece menos predominante una vez que los pacientes llegan al mes 6, acompañado por un incremento en el dolor espontáneo durante el mismo periodo de tiempo. No podemos excluir cambios adicionales en estructuras a más alto nivel como el sistema espinotalámico después de los primeros 6 meses después de la LM en adelante.

Como en el estudio de **Siddall et al. (2003)**, la alodinia mecánica/ sensibilidad estuvo presente en un porcentaje relativamente más pequeño de pacientes (principalmente en los primeros 2 meses). En contraste con el estudio previo de **Siddall et al. (1999)** que examinó el dolor en los primeros 6 meses de LM, no hubo ninguna relación entre alodinia y LM central o incompleta pero la alodinia se relacionó con la presencia de DN al nivel. Esto sugiere que la alodinia mecánica/ sensibilidad puede ser debida a diferentes mecanismos que la alodinia de comienzo temprano (**Siddall et al. 2003; 1999**) en las primeras etapas tras la LM. Esto es consistente con nuestros resultados, ya que el porcentaje de pacientes afectados más tarde cambió.

Una posible explicación será ampliamente explicada en el Capítulo 3, relacionada con posteriores cambios que ocurren en las vías espinotalámicas y el sistema de la columna dorsal, y la posibilidad de que el CPG pueda tener diferente importancia después de los primeros 6 meses de lesión.

Los datos obtenidos indican una disminución en la sumación temporal después de la LM que no ha sido descrita antes, y como tal puede representar un importante diagnóstico para la identificación del CPG en un momento temprano después de la LM.

2.5.3.2. Correlaciones

Como deducimos de nuestro estudio, la hiperalgesia mecánica en ambos niveles de lesión y el “wind up” y la alodinia térmica al nivel (evaluadas mediante las “Pruebas semi-cuantitativas de sensibilidad”) pueden ser herramientas útiles en el diagnóstico del DN en LM.

Nosotros consideramos que existe presencia de signos *evocados* de dolor neuropático cuando el VAS es mayor que 0, ya que algunos de estos signos son descritos por algunos pacientes como desagradables o molestos (VAS<2), pero no dolorosos (VAS>2) (**Ver Discusión del Capítulo 3**). Queda abierta la cuestión de si sólo debería considerarse la presencia de estos signos si el VAS es mayor que 2.

Nuestros resultados obtuvieron correlaciones altas con el estadístico Rho de Spearman en todos los signos de dolor al nivel de la LM y por debajo del nivel a los 2 meses. Las correlaciones negativas entre el VAS 7 días y los signos indica que éstos estuvieron presentes en mayor medida cuanto menos intensidad tenía el dolor espontáneo, ya que parecen presentarse en una etapa muy temprana de la LM. Una posible explicación podría ser debida a la naturaleza continua del DN, primero el paciente no sintió dolor espontáneo, pero a medida que el tiempo avanza, las parestesias se convierten en dysesthesias. También podría ser que la presencia de la hiperexcitabilidad neuronal desencadene el dolor *espontáneo* de los 2 a los 6 meses después de la LM. Por otra parte, tanto la alodinia mecánica, hiperalgesia mecánica, sumación temporal y alodinia térmica se hallan correlacionados positivamente entre ellos. Esto puede significar que los mecanismos implicados en el desencadenamiento de los signos de dolor evocados pueden ser los mismos, y éste podría ser el Generador de Dolor Central, que podría estar actuando ya en una etapa temprana del DN (2-3 meses), modulando las sensaciones anormales que se convertirán más tarde en dolor espontáneo. Una vez este mecanismo está instalado, sería más difícil controlar el dolor. Es por ello que en clínica se ha visto que un tratamiento temprano con Anticomiciales puede ser decisivo en el control del dolor en la fase crónica. Nuestras correlaciones negativas en la fase más aguda de LM indican resultados consistentes con los obtenidos por **Finnerup et al. (2004)**.

En contraste con las medidas a los 2 meses de LM parece desarrollarse una relación entre la alodinia térmica y el VAS 7 días al nivel de lesión a 6 meses, mientras que las correlaciones negativas entre signos de dolor *evocado* y *espontáneo* desaparecen. Las únicas correlaciones positivas y significativas entre signos al nivel de lesión que prevalecen son la sumación temporal y alodinia térmica al nivel en pacientes con lesiones dorsales, que pudo deberse a la mediación, ya que menos pacientes que a los 2 meses la presentaron. Las únicas correlaciones positivas y significativas al nivel que prevalecieron fueron: sumación temporal y sensaciones post-estímulo, alodinia térmica e hiperalgesia mecánica. Por debajo de la lesión, también positivas y significativas, prevalecieron la sumación temporal y sensaciones post-estímulo, y alodinia mecánica y alodinia térmica.

Como puede apreciarse, hay una pérdida de relaciones entre los signos de dolor *evocado* a los 6 meses a ambos niveles, indicando que otros mecanismos pueden estar presentes (quizá las implicaciones del cambio del tipo de lesión de la sustancia gris a sustancia gris y blanca). No obstante, permanecen constantes la sumación temporal y alodinia térmica, ambos al nivel de la LM, presumiblemente por una mayor actividad de las fibras C, asociada con la sensibilización central y posiblemente por la menor inhibición de las fibras A β y A δ sobre la actividad en las fibras C (**Wasner et al., 2004**), y provocada por la ya mencionada hiperexcitabilidad neuronal (**Finnerup et al., 2003b**).

Tanto **Finnerup y Jensen (2004)** como nosotros, proponemos que los mecanismos deberían tener en cuenta el tiempo requerido por el dolor para desarrollarse, es decir, destacamos la utilidad clínica de las medidas longitudinales a un año de la LM.

El hecho de que autores como **Finnerup et al. (2003b)** no detectaran sumación temporal al nivel de la LM se debería con bastante seguridad a que sus lesionados medulares fueron completos y crónicos (de varios años de evolución) y por lo tanto los procesos fisiopatológicos no estaban tan intactos a tiempos agudos (aunque presentaban alodinia), ya que nosotros sí tenemos datos al respecto. Además, otros factores como la sumación espacial de los estímulos puede ser crítica en diagnosticar sensibilización central. La sumación espacial también puede jugar un papel en relación a la hiperalgesia donde las neuronas del asta dorsal expanden sus campos receptivos y por tanto puede ocurrir más sumación espacial de la actividad entrante o de llegada (**Cook et al. 1987**), podría ocurrir también con la sumación temporal, donde las altas correlaciones tanto al nivel como por debajo así lo indican. Recientemente **Arendt-Nielsen et al. (1996a)** mostró facilitación de la sumación temporal en áreas hiperalgésicas, (como en nuestro caso ocurre en la prevalencia de la sumación temporal a los 2 meses tras la lesión) y por tanto sugirió que la sumación espacial estaría así facilitada. La razón para esta sugerencia es

que los antagonistas del NMDA inhiben la sumación temporal y la espacial, indicando que similares mecanismos neurales gobiernan en ambos tipos de sumación.

La presencia de la sensibilización central al nivel de la LM utilizando la técnica de sumación temporal de sensaciones nociceptivas ha sido reconocida como un signo clave de la presencia de dolor neuropático (**Eide et al., 1995**). Sin embargo, la sensibilización central no está presente en todos los pacientes con LM (**Finnerup et al., 2003b**), posiblemente por la falta de activación debido a problemas metodológicos de las pruebas utilizadas o diferencias en las patologías asociadas a la LM (daño a las estructuras periféricas y centrales).

De la Entrevista Basada en Mecanismos de Dolor Neuropático, donde el análisis reveló que fueron significativas las preguntas relacionadas con el dolor continuo y el número de descriptores, tanto al nivel como por debajo de la lesión, y el dolor evocado mecánico dinámico al nivel a lo largo de las medidas, podemos decir que los pacientes no distinguieron claramente entre las áreas del cuerpo afectadas y entre el dolor espontáneo y evocado. Parece que los pacientes no tomaron en cuenta que signos de dolor como la hiperalgesia mecánica, sumación temporal y alodinia térmica realmente incrementaron su presencia desde los meses 3 al 6. Además, observamos que todos los pacientes respondieron a las preguntas con mayores puntuaciones en el comienzo (2 meses tras la LM), posiblemente debido a un peor entendimiento del DN, y al hecho de que hasta el mes 6 comenzaron a aumentar sus puntuaciones quizá debido al final de la rehabilitación y a la vuelta a su actividad, con todas sus implicaciones emocionales (**Ver capítulo 4**). La entrevista reveló que los exámenes de dolor evocado como las “pruebas semi-cuantitativas de sensibilidad” son muy útiles para el estudio de las fibras y vías implicadas en el proceso de DN, información que no pareció apropiadamente proporcionada por los propios pacientes o incluso con la ayuda de la entrevista semi-directiva.

La tendencia observada en el grupo cervical por debajo del nivel a lo largo de los 12 meses fue el decreciente número de dermatomas implicado en dolor espontáneo y evocado, mientras que el grupo dorsal tendió a incrementar el número de dermatomas en ambos. Al nivel de la lesión, el grupo cervical tendió a ser más constante y el dorsal más heterogéneo en el tiempo.

De esta manera, los dermatomas a cualquier nivel encontraron una relación consistente también con las correlaciones espontáneas y evocadas vistas previamente (por ejemplo, en las correlaciones significativas entre el VAS de 7 días y los dermatomas a 6 meses). En pacientes con lesiones dorsales, la correlaciones en el mes 6 al nivel de la lesión indicaron que los dermatomas implicados en el dolor evocado tienen una alta relación con la alodinia mecánica, ya que ninguna correlación significativa fue vista con otros signos, este pareció ser el signo más importante a los 6 meses de lesión. Sin embargo, en el grupo de cervicales, los dermatomas evocados están en relación con el VAS de 7 días de dolor espontáneo más que con los otros signos, lo cual puede predecir que los pacientes con lesiones cervicales presentaron dolor evocado observando las puntuaciones en dolor sufrido.

Así, en general podemos sugerir que a más dermatomas implicados en el dolor (espontáneos y evocados), más intensidad de dolor sufrirá el paciente, al menos como se ha visto en la fase aguda y hasta un año después de la LM.

2.5.4. Lesiones de la Sustancia Gris y Sustancia Blanca

Como se ha demostrado en nuestros datos, existen diferentes tipos de lesiones medulares (completas versus incompletas, cervicales versus dorsales), y las lesiones de la sustancia gris pueden tener distintas características histopatológicas comparadas con las de sustancia blanca (**Catalaa et al. 1999**). Por ejemplo, en los pacientes de **Finnerup (2003b)** con dolor por debajo se observó, con técnicas de neuroimagen, *más hipersensibilidad sensorial al nivel* que en los pacientes sin dolor y estos presentaban a su vez mayores lesiones de sustancia gris en el extremo rostral de la lesión (**Finnerup et al., 2004**).

Aunque nuestro estudio no aporta datos de resonancias magnéticas (**Ver Capítulo 3**), tanto pacientes completos como incompletos evaluados al nivel de lesión presentan un cambio en la intensidad del dolor sobre todo a partir de la fase aguda en adelante (más de 6 meses de lesión) (**Fig.2.12 and 2.14**) así como un aumento de la prevalencia de hiperalgesia mecánica, alodinia térmica y sumación temporal al nivel, lo que también podría significar un aumento de la hiperexcitabilidad mencionada.

Vierck et al. (2002) describe que la lesión medular traumática por desplazamiento vertebral (el caso más común en LM según los facultativos) comienza con daño isquémico y traumático en la sustancia gris y progresa con el tiempo hasta involucrar a la sustancia blanca. Así, la destrucción excitotóxica de la sustancia gris es una característica preliminar y prominente de la lesión medular clínica. Por esto, los tratamientos tempranos dirigidos

a limitar la isquemia, inflamación y excitotoxicidad pueden reducir la típica progresión del daño a la sustancia gris (Yeziarski, 2000), y por lo tanto los síntomas de dolor crónico y síndrome de espasticidad (espasmos y coactivación de antagonistas) pueden ser también eliminados. Dependiendo del patrón inicial de la lesión, el daño a la sustancia blanca también puede ser reducido, ya que mucho de este daño ocurre progresivamente con formación de cavidades quísticas (Yeziarski 2000).

En monos se ha demostrado que los que han recibido cordotomías anterolaterales a nivel medial (con daño de la sustancia gris) desarrollan signos de dolor por debajo del nivel, mientras que las lesiones superficiales (confirmadas por histología) no la presentaban (Vierck et al. 1990). Esto sugiere que, mientras los tractos de la sustancia blanca juegan un papel en el desarrollo del dolor central después de la lesión medular, la combinación de trauma en la sustancia gris y blanca es responsable del comienzo del dolor neuropático por debajo de la lesión. (Gonzalez-Valdizan et al., 2004)

El DN por debajo de la lesión ocurre tanto en sujetos con sección medular incompleta (Beric 1990) como completa (Finnerup et al., 2003b). Esto sugiere que el dolor neuropático por debajo se desarrolla gracias a la lesión de la sustancia gris, o por la completa interrupción de la sustancia blanca y gris. En lesiones experimentales de la sustancia gris con aminoácido excitatorio EEA (Yeziarski, 2000) se ha comprobado que no sólo el glutamato y el receptor NMDA contribuyen al daño tisular, sino también los receptores no-NMDA; lo que ofrecerá interesantes investigaciones futuras en diagnóstico y tratamiento. Un estudio identificó la extensión de sustancia gris-blanca viable en el área de lesión y la utilizó eficientemente como “puente de tejido neural”, como nuevo tratamiento extra-vertebral para lesión medular incompleta (Krishnan, 2003). (Ver Appendix Picture 2.2.)

2.5.5. Beneficios del estudio.

Pudimos determinar el papel de los procesos fisiopatológicos durante el desarrollo del DN al nivel y por debajo del nivel de lesión, a los diferentes tiempos 2, 3, 4, 6 y 12 meses después de la LM. El simple y útil VAS es capaz de guiar estudios como este y centrarse en evaluaciones subjetivas de dolor espontáneo y comparar medidas de dolor evocado, incluso para correlacionar ambas medidas como hemos visto. Las tendencias evolutivas mostradas aquí pueden ser muy útiles como futura base para otros estudios de dolor, ya que el análisis longitudinal ha mostrado que los diferentes mecanismos neurales operan en fases agudas y crónicas de la LM. De hecho, el Generador de Dolor Central (CPG) puede ser el responsable en el desarrollo del DN al nivel y por debajo del nivel en la mayoría de los pacientes en los estadios tempranos, el cual es un importante factor al que prestar atención para la búsqueda de nuevos tratamientos en el proceso de dolor.

También es interesante el que la Entrevista Basada en Mecanismos de Dolor ha mostrado diferentes y nuevos resultados de las “Pruebas semi-cuantitativas de sensibilidad” (BST) en el subjetivo punto de vista de los pacientes que comenzaron a conocer mejor su dolor desde el mes 4º después de la LM.

2.5.6. Limitaciones del estudio.

La principal limitación fue la cantidad de datos perdidos principalmente en el mes 12 después de la lesión, ya que fue menos posible para los pacientes completar la evaluación. Por esta razón, el n fue reducido hasta hacer el análisis imposible en algunas ocasiones y en otras, sólo hizo posible dibujar una tendencia de lo que pudo haber ocurrido evolutivamente en nuestros pacientes. Otra limitación fue la medicación para obtener tasas en la escala VAS de los signos de dolor evocados, aunque el tratamiento farmacológico no pareció afectar al dolor espontáneo informado por los pacientes en ninguno de los VAS examinados. Como el VAS fue en general muy bajo para los signos evocados, quizá no podemos concluir que los pacientes presentaron algunos signos como la alodinia térmica o la hiperalgesia, donde implican una condición de puntuaciones altas de dolor.

2.5.7. Nuevas Líneas de Investigación

El CPG proporciona una explicación basada en mecanismos que trata el desarrollo del DN en fases muy tempranas de la LM, y abre nuevas direcciones en investigación, tales como un análisis de los mecanismos del DN al nivel de la lesión medular basado en la evaluación cuantitativa de la sumación temporal del dolor utilizando un nuevo sistema de estimulación TSAR (tipo Peltier) (Vierck et al., 1997), y a la vez investigar el papel del sistema propioespinal en la modulación del DN debajo de LM junto con la hiperexcitación neuronal ya mencionada (Ver capítulo 3).

Nuestra hipótesis es que la utilización de la técnica TSAR, sola o en conjunto con otros estímulos, es capaz de activar procesos de hiperexcitabilidad central en pacientes agudos después de la LM, ya que parece ser una metodología más potente que las actuales, quizá dando respuesta a por qué signos clave de la presencia de dolor neuropático como la sumación temporal a veces no está presente en todos los pacientes con LM. En el **capítulo 3** identificamos y analizamos las características espaciales y temporales del CPG a diferentes niveles de la LM, llevando a cabo un análisis psicofísico de la función estímulo-respuesta con estímulos nociceptivos de larga duración (**Morin et al. 1998; Koyama et al., 2004**) y examinar la sumación temporal entre otros signos evocados (**Vierck et al., 2002**). En un futuro, los resultados de este proyecto serían capaces de mejorar el diagnóstico y pronóstico del DN asociado a la LM, más concretamente creando una nueva metodología muy útil tanto para Unidades del Dolor y para estudios experimentales de investigación.

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CHAPTER 3.

BEDSIDE/QUANTITATIVE SENSORY TESTING AND TONIC THERMAL PSYCHOPHYSICS FOR THE ASSESSMENT OF SENSORY FUNCTION AFTER SPINAL CORD INJURY

3.1. Introduction

In this chapter we present a detailed diagnostic study of NP in acute (4-6 months after injury) and chronic SCI patients with Syringomyelia compared to No-NP and healthy volunteers using different diagnostic methods: including the DN4 questionnaire, Quantitative Sensory Testing stimulation (QST) and a new peltier stimulation device called the Thermal Stimulus and Response system (TSAR), to reveal which pain mechanisms may be present in patients suffering from SCI-NP, and to investigate further the role of a local Central Pain Generator (CPG) in its generation.

3.1.1. Neuropathic Pain Diagnostic Questionnaire: Discrimination between neuropathic and nociceptive pain.

Clinically, neuropathic pain is generally characterized by the association of unspecified positive and negative sensory symptoms, although there is still no consensus concerning the diagnostic criteria for neuropathic pain (**Jensen et al., 2001; Hansson, 2002; Woolf and Mannion, 1999; Dworkin et al., 2003**). Traditionally, the diagnosis of neuropathic pain has relied largely on sensory examination rather than on pain descriptors, which have not been accepted as sufficient for the diagnosis of neuropathic pain (**Baron, 2000; Jensen et al., 2001; Hansson, 2002; Dworkin, 2002; Rasmussen et al., 2004**). However **Bouhassira et al. (2005)** has developed a questionnaire, useful as a screening tool for the identification of patients with NP compared to those with nociceptive pain, and identifies several pain symptoms that are preferentially expressed in NP patients with a clear discriminant power. In particular, the association of painful symptoms and paraesthesia/dysesthesia using this questionnaire has a high specificity and diagnostic value, and the good discriminant properties of the items based on the interview alone (i.e. DN4-interview) suggests that this questionnaire could be used in a very large range of clinical studies including, for example, telephone surveys and epidemiological studies (**Bouhassira et al., 2005**). Specifically several items such as the descriptors “burning”, “electric shocks” and “tingling” have important discriminatory power between patients with NP and nociceptive pain.

3.1.2. Quantitative Sensory Mechanical Testing (QST) for SCI NP.

Finnerup et al. (2003b) examined sensory detection and pain thresholds above injury level in SCI patients with central NP, SCI patients without NP, and in 20 control subjects. The SCI pain group had significantly higher cold and warm detection thresholds compared with the pain free subjects and higher tactile detection thresholds compared with the SCI pain free group and found no difference in pain or pain tolerance thresholds among pain and pain free SCI patients. These data suggested changes in somatosensory function (hyperexcitability) in dermatomes rostral to the segmental injury level linked to the presence of central NP in SCI patients, and also changes in pain inhibitory and facilitating systems. Standard neurological tests of pain signs (**Finnerup et al, 2003b**) permit an approximation to the central mechanisms present after SCI and include signs like dynamic allodynia, mechanical hyperalgesia and hyperalgesia to cold present at level of the injury though temporal summation was not present (**Finnerup et al, 2003b, Eide et al., 1996**). It is noticeable that the majority of NP patients included in the study of **Finnerup et al. (2003b)** were SCI patients with complete lesions and therefore physiopathological processes that provoke a central sensitization were not so much intact than in NP

patients with incomplete lesion. Based on this research, SCI patients with *central* pain presented hypersensitivity more frequently in the dermatomes corresponding with at level of the lesion than those without pain and found a significant correlation between the intensity of dysesthesia evoked by brush at level of SCI and *ongoing* pain below the level of lesion.

The QST by thermal noxious stimuli is considered a useful model for psychophysical assessment of pain perception in healthy individuals as well as pain patients (**Gruener and Dyck, 1994; Kalman et al., 1999; Khalili et al., 2001; Meier et al., 2001; Verdugo and Ochoa, 1992; Yarnitsky et al., 1995; Granot et al., 2003**). A complete diagnosis of NP after SCI should include a patient description and course of the complaint, and also a psychophysiological evaluation of spinothalamic and dorsal column system dysfunction and clinical neurophysiological assessment of peripheral nerve and spinal cord functions below the level of the lesion (**Beric et al., 1988**). Routine QST can often be performed using inexpensive and reliable tools like the Rydell–Seiffer graduated tuning fork, which measures vibration thresholds and is clinically useful, particularly as a statistically significant decrease in vibration sensitivity in individuals with PHN versus age-matched healthy controls (**Whitton et al., 2005**). **Eide et al., (1996)** obtained significant results in QST using 6.65 units von Frey filaments for rating the temporal summation. Several of the patients reported a stinging, pin prick-like sensation in denervated skin areas that was more prominent than the thermal sensation, that was demonstrated three times more often in painful than non-painful denervated skin areas. Their tactile sensibility was more reduced in non-painful than in painful denervated areas (though not significant). QST technique of two point discrimination found to be reduced in Syringomyelic patients versus non NP patients only at level, which could mean an increased cortical representation (**Song et al., 1993; Ducreux et al., 2006**) of the level of lesion only in chronic patients with central pain and an extensive lesion, as no difference was found with NP acute patients.

The pathophysiology of sensory loss which accompanies chronic pain after SCI has led to several hypotheses (**Defrin et al., 2001**). An early case reported by **Browder and Gallagher (1948)** suggested that chronic pain might develop following lesion of the dorsal columns (DC). This hypothesis was not supported by subsequent observations showing that discrete lesions of the lemniscal system gave rise only to paraesthesias and not to chronic pain (**Cassinari and Pagni, 1969; Pagni, 1977**). In a later study **Beric et al. (1988)** examined 13 SCI subjects with chronic pain. These subjects exhibited an almost complete loss of temperature and thermal pain sensations below the level of lesion, whereas vibration and touch sensations were significantly less impaired (**Beric et al., 1988**). **Beric et al. (1988)** found vibratory sensibility was present, although reduced in the 77%, and touch perception was diminished but preserved in the 69% of incomplete SCI patients. Statistical analysis showed highly significant difference between vibratory perception and light touch perception. The authors concluded that an imbalance in function between the spinothalamic and DC systems was the main underlying cause of this central pain.

3.1.3. Psychophysics to Quantitative Sensory Thermal Testing

The Thermal Stimulus and Response system (TSAR), developed by some authors (**Mauderli et al., 2003; Vierck et al., 1997**) provides stimulus-response characteristics over the combined intensity and frequency stimulus configuration. Previous studies, like **Morin and Bushnell's (1998)** used various cold temperatures ranged from -5° to 23° C and heat temperatures from 41° to 48° C and found that 47° C and 9° C were heat and cold pain threshold respectively (VAS=5) in healthy subjects. With fibromyalgia patients, a gradual method was used to tolerate painful stimuli with a rate of continuous temperatures and the area of the body could habituate better to a noxious stimulation (**Staud et al., 2004**).

Defrin et al.(2002) conducted quantitative and qualitative somatosensory testing in spinal cord injury subjects who suffered from partial or complete loss of thermal sensibility. In areas lacking any thermal sensibility, warm and cold stimuli produced a sensation of pricking pain, with no thermal quality and was detected at significantly higher thresholds than in normal controls (48.5 ± 1.8 and 9.7 ± 5.1 degrees C for noxious heat- and noxious cold-induced pricking pain, respectively). Cold stimuli were

perceived as warm in areas in which only warm sensation was preserved, and vice versa. These data suggest that the integrity of non-noxious thermal systems is essential for the normal perception of thermal pain, and that the subjective sensation of pain depends on the integration of information from nociceptive and non-nociceptive channels.

Using threshold values for detection of thermal (heat, cold, heat pain, or cold pain) stimuli **Beric et al. (1988)** identified that in a majority of patients with incomplete SCI lesions that thermal detection and pain thresholds below the level of injury were absent in 77% of patients and only 15% detectable thermal pain but impaired perception. Statistical analysis showed highly significant difference between temperature and pain perception, and a difference between temperature and pain perception. In a recent study conducted by **Eide et al. (1996)**, painful and non-painful skin areas below the level of lesion, were examined in 16 SCI patients with chronic pain. Both skin areas showed a reduction in thermal (temperature and thermal pain) compared to normal areas above the lesion, but the reduction in thermal sensibilities in the pain free areas was much smaller in magnitude, although there was no significant difference in thermal (or tactile) sensibilities between painful and pain-free areas (**Eide et al., 1996**). Based on these findings the authors concluded that central pain was not dependent on the damage to either the spinothalamic tract or dorsal column pathways, but more probably on hyperexcitability of nociceptive neurons.

3.1.4. Central Pain Generator Hypothesis (CPG) and SCI Neuropathic Pain

SCI patients with and without pain present similar levels of reductions in thermal or mechanical detection thresholds and pain thresholds, and sensory-evoked potentials (see **Chapter 2, section 2.1.3**), although patients with pain below the level of the lesion showed significantly more *hypersensitivity* at level than patients without pain (**Finnerup and Jensen, 2003b**), and presented greater grey matter lesions at the rostral end of the injury, observed by magnetic resonance (**Finnerup et al., 2003a**).

This data, taken together with **Vierck and Light's (1999; 2000)** original suggestion that a spinothalamic pathway lesion by itself does not fully explain the development of central pain in patients, implicates the required additional activation of neuronal hyperexcitability initiated by excitotoxic changes and injury to local inhibitory neurons at the rostral end of the lesion, maybe an important additional mechanism for below level pain. Thus, SCI central pain may be the result of deafferentation-induced supraspinal changes and abnormal sensory input from a local spinal generator (**Finnerup and Jensen, 2004**). However not all patients with SCI present signs of central hyperexcitability (**Finnerup et al., 2003b; Finnerup and Jensen, 2004**), indicating that other mechanisms must also be present. Indeed NP following SCI represents a heterogeneous pain condition which may depend on the presence of different mechanisms (**Finnerup and Jensen, 2004**).

3.1.5. Central sensitization measured with tonic heat and cold stimuli

Although it is assumed that the process of “temporal summation” to repeated noxious stimuli cannot plausibly explain the long-lasting perceptual changes experienced in chronic pain (e.g. **Woolf, 1996**) and that “wind-up” is not central for the development of chronic pain, the clinical observation of enhanced sensitization as a clinical marker in some chronic pain syndromes remains. Indeed long-term-potential (LTP) in spinal nociceptive neurons (**Li et al., 1999**) and cerebral nociceptive neurons (**Chen et al., 2000; Kleinböhl et al., 2002**) has been observed. Furthermore mid- and long-term changes in perception, such as hyperalgesia and habituation, occur and may interact with short-term processes of central sensitization.

In general there is a lack of psychophysical experimental pain procedures that provide a basis for the characterization of dynamic aspects of pain plasticity such as changes in sensitization. To date perceptual sensitization has been studied with temporal summation models for contact or radiant heat (**Nielsen and Arendt-Nielsen, 1998; Price et al., 1977**), electrical (**Arendt-Nielsen, 2000**) and finally mechanical stimuli (**Magerl et al., 1998**). **Kleinböhl et al. (1999)** used a tonic heat paradigm - the

“dual sensitization” procedure which provided a subjective and behavioural index of sensitization (Kleinböhl et al, 1993; Van Ackern et al., 1994; Kleinböhl, 1996) - to assess early sensitization (15-100 sec), concluding that the degree of sensitization was linearly related to stimulus temperature, and that the “sensitization gradient” was significantly earlier in musculoskeletal pain patients than in healthy subjects. A further development has recently been made with this technique Kleinböhl et al. (2006) permitting concurrent assessment of short-term sensitization and medium-term habituation, assumed to be related to spinal “wind-up” and cutaneous nociceptive fibre fatigue, respectively.

3.1.6. Sensory function in Syringomyelia neuropathic pain patients.

In general very few studies have been performed examining pain related Syringomyelia, the chronic development of fluid-filled cavities in the spinal cord that may lead to spasticity and other sensory disturbances. Beric et al., (1988) reported a case of a patient with burning dysesthesias below the level of the cyst (C7) and absence of touch but patchy preservation of sensory functions (vibration, thermal sensation, thermal pain) in the lower extremities possibly indicating the importance of disproportionate spinothalamic system dysfunction in contrast to the dorsal column system. In a more specific study, Attal et al., (1999) found central neuropathic pain in 66% of their Syringomyelia patients and deficits in temperature and pain sensibility in 94% of the cases, often associated with deficits in vibration and touch sensitivity. Somatosensory evoked potentials were abnormal in 61% of the cases at level, and showed good correlation with deficits in vibration. The magnitude of the thermal and tactile deficit was similar between areas of spontaneous pain and adjacent non painful areas. More recently, Bouhassira et al. (2006) found no significant difference in the magnitude of sensory deficits between Syringomyelia patients with or without NP, but a different pattern of sensory deficits was observed between patients with spontaneous pain only and both spontaneous pain and allodynia, suggesting that central neuropathic pain due to this pathology cannot be considered as a simple central amplification of normal pain. Both psychophysical and functional neuroimaging data demonstrated that different central NP symptoms are sustained by distinct mechanisms. Perhaps it is important to note that a role for a CPG, as identified previously in SCI and NP (Finnerup et al., 2003b), is not thought to be an overriding mechanism in patients with pain after Syringomyelia.

3.2. Objectives

3.2.1. Study objectives

1. To examine the differences between SCI Neuropathic Pain (NP) patients and subjects without NP (Syringomyelia-SYR; SCI without Neuropathic Pain SCI-NoNP; and Healthy Volunteers-HV) using standard QST tests, and assess the possible involvement of the Central Pain Generator (CPG) operating at, below and above the level of the injury.
2. To identify differences between SCI-NP patients and subjects without pain (NP, SYR vs NoNP, HV) using noxious controlled thermal stimulation applied with the TSAR system, and identify the involvement of the CPG operating at, below and above the level of the injury.
3. To assess whether patients with NP after Syringomyelia (SYR) are distinct from the other subject groups (NP, NoNP, HV) with respect to sensitivity and response to noxious thermal stimulation (QST and TSAR).
4. To examine the utility of the DN4 Questionnaire in discriminating between NP patients and patients without NP (SYR vs NoNP) and with regard to pain descriptors previously identified in other SCI pain studies.

3.2.2. Study hypothesis

The CPG and associated damage to the mayor ascending tracts (spinothalamic and dorsal column) are responsible for the development of NP at and below the level of SCI in the majority of patients, and that Bedside Sensory Testing, Quantitative Sensory Testing and the Peltier TSAR systems are valid instruments for its assessment.

3.3. Methods

3.3.1. Criterion of Selection

3.3.1.1. Inclusion Criteria

Subjects of the present study were recruited at the Paraplegic National Hospital of Toledo (Spain), originally from most of the autonomic regions in Spain. We revised a total of 1630 clinical histories of in-patients from September 2004 to December 2005, finding that 52 of them were appropriate for our study according to the strict criteria defined below. All of these subjects participated as volunteers, from the 1st of October 2004 to the 22nd of December 2005. All procedures were approved by the Human Ethics Committee (Comité Ético de Investigación Clínica del “Complejo Hospitalario de Toledo”-SESCAM). The patients were informed of the nature and purpose of the study and then recruited after voluntarily signing a consent form and were free to withdraw the study at any time.

The inclusion criteria were similar to those described in Chapters 2 and 4: patients with central neuropathic pain initially described as “burning” and/or “pressing”, scoring more than 3 out of 10 on the VAS ratio scale (where “0” – no pain and “10” maximum pain imaginable). Patients with complete or incomplete motor-sensitive spinal cord lesion (according to the American Spinal Injury Association - ASIA scale A, B or C) above the T10 level, and were assessed from 4-6 months after the trauma (acute phase). The accepted age was between 18 and 75 yrs and all subjects understood and spoke Spanish. In addition patients could manifest any other type of pain distinct from neuropathic pain, as long as that it was less severe (nociceptive, osteomuscular, oncological etc.). Patients with spasm-related NP were permitted, independent of the level of localization. Most patients received standard analgesic treatment that was prescribed in our hospital at the time of diagnostic assessment. A total of 36.7 % of our patients were medicated with Amitryptiline and/or Gabapentin, and 42.9 % described some “unpleasantness” or dysesthesia/ pain although were not medicated. A total of 11 healthy subjects were chosen in ratio male-female 60 /40 as male population in patients were found higher than female in all the groups tested.

3.3.1.2. Exclusion Criteria

Patients presenting psychogenic pain, multiple sclerosis, cognitive impairment, absence of oral language, severe hypoacusia, demency or only peripheral neuropathies or complex regional pain syndrome (CRPS) were excluded, as well as the patients who were not able to be tested in the first pre-treatment diagnostic session. No signs of peripheral nerve disease were encountered in our study (data from one subject was discarded because of a probable peripheral neuropathy in both feet. Patients with spasms not related to NP were also excluded.

3.3.1.3. Experimental study groups

The subjects were assigned to one of the following groups: SCI patients (No Neuropathic Pain “NoNP”, Neuropathic Pain ‘NP’, Syringomyelia ‘SYR’) and lastly Healthy Volunteers as controls “HV”. Moreover, in some diagnostic tests (TSAR test) SCI patients were subdivided into those with cervical and thoracic lesions, according to the trends observed in Chapter 2. The NoNP group (n=10) was constituted by 5 patients with cervical lesion and 5 with thoracic lesion. The NP group (n=19) was represented by 9 patients with cervical lesion and 10 with thoracic lesion. The SYR group (n=10) was constituted by 5 patients with cervical lesion and 5 with thoracic lesion. Finally in the HV group (n=11) 6 subjects were tested at the cervical site and 5 at the thoracic site.

3.3.1.4. Patient Study General Design

All procedures were approved by the Human Ethics Committee (Comité Ético de Investigación Clínica del “Complejo Hospitalario de Toledo-SESCAM”) in accordance with the Declaration of Human Rights, Helsinki, 1975. The patients were informed of the nature and purpose of the study and

voluntarily signed the informed consent form by which they entered to participate in our research project, allowing them to abandon the study of their own free will.

3.3.1.5. Experimental procedure

The complete sensory testing procedure was performed the same in healthy volunteers and those with SCI. Initially the informed consent was signed voluntarily by the patient after a brief description of the objectives and experimental procedures involved. The researcher first applied the brief DN4 questionnaire to patients and healthy volunteers alike. The subject was instructed to close his eyes during the mechanical punctate threshold determination using von Frey filaments, and then the other tests were performed. The exact experimental procedures for each sensory test is described below (**section 3.3.2.2**).

Thermal QST examination with the Peltier-TSAR device was realized in the following manner. The subject was guided in his wheelchair or chair in close approximation to the thermode so that the desired dermatomes were easily accessible for testing. A brief training session of approximately 10 minutes was followed for all subjects, which consisted of a practice session with electronic-VAS potentiometer with when possible with the dominant hand (see section below) and visual feedback screen, and understanding of the four groups of qualitative verbal descriptors (see section below). The cervical or thoracic dermatomal areas associated with the most unpleasant or painful sensation in each patient was tested. Below level thermal failed to induce either sensory or pain perception following thermal stimulation. As such the data was not analyzed.

When possible subjects were tested in one session, with small breaks of at least 1 minute between the different temperatures applied and about 5-10 minutes between the different sites tested in the body. The thermode was placed slightly adjacent to each testing site to avoid sensitization of the skin. Subjects first received a 30s heat stimulus (48°C in the majority of subjects when it was well tolerated during the first 10 sec, and at 43°C if not tolerated). Following a 1 min. interval, the 30s “dummy” stimulus (33°C) was applied, and then after another 1 min. break, the 30s cold stimulus (3°C in the majority of subjects when it was well tolerated during the first 10 sec, and at 13°C if not tolerated). Each of the three temperatures were presented to the three testing sites: below the level of the lesion (usually L4 or L5), at the level of the lesion (on the dermatome coinciding with his own lesion) and above the lesion level (at the C2 dermatome, face, in all subjects). In healthy volunteers the C2 and L4/L5 dermatomes were stimulated, while the C6 area (dorsum of the hairy forearm) and T6-7 dermatomes were adopted to assess “typical” at level cervical and thoracic testing sites.

During the 30s thermal stimulus, and for the subsequent 120s, the subject continuously rated his thermal sensations using the e-VAS and visual feedback presented by a PC monitor screen, and at the same time chose one or more descriptors from the list of four groups of sensory adjectives. The location of post-stimuli sensations were assessed for each subject with the help of the dermatomal map presented on a board.

3.3.2. Diagnostic Questionnaire and Quantitative Sensory Testing

3.3.2.1. DN4 Questionnaire

The questionnaire called the “Douleur Neuropathique 4 questions” was created by the French Neuropathic Group lead by Dr. Bouhassira, based on a prospective study designed to discriminate patients with chronic neuropathic pain associated with neurological (peripheral or central) or somatic tissue injuries with other types of pain (musculoskeletal, visceral). The “DN4” is a clinician-administered questionnaire which has been deliberately simplified to a minimum number of items. A score of “1” is given to each positive item and a score of “0” to each negative item. The total score is calculated as the sum of the 10 items and the cut-off value for the diagnosis of neuropathic pain is a

total score of “4”. Thus, this new diagnostic tool can be easily used by pain specialists or non-specialists in daily clinical practice as a screening tool to better those patients with neuropathic pain. In addition the “DN4” presents good discriminant properties based on the 7 descriptor items obtained from the interview alone and not with bedside sensory testing. The adopted adjectives and clinical relevance of these items, and indeed the whole questionnaire has been considered as useful by a large majority of patients and investigators (90–95% in **Bouhassira et al., 2005**).

The Spanish version of the DN4 questionnaire (included in **Appendix Protocol 3.1.**) has just been developed by us in collaboration with another three Spanish national hospitals and the support of Dr. **Bouhassira** and the pharmaceutical company **Pfizer**. We translated the questionnaire into Spanish reviewing the original DN4 in French and the English translation (**Bouhassira et al. 2005** and contact via e-mail in 2005). This translation was performed using the iterative forward–backward translation sequence. The McGill-SF-MPQ (Spanish version) and the Health Utility Index Mark 3 (Spanish version) were used to validate the DN4. Although the Spanish validation of the DN4 was not an objective of this thesis work, the major results are presented here in the methodology section.

This questionnaire included a series of four questions consisting of both sensory descriptors and signs related to bedside sensory examination (see **Appendix Protocol 3.1.c**). Sensitivity to touch and pin prick was made by means of a soft brush (No.10 “Pappel” 972 Germany) and a Von Frey hair (16 mN). The soft brush (three strokes of 4-5 cm) was also used to evaluate tactile (i.e. dynamic mechanical) allodynia. Pressure allodynia (i.e. static mechanical allodynia) was tested by blunt pressure with a finger at a pressure that did not provoke pain in a normal area (see **Bouhassira et al., 2005**).

In the first analysis for the Spanish validation of the DN4 a total of 164 subjects (99 women, 60.4%; mean age: 60.4±16.0 years), 94 (57.3%) with NP and 70 with NoNP, were included in the study. DN4 showed good reliability estimators; Cronbach’s alpha coefficient: 0.71, inter-rater agreement coefficient: 0.80 (0.71-0.89), and the test-retest intra-class correlation coefficient: 0.95 (0.92-0.97). Validity for a cut-off value ≥ 4 points, which was the best value to discriminate between patients with NP component of pain, was acceptable: Kappa’s agreement coefficient; 0.57 (0.44-0.69), area under the curve 0.846 ($p < 0.0001$), sensitivity; 80.9% (72.9%-88.8%), specificity; 75.7% (65.7%-85.8%), predictive positive value; 81.7% (72.4%-89.0%), and predictive negative value; 74.6% (64.5%-84.8%). With this analysis we concluded that the Spanish version of DN4 scale was reliable, stable and valid for the differential diagnosis of neuropathic pain conditions.

A second analysis was done with the same sample (164 subjects) divided in different groups: 57.3% with NP [36 (38%) peripheral, 32 (34%) central], 26 (28%) with musculoskeletal pain (MP), and 43% of the total with NoNP, were included in the study. A cut-off value ≥ 4 points was the best value to discriminate between types of pain. Kappa’s agreement coefficients were 0.57 (IC 95%: 0.44-0.69), 0.58 (0.45-0.71) and 0.55 (0.40-0.71) in all patients, and after excluding MP and central NP subjects, respectively. Sensitivity and specificity values were 80.9% (72.9%-88.8%) and 75.7% (65.7%-85.8%) in the whole sample, 82.4% (73.3%-91.4%) and 75.7% (65.7%-85.8%) excluded MP patients, and 83.3% (71.2%-95.5%) and 75.7% (65.7%-85.8%) excluded central NP patients.

In conclusion, the Spanish version of DN4 scale was reliable, stable and valid for the differential diagnosis of neuropathic pain conditions, as it was able to differentiate the neuropathic and nociceptive component of pain, with the same cut-off value than in the original version. These properties were maintained in patients with central pain or mixed pain component (radiculopathies) (**Huelbes et al., 2006, to be publish**).

3.3.2.2. *Quantitative Sensory Testing (QST)*

All sensory tests were carried out by the same examiner (S.H.A), and care was taken to avoid patient stress during testing. The subject was comfortably seated in his wheelchair or a chair in a quiet room, and was instructed to close his eyes only during the von Frey assessment. Somatosensory testing was

achieved on the site of the cervical or thoracic area more unpleasant or painful to the patient in case we could choose between different dermatomes. We stimulated within three different areas of the body: below the level of the lesion (usually L4 or L5 vertebral), at the level of the lesion (on a dermatome coinciding with his own level of the lesion) and above of the level of the lesion (C2 corresponds with the face and was the control site for all the subjects). At and below the level of the lesion could or could not be a denervated skin area. In healthy volunteers we stimulated the same sites, and chose C6 (dorsum of the forearm, hairy skin) as the dermatome for cervical stimulation and T6-7 for thoracic stimulation.

The following pain signs were rated for the intensity induced following mechanical stimulation using a modified visual analogue scale (VAS, **see Chapter 1**), that included pain threshold as “2”: Heat and cold pain/sensibility (tested using a heated test-tube filled with water at 48°C, one drop of Acetone and the Tip Therm® to assess cold pain), Mechanical allodynia/sensibility (Dynamic Allodynia) using 5 strokes with a coarse brush (**see characteristics below**), Temporal Summation to 50 brush strokes applied approximately every 0.5 s, from initial to final intensity VAS response, Static allodynia/sensibility (Punctate allodynia, assessed using 5 von Frey stimulation applied at patient threshold at approximately every 0.5 s), Temporal summation to 50 repeated von Frey filament stimuli applied at 3 times patient threshold for pain detection (from initial to final intensity VAS response). The following sensory tests were assessed by detecting an affirmative perceptual response from the patient: Mechanical threshold (Tactile sensation using von Frey filaments), Vibration sensation (Rydell-Seiffer tuning fork) and two-point discrimination (identifying the minimum separation detected in mm, **see Picture Appendix 3.1**).

Sensory testing was based on the original QST studies performed by **Eide et al. (1996)** and **Gottrup et al. (1998)**, with further refinement of the methodology acquired by the examiner (S.H.A) following her supervision by Professor Nurmikko and Bowsher of the the Pain Relief Foundation in Liverpool (United Kingdom) and finally helpful comments from Dr. Schweinhardt (Oxford, United Kingdom). The QST tests for the sensory assessment in patients were performed and completed in the following order (see **Chapter 3 Appendix** for sensory protocol testing):

1) Punctate tactile detection threshold was defined as the smallest force necessary for patient perception in response to one von Frey filament bending On the skin (Marstock-Nervtest Optihair₂ von-Frey filaments, Dr Fruhstorfer, Marburg, Germany, with a range of force strengths graded from 0.50 mN to 512 mN - equivalent to 0.051 g and 52.2 g respectively). The examiner used increasing von Frey filament strengths until the subject perceived sensation (ascending order) and then decreased the von-Frey force until the subject affirmed that he could not perceive it (descending order). This up/down protocol was repeated three times until threshold was defined. A “dummy” von Frey test was performed between the series by attempting to apply the von-Frey on the skin, ensuring that no contact was made with skin using the filament.

2) Vibration perception was tested over a bony site at the three levels, with a portable tuning fork (Rydel-Seiffer graduated tuning fork). The objective was to evaluate whether vibratory perception was reduced in painful and non-painful skin areas, compared with normal skin areas for the four subject groups. Both arms of the fork bore calibrated weights at their extremities which could be positioned according to a nine-point arbitrary scale from 0 to 8 (where “0” represented the most accurate perception and “8” the least accurate perception). Once the tuning fork was struck and the arms vibrating at 64 Hz the imprinted triangles on each arm appeared as two virtual, intersecting triangles. The intersection moved exponentially up the scale with decreasing vibration amplitude of the arms. When the subject was no longer able to perceive vibration, the nearest value on the 0-8 scale was recorded (**Whitton et al., 2005; see Appendix Fig.3.1**).

3) Temporal summation of repeated von Frey filaments above pain threshold was performed stimulating the site at 2 stimuli/ sec with a von Frey filament at 2-3 times higher than his pain threshold (VAS=2) in mN. Pain intensity measured using the VAS ratio scale following every 10 stimuli. The increment in pain intensity was measured from the 1st to the last 50th stimuli.

4) Two point discrimination was tested with a precision millimetre gauge (assessed in cm) in this distance was measured in either painful or non-painful skin areas and finally compared to normal skin areas. The cut-off used to determine “normal” discrimination was < 7 cm (as measured from the HV population). Values higher than that more and values associated with the maximum distance tested (12 cm) were considered as “abnormal”.

5) Static Allodynia (Punctate Allodynia) was examined by stimulating the skin 5 times with a von Frey Filament (mN) at 2-3 times higher than his pain threshold (VAS=2) to ascertain whether this stimuli provoked unpleasant or painful sensations in painful and non-painful skin areas.

6) Heat pain sensitivity was assessed by touching the subject with a glass test-tube filled with water and heated to 48°C.

7) Cold pain sensitivity was assessed with a drop of acetone (100%) and by touching the skin of the subject with a TipTherm® tool which also applied cold stimuli due to the metal surface. Results obtained using both tests were equivalent.

8) Dynamic Allodynia (Brush-evoked allodynia) was examined by gently moving a coarse brush (No.10 “Pappel” 113 Germany) over the skin 5 times at an interstimulus interval of 1–2 cm/sec, to ascertain whether the sensation to brush provoked unpleasant or painful sensations in painful and non-painful skin areas. Efforts were made to keep the manual stimulation as constant as possible.

9) Dynamic Allodynia was also assessed with a softer brush (No.10 “Pappel” 972 Germany) in those patients which could not tolerate the coarse one above (8).

10) Temporal Summation (to repeated brush stimuli) was evoked by repeatedly stroking the skin site at a rate of 2 strokes/s with coarse brush. The pain intensity was measured with the VAS after every 10 stimuli. The increment in sensation was rated from the 1st to the 50th brush stroke.

3.3.2.3. TSAR System

Based on **Vierck et al. (1997)**, this method mimicked natural conditions of nociceptive thermal stimulation, as when one touches a hot object. The target skin site was positioned 5 mm from the surface of a square (2.56 cm²) Peltier thermode that was preheated to temperatures ranging from 45 to 53°C. When activated, a spring-loaded solenoid moved the thermode 1cm, ensuring unambiguous contact with the skin. The solenoid was activated for 700 ms, which usually produced only late thermal sensations for the stimulus intensities used. When rating sensory magnitude, the subjects attended to the peak of late sensations that occurred ~2 s after the probe left the skin on each presentation. The temperature of the probe was calibrated immediately before each testing session, using an attachable surface temperature thermistor.

Similar to the study by **Morin and Bushnell (1998)**, we used a 2 cm² Peltier-type contact thermode (See **Appendix Picture 3.5.**) and the temperature at the skin/thermode interface was monitored using a thermocouple attached to the thermode surface. The thermode temperature was controlled by computer within ±0.1°C, and the slope of all temperature ramp stimuli held constant at 0.5°C/s for heat and at 1.0°C/s for cold stimulation. In contrast to the study presented by **Morin and Bushnell (1998)** and **Vierck et al. (1997)** a constant thermal stimuli was presented to the skin once the required temperature was reached (see **Appendix Fig 3.6.**) Thus the Peltier was pre-cooled or pre-heated for a period of 40s before skin contact.

Pilot studies were made in healthy volunteers to choose stimulus intensities that produced an evoked pain intensity of between “2-3” on the VAS scale where “2” represented pain threshold, in response to heat and cold stimuli. Thus, heat stimuli at 48°C for a period of 30s produced pain sensation in 47

subjects (HV and SCI). However some volunteers were not able to tolerate 48°C temperature stimulation for 30s or indeed did not identify pain sensation after this thermal stimuli. Thus 47°C (in 1 subject with cervical NoNP), 43°C in another 8 subjects (thoracic NP group, cervical SYR group, thoracic NoNP group, and HV at the cervical and thoracic dermatomal level – see above), 49°C (in 1 subject in the cervical NP group). In contrast a 30s 3°C thermal stimuli was applied in 51 subjects and 13°C in one subject with NoNP in the thoracic SCI group). A “dummy” temperature applied at 33°C for 30s was used which had been previously identified as a stimuli that produced no sensation of heat or cold in healthy volunteers, according to previous pilot studies. Actual data associated with thermal stimulation in real time was saved to hard disk as Excel files, ready for later analysis.

3.3.2.4. *Electronic VAS (e-VAS)*

Evoked pain intensity following thermal stimulation with the Peltier device was continuously measured by the patient using an electronic VAS scale, similar to the standard VAS scale used in **Chapters 2 and 4**, where pain threshold was associated with a score of “2” out of “10”. Continuous ratings of perceived pain intensity was performed with a linear potentiometer with visual feedback provided by computer screen presented to the patient every second. The monitor presented a 350 mm scale with a moveable cursor line adjusted by the patient according to his pain rating that filled the VAS box with either a blue or red colour (see pictures in **Appendix 3.2.-3.4**). The colour of the moveable VAS cursor was shown as blue when the it was between 0 and 2/10 (associated with unpleasantness but no pain sensation), and the line was shown as red when the cursor lay between “2” and the end of the scale (representing sensation from pain threshold to the maximum possible pain). The descriptive words of “no sensation” and “maximum pain” were placed at the ends of the scale. Importantly the length of the potentiometer was exactly 100mm thus facilitating the valuation of pain according to a normal 10 cm manual VAS line (**See Appendix of the present Chapter 3**).

Subjects provided a continuous rating of evoked pain intensity, using the e-VAS before, during the 30s thermal stimuli, and up to a maximum of 120s. after the stimulus application, which was observed on the PC screen and received feedback every second. Data obtained from the eVAS scale (with a 10Hz resolution) in real time was saved to hard disk for its analysis later. The analysis of the pain response curve was performed with the Spike 5.11 version program, based on different curve patterns and analyzing each parameter of the curve (Slope, Modulus 10s, Modulus 30s, Maximum pain intensity) (**see Appendix Picture 3.6 and 3.7**).

3.3.2.5. *Description of Pain Quality and Location: Thermal Pain Descriptors and Dermatomal Mapping.*

We presented a list of thermal pain descriptors (**See Table 3.1.**) and a dermatomal map (similar to that included in the **Protocol Appendix 3.1.**) on a board placed close to the subject so that information regarding the quality of thermal pain and the exact dermatomal location of the evoked thermal pain could be described. The descriptive adjectives were selected to provide useful information regarding the quality of sensation to cold and heat stimuli, pre and after the thermal stimuli, which were recorded by the researcher. The list of adjectives consisted of 13 words initially selected from the McGill Pain Questionnaire (**Melzack, 1975**) corroborated by descriptors already used in previous psychophysical studies (**Morin and Bushnell, 1998**) and following the application of thermal stimuli below the level of SCI (**Finnerupp et al., 2004**). The final list of descriptors was organized into four groups:

Frío (Cold) Fresco (Cool) Templado/Calor (Warm) Caliente (Hot) Quemante (Burning)	Sin sensación (Without Sensation)
Agudo (Acute) Sordo (Dull)	Hormigueo (Tingling sensation) Punzante (Sharp) Presión (Pressure) Difuso (Diffuse)

Table 3.1. Final list of sensory descriptors provided to the subject

Some patients also characterized their sensation to thermal stimuli as “Frozen (Helado)” and “Numbness (Dormido)”, which was analyzed independently in the statistical analysis along with the descriptors shown above. We asked the subject to communicate any sensation felt either during or after the presentation of the thermal stimulus. Information regarding the exact location of evoked pain was identified using the dermatomal map.

3.3.3. Statistical analysis of the data.

Data was evaluated using non-parametric statistical tests and significance was accepted at the 5% level. The Mann Whitney rank sum test was used to calculate significant differences between subject groups, and also between cervical/thoracic lesions within groups. The DN4 Questionnaire analysis was performed using the Cochran’s test for comparison between groups. Calculations were performed using the computer program SPSS 13.0 version.

3.4. Results

3.4.1. Characteristics and demographic data

A total of 52 subjects were recruited from the “Hospital Nacional de Paraplégicos de Toledo” (Spain) and participated in the study, following their selection according to the criterion described above in the methodology section (**Table 3.2**). Patients and healthy volunteers were divided into the following groups: No-Neuropathic Pain group (NoNP, n=10; cervical SCI=5; thoracic SCI= 5); Neuropathic pain group (NP, n=20; cervical SCI = 9; thoracic SCI = 11); Healthy volunteer group (HV, n=11; tested on the cervical C6 site = 6; tested on the thoracic Th6/7 = 5); Syringomyelia group (SYR, n=11; n cervical SCI= 6; n thoracic SCI = 5).

Group	Gender	Age	Acute/Chronic lesion	Aetiology	Level of the Lesion	Completeness of the lesion	NP medication	Patients with disesthesia
Non-Neuropathic Pain (n=10)	10% female 90% male	$\mu=30.4$ SD=8.9	100% acute (4-6 months)	100% traumatic	50%cervical 50%thoracic	40% incomplete 60% complete	100% non medicated	60% without disesthesia 40% with osteomuscular pain
Neuropathic Pain (n=20)	17% female 83% male	$\mu=39.3$ SD=14.1	100% acute (4-6 months)	6% atraumatic 94% traumatic	44%cervical 56%thoracic	33% incomplete 67% complete	33% non medicated 67% medicated	6% with paraesthesias 94% disesthesia
Syringomyelia (n=11)	64% female 36% male	$\mu=53.7$ SD=13.7	100% chronic (>1year)	64% atraumatic 36% traumatic	64%cervical 27%thoracic 9%lumbar	73% incomplete 27% complete	18% non medicated 82% medicated	9% with paraesthesias 91% disesthesia
Healthy volunteers (n=11)	40% female 60% male	$\mu=32.4$ SD=9.4	---	---	60% tested in cervical 40% tested in thoracic	---	100% non medicated	100% without paraesthesia or dysesthesia

Table 3.2. Demographic and physical characteristics of the healthy and SCI patients (N=52) studied in the four study groups: No Neuropathic Pain, Neuropathic Pain, Syringomyelia and Healthy volunteers.

The subjects’ mean ages was 30.4 ± 8.9 (range=21-51) in the NoNP group; 39.33 ± 14.1 (range=19-64) in the NP group; 53.73 ± 13.7 (range=35-73) in the SYR group; and 32.40 ± 9.4 (range=22-57) in the HV group. The higher percentage of male was 90% in the NoNP group; followed by 83% in the NP group; 60% in the HV group and 36% in the SYR group.

Traumatic SCI was the most frequent cause of the lesion identified in our hospital (100% in NoNP, 94 % in NP group) except in the SYR group (only 36%). Patients with thoracic lesions were more prevalent in the NP group (56%), followed by 50% in the NoNP group and 27% in the SYR group. Complete SCI (ASIA A) was identified in 67% of patients in the NP group, 60% in the NoNP group, and only 27% in the SYR group (See Table 3.2). Pharmacological management of the patient groups was present in the majority of pain patients: 67% of the NP group and 82% of the SYR group. Treatment usually was a combination of the following analgesic agents (Amytryptiline, Clonazepam or Gabapentin/Pregabalin) following an initial/later diagnosis of dysesthesias (94% in the NP group and 91% in SYR group).

Pain onset time in the NoNP group was 4.45 ± 0.91 (range = 4-6.5) from the time of SCI and 6.5 ± 0.91 (range = 6-6.5) for the cervical SCI group and finally 4.20 ± 0.4 (range = 4-5) months for the thoracic SCI group. In the NP group the mean was 5.44 ± 1.83 (range = 4-9) months since the time of injury for the cervical group and the mean was 4.18 ± 0.60 (range = 4-6) months for the thoracic group. In the SYR group the pain onset time was 4.28 ± 2.05 (range = 1-8) years in the cervical SCI group, 14.00 ± 10.61 (range = 7-29) years after injury in the thoracic group, and one patient with a lumbar SYR 6 years after injury.

3.4.1.1. Patient response rate with QST

Analysis of the percentage of patients with von Frey stimulation revealed that 100% of the HV subjects detected a response to mechanical stimulation compared to 60% in the NoNP group, 55% in the SYR group and 28% in the SCI-NP (with a higher respondent rate at the cervical level (see **Table 3.3**).

In response to the the Rydell-Seiffer tuning fork revealed that in general a low rate of response below the level of the injury in patients (20-27% following SCI); although at the level of NP responded in the 78-81% following SCI. Above the level, the response rate was 100% except SYR which responded at 91% of the total population.

The response percentage to many repeated 10-50 von Frey stimuli (applied manually every 0.5 s at 2-3 times threshold) showed a diminished response rate at the level of SCI with SYR associated with the lowest rate of response 36%. In contrast the range of response percentage below the SCI was represented by SYR as the highest response rate (36%).

Two point discrimination at and below level of SCI was poorer in the NP (28-89%) and SYR groups (27-73%); and all subject groups responded well above the lesion level. The response rate following 5 von Frey pokes (2-3 times higher than threshold) at the level of SCI (9-50%), identified the SYR patients with least response (9%) and the NP group with the most response frequency (77%). Below the level of lesion (0-27%) the SYR group responded most (27%).

The 48°C test tube test indicated that the SYR patients were the higher respondents at all levels of stimulation (91% at level, 55% below and 80% above). Similar responses were obtained with the drop of acetone / Tip Therm® except at the control site presenting in the NP group (78%) the highest rate of respondents.

Coarse brush stimuli applied at the level of SCI (22-50%) showed more respondents in the NoNP group (50%); while only 50% in healthy volunteers responded most below the level of injury (6-50%).

% Response	Level tested	HV			NoNP			NP			SYR		
		Cervic (n=6)	Thorac (n=5)	Total (n=11)	Cervic (n=5)	Thorac (n=5)	Total (n=10)	Cervic (n=9)	Thorac (n=10)	Total (n=20)	Cervic (n=6)	Thorac (n=5)	Total (n=11)
Tactile detection threshold (mN)	At level	100	100	100	100	100	100	100	100	100	100	100	100
	Below level	100	100	100	80	40	60	50	20	28	66	40	55
	Above level	100	100	100	100	100	100	100	100	100	84	100	91
Tuning fork (0-8 AU)	At level	100	100	100	100	80	90	88	70	78	66	100	81
	Below level	100	100	100	20	20	20	77	80	22	16	40	27
	Above level	100	100	100	100	100	100	100	100	100	80	100	91
10-50 vF pokes 2-3 times pain detection (VAS)	At level	66	100	80	40	40	40	33	60	45	33	40	36
	Below level	66	100	80	20	0	10	11	10	11	50	20	36
Two point discrimination (cm)	At level	100	100	100	100	100	100	100	90	89	50	100	73
	Below level	100	100	100	60	60	60	33	20	28	0	60	27
	Above level	100	100	100	100	100	100	100	100	100	100	100	100
5 vF pokes 2-3 times pain detection (VAS)	At level	33	25	30	20	0	50	11	30	77	16	0	9
	Below level	20	25	20	0	0	0	11	0	6	33	20	27
48°C Test Tube (VAS)	At level	66	0	40	40	60	50	44	70	61	80	100	91
	Below level	66	0	40	0	0	0	0	10	6	50	60	55
	Above level	66	0	40	60	80	70	66	80	78	80	80	80
One Drop of Acetone/Cold Tip Therm (VAS)	At level	66	75	70	40	60	50	44	80	72	80	100	91
	Below level	50	50	50	0	0	0	0	10	17	50	60	55
	Above level	66	25	50	60	60	60	77	80	78	50	40	45
Coarse brush (VAS)	At level	16	75	40	60	40	50	77	60	22	16	40	27
	Below level	33	75	50	20	0	10	11	0	6	16	20	18

Table 3.3. Percentage of patients that respond to different mechanical and thermal QST testing procedures.

3.4.1.2. Patient pain response rate to heat and cold stimuli

The results obtained following *heat* stimulation at the level of the lesion in responding patients (See **Table 3.4**) showed that in the NoNP group only 2 (40%) of patients in the cervical SCI group responded compared to 4 (80%) with thoracic SCI. In the NP group, 3 patients (33.3%) with cervical SCI and 4 patients with thoracic lesion (40%) showed a response. In the SYR group only 1 patient responded in the cervical group (16.6%) whilst none of the patients responded with thoracic SCI. Among the HV group, 3 (50%) responded following cervical stimulation compared to 4 (80%) following thoracic stimulation. The descriptive results reported in **Appendix Fig 3.1.** and **3.2** show the percentage response rate to heat and cold stimuli trials for the NoNP, NP, SYR, HV groups that responded with a pain intensity of greater than 2 out of 10 (pain threshold).

Patients that responded to *cold* stimulation at the level of the lesion was in general less than those to heat stimulation. In patients with NoNP, none of the cervical lesion group responded and only 1 (20%) in the thoracic lesion group. In the NP group, 1 patient (11.1%) with a cervical lesion and 3 patients with thoracic lesion (27.3%) showed a response. In the SYR group 3 patients with cervical injury responded (50%) compared to none of the patients with thoracic SCI. In the HV group, 3 subjects (50%) responded to cervical level stimulation and 2 of them (40%) to thoracic level stimulation.

Heat stimulation in patients above SCI showed that in the NoNP group, 3 patients (60%) from the cervical lesion group responded compared to 2 (40%) from the thoracic lesion group. In the NP group, 5 patients (55.5%) with cervical lesion and 4 patients with thoracic lesion (36.3%) showed a response. In the SYR group 2 patients with cervical injury (33.3%) and 1 patient (20%) responded in the thoracic group. Among the HV, 2 (33.3%) responded to cervical site stimulation and 3 of them (60%) with thoracic site stimulation.

The results of *cold* stimulation above the level of the lesion in patients showed that in the NoNP group, 3 (60%) of the cervical lesion group provided a response compared to 2 (40%) in the thoracic lesion group. In the NP group, 5 patients (55.5%) with cervical lesion and 5 patients (50%) with thoracic SCI showed a response. The SYR group indicated that 3 patients in the cervical group (50%) and 1 patient (20%) responded in the thoracic group. Among HV, 2 (33.3%) responded to cervical site stimulation and 2 of them (40%) following thoracic stimulation.

% Response	HV			NoNP			NP			SYR		
	Cervic (n=6)	Thorac (n=5)	Total (n=11)	Cervic (n=5)	Thorac (n=5)	Total (n=10)	Cervic (n=9)	Thorac (n=10)	Total (n=20)	Cervic (n=6)	Thorac (n=5)	Total (n=11)
Heat At Level	50	80	64	40	80	60	33	40	35	16	00	10
Cold At Level	50	40	45	0	20	10	11	30	20	50	00	30
Heat Above Level	33	60	45	60	40	50	55	36	45	33	20	30
Cold Above Level	33	40	36	60	40	50	55	50	50	50	20	40

Table 3.4. Percentage of respondents to thermal stimulation with the TSAR system.

An examination of the thermal pain responses at the cervical and thoracic level provided further information. Stimulation of the cervical dermatomes was associated with a higher response rate in the HV group for both heat and cold stimuli at level compared to the responses above the level of injury

NoNP and NP did for heat and cold. SYR group presented the least responses to heat at level compared to the other groups. As we observed, NP group is similar to nNP one on this site, but at thoracic site presented lower responses on heat than NoNP and HV. Responses to stimulation of the thoracic dermatomes produced more were higher in the NoNP and HV groups for heat; HV for cold at that level and also above the level for heat meanwhile for cold above the lesion NP did. SYR group presented the least responses to any temperature and at any level compared to the other groups and is noticeable the total absence of responses at level of lesion in the thoracic site.

3.4.1.3. DN4 Questionnaire Analysis

The Medians, 25P and 75P for the DN4 Questionnaire showed similar values in NP and SYR groups, between 4 and 6 points out of 10, whilst the maximum obtained for NoNP group is only of 4.75 points (See Table 3.6).

We performed Non Parametric analysis for several related samples (Cochran’s test, two-tailed asymptotic distribution used) between groups NoNP, NP and SYR. Question 9 (Hypoesthesia to pin-prick) was significant between NoNP and SYR (p=0.046; presented in all NoNP patients), and also between NP and SYR groups (p=0.046; more present in SYR patients). Question 10 (Painful Brush) was significant between NoNP and NP (p=0.025; more present in NP patients) (See Table 3.7). When DN4 was considered in total points score (Mann-Whitney U test, two-tailed asymptotic distribution used) no significance was seen between groups: NoNP and NP (p=0.410); NoNP and SYR (p=0.071); NP and SYR (p=0.964).

DN4 Spanish version	HV			NoNP			NP			SYR		
	Median	25P	75P	Median	25P	75P	Median	25P	75P	Median	25P	75P
1. Burning sensation	1.00	1.00	1.00	1.00	0.00	1.00	1.00	0.25	1.00	1.00	1.00	1.00
2. Painful cold	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	1.00	0.00	0.00	0.50
3. Electric shocks	0.00	0.00	0.00	1.00	0.25	1.00	1.00	0.25	1.00	1.00	1.00	1.00
4. Tingling sensation	0.00	0.00	0.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	0.50	1.00
5. Pins and needles	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	1.00	0.00	0.00	1.00
6. Numbness	0.00	0.00	0.00	0.00	0.00	1.00	1.00	1.00	1.00	1.00	0.00	1.00
7. Itchiness	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.75	0.00	0.00	0.00
8. Hypoesthesia to touch	0.00	0.00	0.00	0.50	0.00	1.00	1.00	0.00	1.00	1.00	0.00	1.00
9. Hypoesthesia to pin-prick	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	1.00*
10. Painful Brush	0.00	0.00	0.00	0.00	0.00	0.00	0.50*	0.00	1.00	0.00	0.00	1.00
Total (0-10 points)	0.00	0.00	0.00	2.25	2.25	4.75	4.00	4.00	6.00	4.00	4.00	6.00

Table 3.6. Median, 25P and 75P DN4 Questionnaire for the 4 groups: noNP= non Neuropathic Pain and SCI patients; NP= Neuropathic Pain and SCI patients; SYR=Syringomyelia and SCI patients. * - p<0.05, NP versus NoNP ; SYR versus NP.

DN4 Question	NoNP & NP % of patients descriptor present			NoNP & SYR % of patients descriptor present			NP & SYR % of patients descriptor present		
	Cochran p=	%NoNP	% NP	Cochran p=	%NoNP	%SYR	Cochran p=	%NP	%SYR
1. Burning	1.000	60.0	72.2	.655	60.0	63.3	.655	72.2	63.3
2. Cold	.655	20.0	33.3	1.000	20.0	37.3	1.000	33.3	37.3
3. Shock	.655	70.0	72.2	.655	70.0	81.8	1.000	72.2	81.8
4. Tingling	.083	100.0	77.8	.157	100.0	72.7	1.000	77.8	72.7
5. Pinprick	1.000	20.0	33.3	.317	20.0	45.5	.317	33.3	45.5
6. Numbness	.083	40.0	77.8	1.000	40.0	45.5	.180	77.8	45.5
7. Sting	.317	10.0	28.8	1.000	10.0	9.1	.317	28.8	9.1
8. Hypoesthesia to touch	1.000	50.0	61.1	1.000	50.0	54.5	.564	61.1	54.5
9. Hypoesthesia with pin-prick	1.000	100.0	16.7	.046*	100.0	45.5	.025*	16.7	45.5
10. Painful Brush	.025*	10.0	50.0	.102	10.0	45.5	.317	50.0	45.5

Table 3.7. DN4 questions significant levels Cochran’s non parametric analysis for the four groups noNP= non Neuropathic Pain and SCI patients; NP= Neuropathic Pain and SCI patients; SYR= Syringomyelia and SCI patients; *= p = .05.

3.4.1.4. Radiating Pain

Radiating pain was identified more readily following heat stimulation at the level of the lesion (n=8) although no relationship was observed according to patients with or without NP or to the level of injury; consisting of 2 patients (40%) with cervical and 1 (20%) with thoracic SCI in the NoNP group, and 3 patients (33%) with cervical lesion and 2 (18%) following thoracic lesion in the NP group. Cold stimulation at the level of the lesion produced radiating pain in only 2 patients (40%) with cervical lesion and NP. Heat stimulation above the level of the lesion produced this type of pain in only one patient with and one without NP following thoracic NP. Responses to cold stimulation above the level of the lesion were identified in only 1 patient (20%) with thoracic SCI without NP (See Table 3.5).

Thermal Stimulation and Level	Subject	Group	Lesion	In/complete	48°C heat or 3°C cold applied at level	Location of Rad Pain
HEAT AT LEVEL	FCC	No NP	C4	Incom	None	C5
	DFMM	No NP	C5	Com	None	L2
	JLDJ	No NP	T8	Com	48°	S3;L5-S1
	ADG	NP	C5	Incom	None	L5
	IDE	NP	C6	Incom	48°	C6; L5
	LRM	NP	C4	Incom	48°	S1
	ADVC	NP	T6	Com	None	L2
	JTR	NP	T11	Com	48°	C7-8
HEAT ABOVE LEVEL	JLDJ	NoNP	T8	Com	48°	L2-L3
	ADVC	NP	T6	Com	None	L2
COLD AT LEVEL	ADG	NP	C5	Incom	None	L5
	LRM	NP	C4	Incom	None	C6
COLD ABOVE LEVEL	JLDJ	NoNP	T8	Com	3°	L2-L3

Table 3.5. Presence and location of radiating pain responses following thermal stimulation at and below the level of the lesion in each patient. NoNP-non Neuropathic Pain group; NP- Neuropathic Pain group. C-Cervical lesion ; T -Thoracic lesion. Incom- Incomplete lesion (ASIA B or C); Com- Complete lesion (ASIA A). None-no radiating pain response to heat or cold stimulation at level of the lesion; Rad Pain-Radiating Pain localized in another area of the body.

3.4.2. Sensory response rate to QST

Temporal Summation (to a brush) evoked by repeatedly stroking the site with coarse brush scored each 10 strokes did not provoked the desired effect of prevalence in response, being only one NoNP patient who responded to this test. Therefore we did not considered these results for the analysis, since we cannot compare the values, except NP that were compared with higher n, but was neither significant with Mann-Whitney test: 0.418 at level; 0.264 below level; 0.807 above level (n= 4 cervical and n=3 thoracic); and also we could compare SYR group with Mann-Whitney test: 0.813 at level; 0.513 below level; 0.626 above level (n= 4 cervical and n=3 thoracic). And for NP and SYR groups with Mann-Whitney test: 0.275 at level; 0.287 below level; 0.289 above level (n= 4 cervical and n=3 thoracic).

The Medians, 25P and 75P are shown in **Table 3.8**.

	Level tested	HV			NoNP			NP			SYR		
		Median	P25	P75	Median	P25	P75	Median	P25	P75	Median	P25	P75
Tactile detection threshold von Frey (mN)	At level	0,50	0,50	0,87	9,89	0,50	0,87	1,50 HV	0,50	4,00	4,00 NoNP	1,50 NP	6,00
	Below level	0,50	0,50	0,87	263,74	0,50	385,00	4,00	0,50	4,00	4,00	0,00	6,00
	Above level	0,50	0,50	0,50	0,00	0,50	0,50	0,50	0,50	0,50	0,50	0,50	1,00
Vibration Rydel Seiffer (0-8 AU)	At level	7,50	5,00	8,00	0,83	6,00	7,00	6,50 HV	5,25	7,00	5,00	4,00	6,00
	Below level	5,00	4,25	6,00	1,41	6,50	7,50	6,00	5,00	7,25	5,50	5,25	6,25
	Above level	6,00	5,00	7,75	1,71	5,25	8,00	6,50	5,25	8,00	6,00	5,00	6,75
Coarse brush (VAS)	At level	0,00	0,00	0,50	1,03	0,00	1,00	0,75	0,00	2,75	0,00	0,00	1,00
	Below level	0,25	0,00	0,50	0,63	0,00	0,00	0,00 HV	0,00	0,00	0,00	0,00	0,00
Two-Point Discrimination Millimetre gauge (cm)	At level	2,25	1,62	2,50	1,43	2,00	3,37	3,75	2,87	5,12	2,75 NoNP	2,00	4,13
	Below level	1,50	1,50	4,12	0,93	3,00	3,87	2,50	2,00	2,50	3,50	3,25	3,50
	Above level	2,00	1,50	3,00	1,75	1,13	2,00	2,00	1,88	2,50	2,00	2,00	3,00
5 von Frey pokes 2-3 times higher threshold (VAS)	At level	0,00	0,00	0,37	0,47	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00
	Below level	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,25
48°C Test-Tube (VAS)	At level	0,00	0,00	1,00	0,53	0,00	1,00	1,00	0,00	1,00	1,00 HV	1,00	1,00
	Below level	0,00	0,00	1,00	0,00 HV	0,00	0,00	0,00 HV	0,00	0,00	1,00 NoNP	0,00	1,00
	Above level	0,00	0,00	1,00	0,48	0,25	1,00	1,00 HV	1,00	1,00	1,00 HV	1,00	1,00
Drop of Acetone/ Tip-Therm (VAS)	At level	1,00	0,07	1,00	0,53	0,00	1,00	1,00	0,12	1,00	1,00 NoNP	1,00	1,00
	Below level	0,15	0,00	0,875	0,00 HV	0,00	0,00	0,00	0,00	0,00	0,00 NoNP	0,00	1,00
	Above level	0,25	0,00	1,00	0,52	0,00	1,00	1,00	1,00	1,00	1,00	0,50	1,00
10-50 von Frey pokes 2-3 times higher than threshold (VAS)	At level	0,75	0,50	1,75	0,57	0,00	0,87	0,00	0,00	1,75	0,00 NoNP	0,00	2,50
	Below level	0,75	0,50	2,50	0,63	0,00	0,00	0,00	0,00	0,00	0,00	0,00	2,00

Table 3.8. QST Medians and Percentiles (25P and 75P) at, below and above the level of the lesion stimulation for the four groups: noNP= non Neuropathic Pain and SCI patients; NP= Neuropathic Pain and SCI patients; SYR=Syringomyelia and SCI patients; HV= Healthy volunteers. Values in bold represent significant differences (see Table 3.9) with regard to the subject group mentioned.

We performed Non Parametric tests for two independent samples for the rest of the tests (Mann-Whitney U test, two-tailed asymptotic distribution used, $p = 0.05$) at, below and above the level of the lesion (**See Table 3.9 and Table Appendix 3.25**).

Significant results *at level* of the lesion were found in Thresholds (mN) presenting NP group worse sensitive detection than HV ($p=0.029$); NoNP lesser than SYR ($p=0.050$) and SYR worse than NP ($p=0.009$). Sensation of vibration (0-8 AU) was better detected in HV than NP subjects (0.037). Two point discrimination (mm) was better detected in NoNP group than SYR ($p=0.044$). Heat (48°C Tube) presented higher scores in VAS scale in SYR than HV ($p=0.016$) and SYR than NoNP ($p=0.043$). Cold (Drop of Acetone) showed the same higher response in VAS in SYR than NoNP ($p=0.043$).

Below the level of the lesion some differences were also found between groups. Temporal Summation (mN) showed higher intensity levels in NoNP than SYR ($p=0.033$). NP and SYR groups have also significance ($p=0.049$) but is not clearly known which group has higher levels observing the medians (presumably SYR since $75P=2$). Heat (48°C Tube) presented higher scores in VAS scale in SYR than NoNP ($p=0.007$) and SYR than NP ($p=0.003$). Cold (Drop of Acetone) showed higher response in VAS in HV and SYR than NoNP ($p=0.017$). Dynamic Alodinia (brush) presented higher scores in HV than NP ($p=0.010$).

Above the level of the lesion we only could find a significant difference in Heat (48°C Tube) between NP with higher VAS than HV ($p=0.050$) and close to significant between higher VAS in SYR than in HV ($p=0.054$).

	Level tested	NoNP	NP	SYR
Tactile detection threshold von Frey (mN)	At level		0.029 HV	0.05 NoNP 0.009 NP
	Below level			
	Above level			
Vibration Rydel Seiffer (0-8 AU)	At level		0.037 HV	
	Below level			
	Above level			
Coarse brush (VAS)	At level			
	Below level		0.01 HV	
Two-Point Discrimination Millimetre gauge (cm)	At level			0.044 NoNP
	Below level			
	Above level			
5 von Frey pokes 2-3 times higher threshold (VAS)	At level			
	Below level			
48°C Test-Tube (VAS)	At level			0.016 HV 0.043 SYR
	Below level	0.029HV	0.025HV	0.007NoNP
	Above level		0.05HV	
Drop of Acetone/ Tip-Therm (VAS)	At level			0.043NoNP
	Below level	0.013HV		0.017 NoNP
	Above level			
10-50 von Frey pokes 2-3 times higher than threshold (VAS)	At level			0.033 NoNP
	Below level			

Table 3.9. QST analysis (Mann-Whitney U analysis) for the four groups: NoNP= non Neuropathic Pain and SCI patients; NP= Neuropathic Pain and SCI patients; SYR=Syringomyelia and SCI patients; HV= Healthy volunteers. Bold : p = 0.05. (For non significant values of the analysis see **Table Appendix 3.25**).

3.4.3. Descriptors Reported During the Thermal Test

The descriptors reported by the subjects for groups NoNP, NP and SYR at level of the lesion with Heat stimulation showed that “punctual” and “burning” were the most present before the stimulation, whilst “no sensation” was the most present after the stimulus (See Fig Appendix 3.4).

The descriptors reported at level of the lesion with Cold stimulation showed that “punctual”, “cold” and “diffuse” were the most present before the stimulation, whilst “no sensation” was the most present after the stimulus (See Fig Appendix 3.5). The descriptors reported above level of the lesion either with Heat or Cold showed that “punctual” and “cold” were the most present before the stimulation, whilst “no sensation” and “cold” were the most present after the stimulus (See Fig Appendix 3.6 and 3.7).

3.4.4. Pain Curve Response Analysis

We found no responses below the level of the lesion in patients, except in one patient from the NoNP group; therefore no analysis could be done with it. We performed Non Parametric tests for two independent samples (Mann-Whitney U test, two-tailed asymptotic distribution used) at and above the level of the lesion for heat and cold stimulation. See Tables App 4.1-4.25 in Appendix for all the analysis made. The significant results are shown below in Graphs 3.1-3.6. Table 3.10 shows the medians at each level and the significance (complementary to the graphs). We could observed that the medians for maximum e-VAS scores at-level testing with either tonic heat (VAS=3.7) or cold (VAS=3.7) stimuli were generally higher in HV than the sensory response obtained at the C2 dermatome (VAS=1.8-1.9), while the highest pain score was registered by the SYR group at level in response to cold stimuli (VAS =4.5). In contrast, the NP group generally presented higher pain scores during tonic at-level cold stimulation (VAS=3.2 in NP group) compared to heat stimulation (VAS=2.5 in NP group). Maximum VAS as a pain variable was sufficiently sensitive to distinguish between SCI-NP patients from the NoNP group (VAS=1.7), although the highest level of pain experienced was not greater than that identified in the HV group (VAS=3.8).

		Stimulated site	HV	NoNP	NP	SYR
Heat	slope	At	1.38	0.54	0.76	0.61
		Above	0.33	0.23	0.35	0.02
	Max	At	3.74	2.93	2.45	3.06
		Above	1.89	2.90	2.41	3.86 HV
	Mod10	At	2.38	16.98	20.44	24.45
		Above	14.7	22.25	19.62	0.00 SYR
Cold	slope	At	0.10	0.05	0.74	0.27
		Above	0.05	0.06	0.10	0.20
	Max	At	3.68	1.66	3.17	4.49
		Above	1.80	2.89	2.46	4.50
	Mod10	At	14.23	5.15	29.77	28.69 HV
		Above	14.03	5.46	12.34	27.04# NoNP

Table 3.10. Medians of thermal stimulation by TSAR system and significant results obtained.

* = significant P = 0.05 ; # = significant only p = 0.059.

In **Graph 3.1**, the initial response slope for Heat stimulation at level for the four groups is shown on cervical and thoracic sites, being significant ($p=0.032$) in NP group. In **Fig.3.1** we can observe an example of pain curve for two patients with cervical and thoracic injuries with Heat at level stimulation screening the first 30s of response.

In **Graph 3.2**, the initial response in Modulus 10s for Heat stimulation above the level was significant between NP and SYR groups ($p=0.014$).

Graph 3.3 shows an initial response in Maximum VAS for Heat stimulation above the level significant ($p=0.024$) for HV and SYR.

Graph 3.4 shows the initial response in Modulus 30s for Heat stimulation above the level which was significant ($p=0.033$) for NP and SYR groups.

Also in **Graph 3.5**, the initial response Modulus 10s for Cold stimulation at level shows significance ($p=0.025$) for SYR and HV groups. In **Fig.3.2** we can observe an example of pain curve for a SYR patient and HV subject with Cold at level stimulation screening the first 10s of response.

Interestingly, in **Graph 3.6** the initial response Modulus 10s for Cold stimulation above level shows no significance difference, but was close ($p=0.059$) for groups NoNP and NP.

Analysis of the early integrated (10s) pain response to tonic cold stimulation provided better differential diagnosis between subject groups and SCI levels, including HV, than the max VAS pain variable. While tonic cold stimulation applied to healthy subjects produced the same integrated VAS score at or above the level of SCI (14.2 versus 14.0 VAS.s), tonic heat stimulation revealed a much higher pain response in the HV group when applied at the C2 dermatomal level (at level=2.4 versus above level=14.7 VAS.s). A better differential diagnosis was also reached with at-level tonic cold stimulation when NP patients (NP=29.8 and SYR=28.7 VAS.s) were compared with either the HV (14.2 VAS.s) or NoNP (5.2 VAS.s) groups, suggesting that NP after SCI is more readily detectable using cold stimuli. Furthermore, SYR patients presented no difference between the integrated 10s pain response applied either at level (28.7 VAS.s) or below level (27.0 VAS.s), in contrast to tonic cold stimulation testing in the NP group (at-level=29.8 versus above-level=12.3 VAS.s). Further evidence for a sensory dysfunction in SYR patients at the supraspinal level is supported by a sub-modality differences when the 10s integrated pain response to cold stimuli (27.0 VAS.s) is compared in response to tonic heat stimuli (above-level=0.0 and at-level=24.5 VAS.s).

Higher pain sensitivity slopes in response to tonic heat (1.4 VAS/s) were observed compared to cold (0.1 VAS/s) in healthy controls. Furthermore heat sensitivity in the HV group was higher at the level of injury than that identified at the C2 dermatomal level (At-level=1.4 versus Above-level=0.3 VAS/s). Sensitivity to at-level tonic heat stimuli was significantly higher in thoracic NP (1.8 VAS/s) when compared to the cervical NP group (0.1 VAS/s). However in general, spinal cord injury presented reduced slope measures at-level tonic heat compared to the HV group but had increased sensitivity to cold stimulation in pain patients (HV= 0.1, NP=0.7 and SYR=0.3 VAS/s) with the response in the NoNP group considerably lower (NoNP=0.05 VAS/s). Above level changes in sensory function to tonic thermal testing were similar to that described using the 10s integrated pain response, where patients with SYR presented higher sensitivity to tonic cold (SYR=0.2 versus HV=0.05 VAS/s) and a dramatic loss of sensitivity to tonic heat (SYR=0.02 versus HV=0.33 VAS/s).

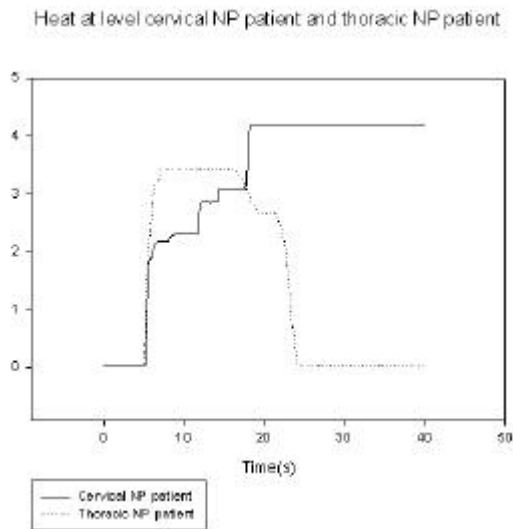
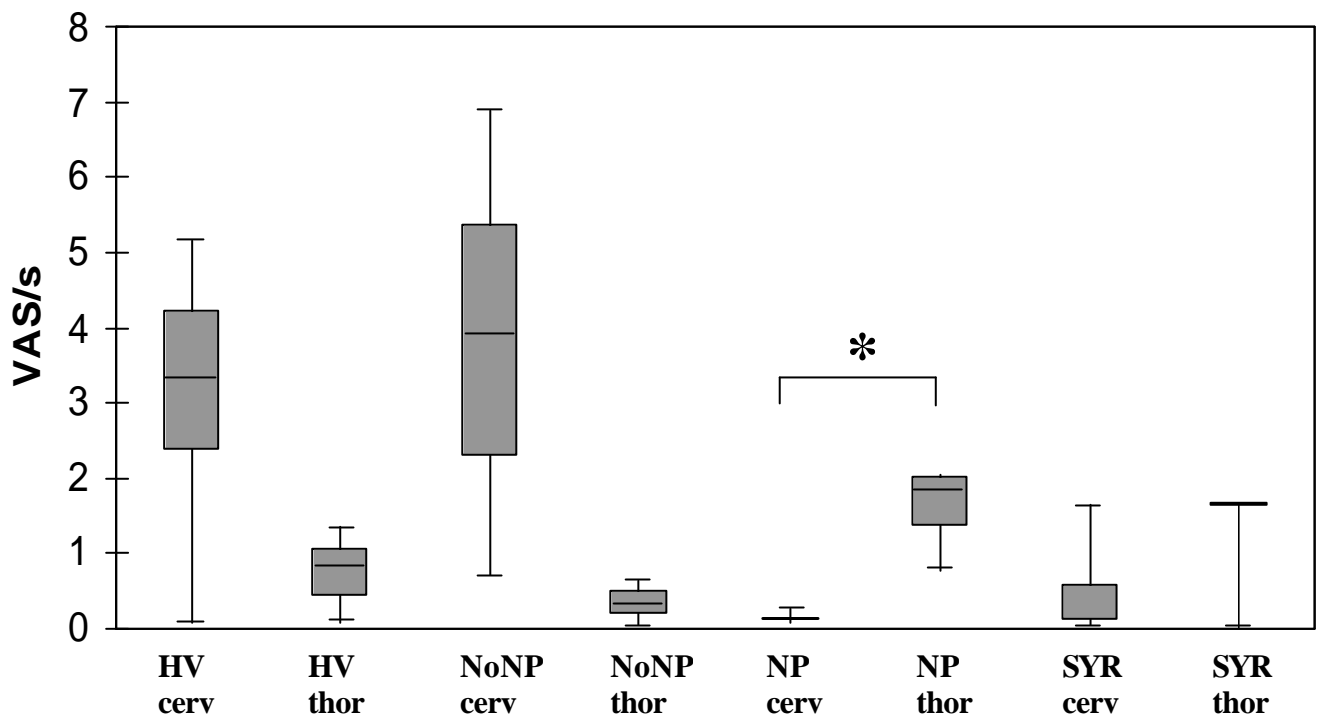
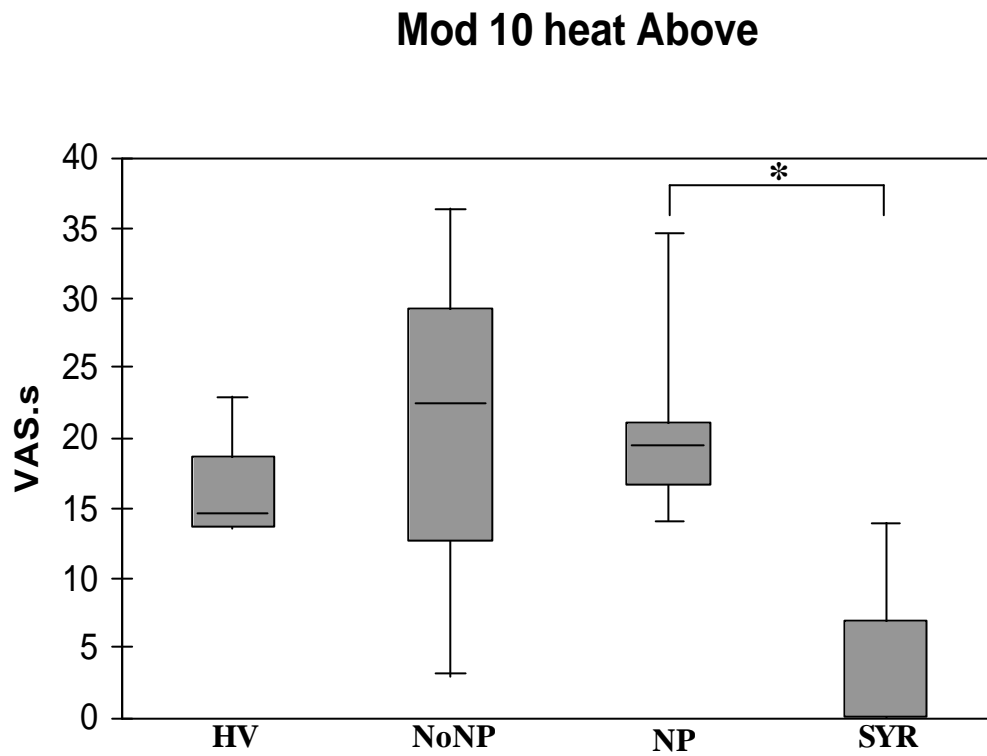


Fig.3.1. Example of Pain Curve of two NP patients with cervical and thoracic injury respectively with Heat at level stimulation showing the first 30 s of response.

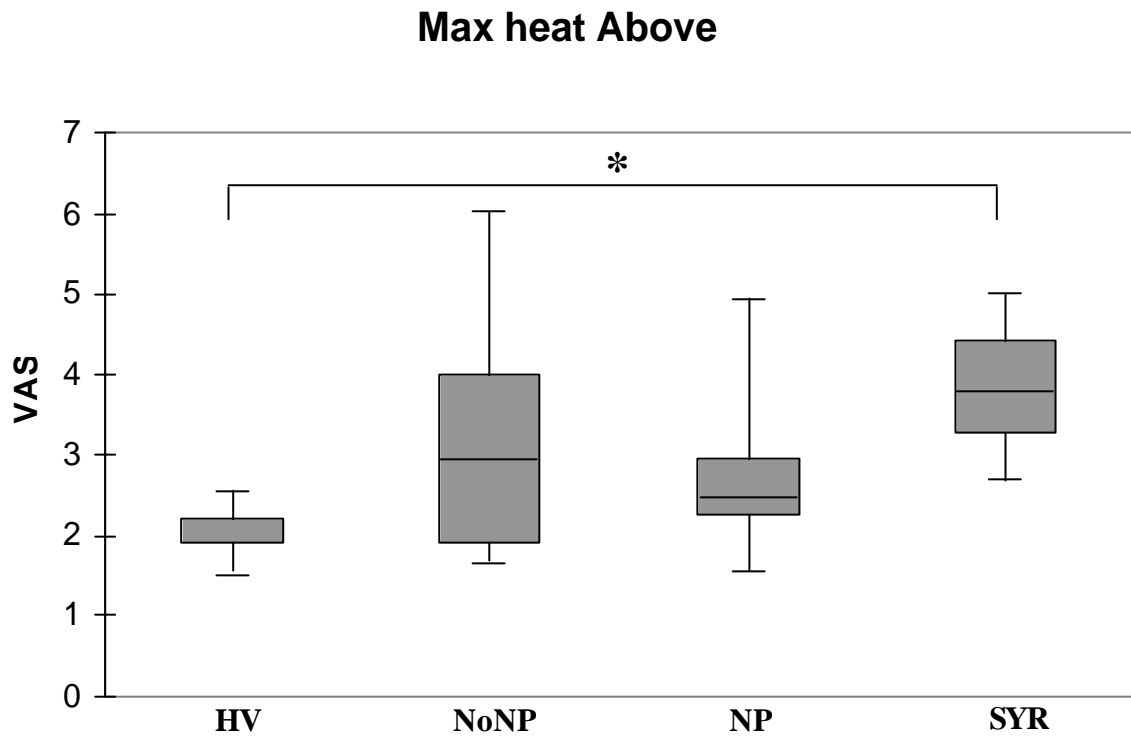
Slope C/T heat at



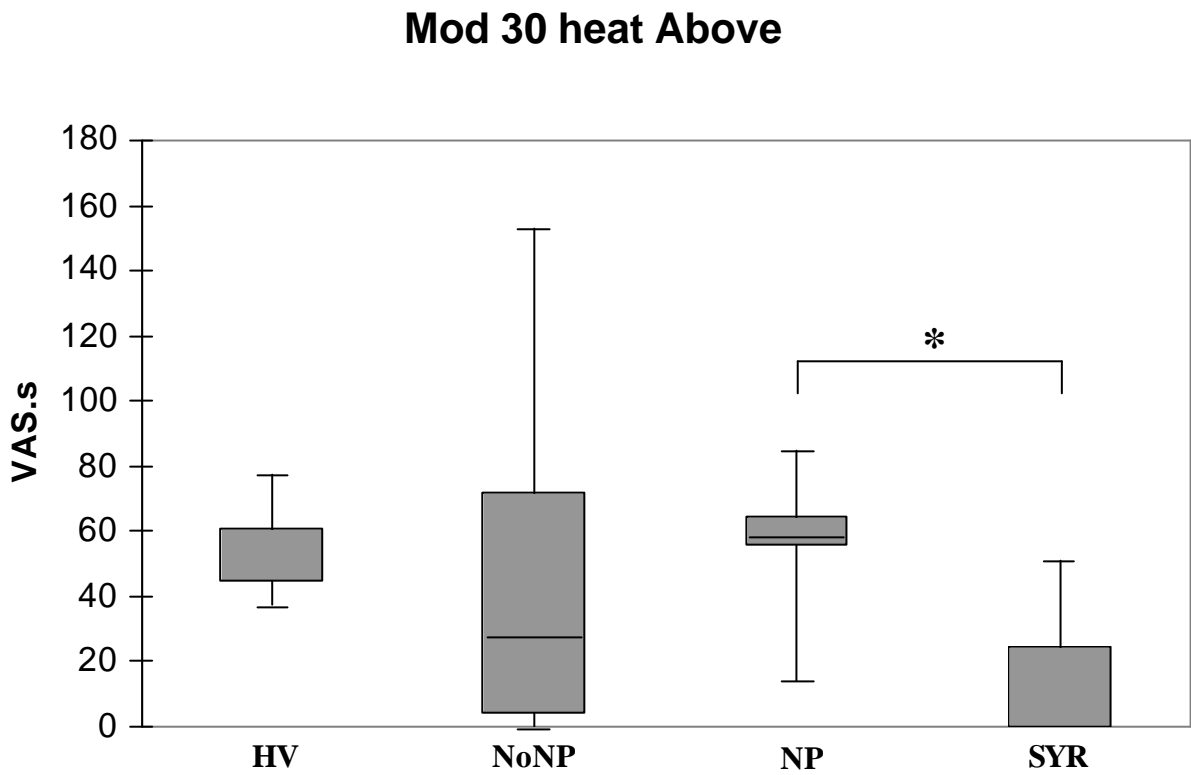
Graph 3.1. Initial response slope for Heat stimulation at level for the four groups: NoNP= non Neuropathic Pain and SCI patients; NP= Neuropathic Pain and SCI patients; SYR=Syringomyelia and SCI patients; HV= Healthy volunteers, on cerv= cervical and thor=thoracic site. * = significant $p = 0.032$



Graph 3.2. Initial response Modulus 10s for Heat stimulation at level for the four groups: NoNP= non Neuropathic Pain and SCI patients; NP= Neuropathic Pain and SCI patients; SYR=Syringomyelia and SCI patients; HV= Healthy volunteers. * = significant $p = 0.014$



Graph 3.3. Initial response Maximum VAS for Heat stimulation above level for the four groups: NoNP= non Neuropathic Pain and SCI patients; NP= Neuropathic Pain and SCI patients; SYR=Syringomyelia and SCI patients; HV= Healthy volunteers. * = significant $p = 0.024$



Graph 3.4. Initial response Modulus 30s for Heat stimulation above level for the four groups: NoNP= non Neuropathic Pain and SCI patients; NP= Neuropathic Pain and SCI patients; SYR=Syringomyelia and SCI patients; HV= Healthy volunteers. * = significant $p = 0.033$

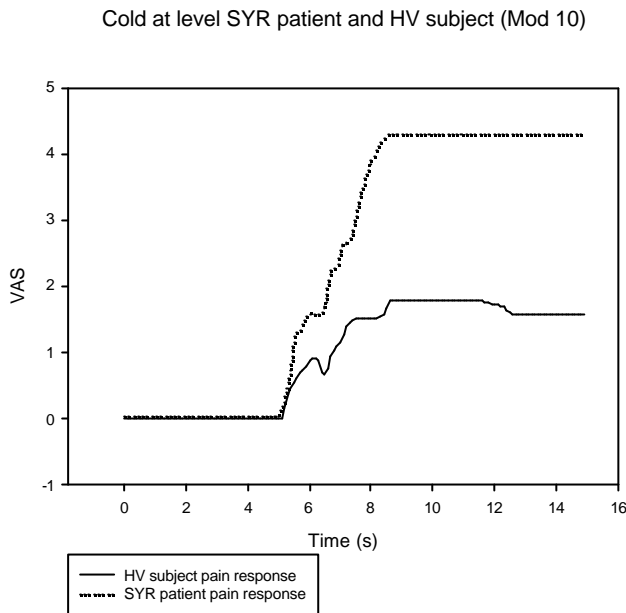
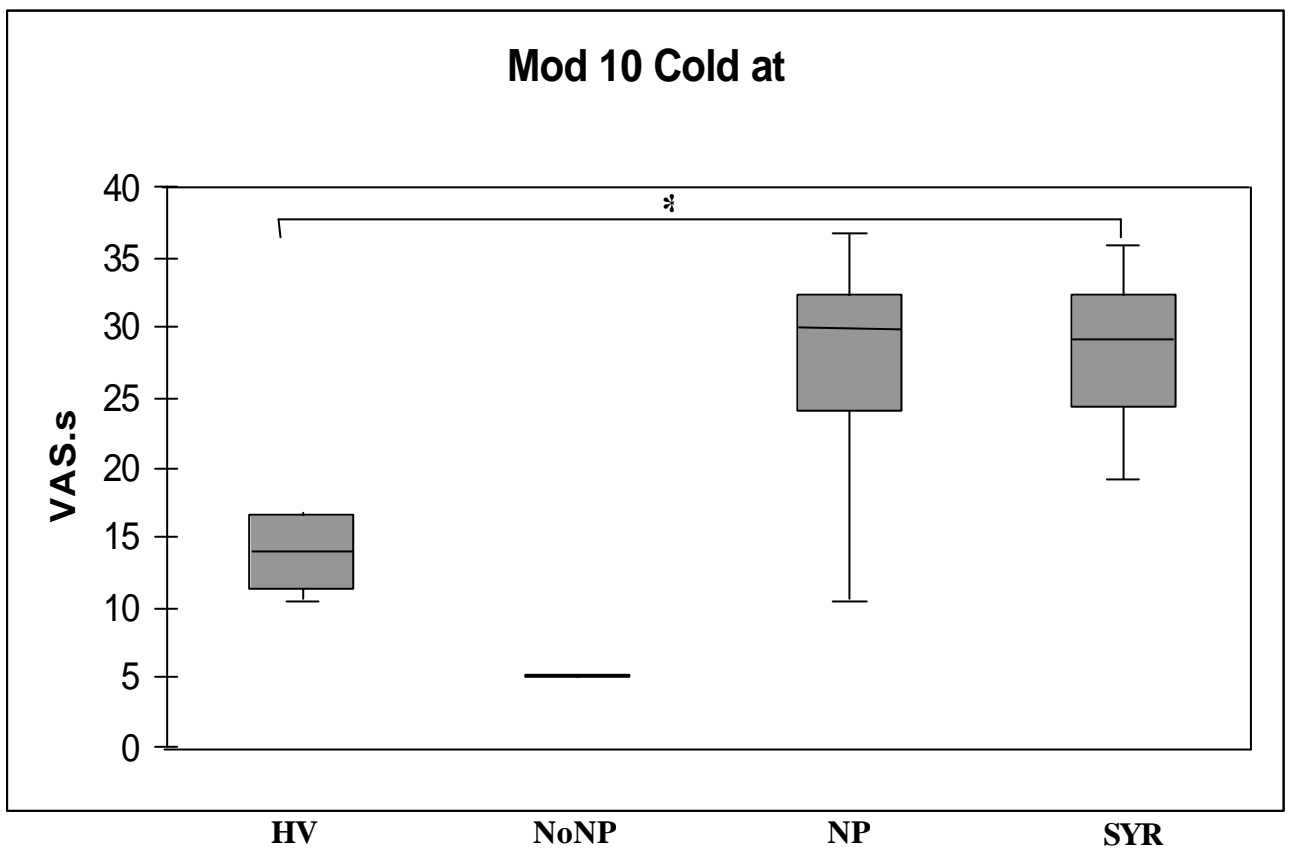
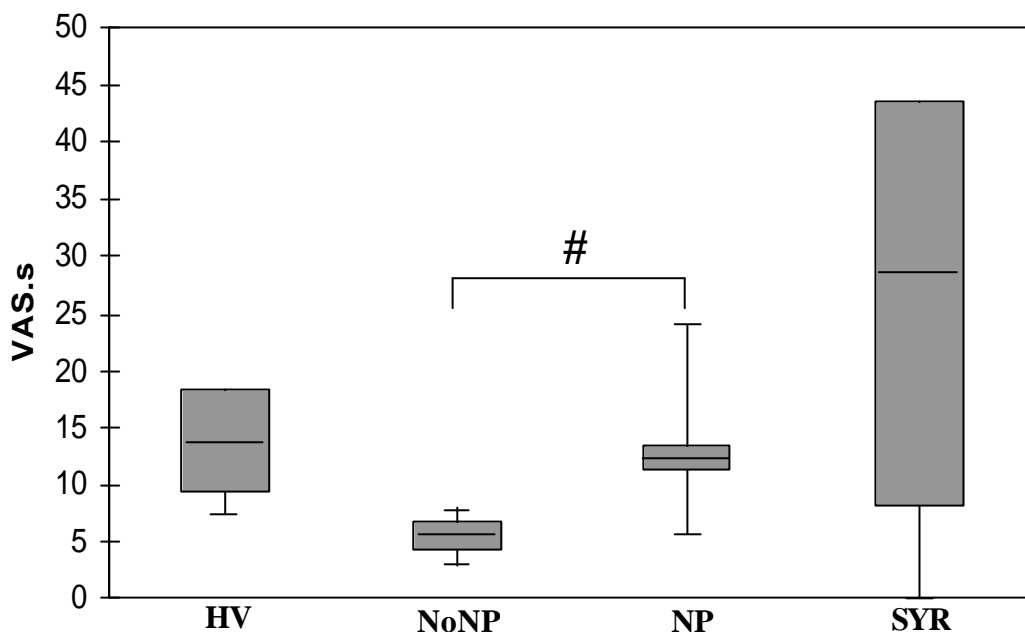


Fig.3.2. Example of the eVAS response for a SYR patient and HV subject with cold at level stimulation showing the first 10 s of response.



Graph 3.5. Initial response Modulus 10s for Cold stimulation at level for the four groups: NoNP= non Neuropathic Pain and SCI patients; NP= Neuropathic Pain and SCI patients; SYR=Syringomyelia and SCI patients; HV= Healthy volunteers. * = significant $p = 0.025$

Mod 10 Cold Above



Graph 3.6. Initial response Modulus 10s for Cold stimulation above level for the four groups: NoNP= non Neuropathic Pain and SCI patients; NP= Neuropathic Pain and SCI patients; SYR=Syringomyelia and SCI patients; HV= Healthy volunteers. # = significant only p = 0.059.

3.5. Discussion

3.5.1. Summary

Neuropathic pain, based on the identification of common pain descriptors and key sensory tests obtained with the DN4 questionnaire, was identified in both pain groups with scores of between 4-6 out of 10, specifically with the presence of “painful brush” in the NP and “hypoesthesia to pinprick” in SYR patients. When the sensory responses of the NP patients were compared with the HV group using standard BST/QST techniques, a reduction in at-level mechanical tactile and vibration detection threshold was identified, with an associated increase in sensory response intensity to 48°C (below and above level) and brush (below level). However, in general no significant differences were observed in at-level sensory function between NoNP and NP patients with standard pain tests or with tonic thermal testing methods, which may reflect the limited number of patients recruited in this study or the exclusion of non-painful responses to tonic thermal stimuli in the final analysis. Indeed the at-level sensory intensity in response to both innocuous and noxious stimuli in NP and SYR patients using standard BST/QST tests only scored 1/10 on the VAS, clearly below our defined pain threshold of 2. Furthermore, the at-level pain response rate to tonic thermal stimuli using the TSAR method was low, with responses to heat (HV 64%, NP 35%) being slightly higher than that for cold tonic stimuli (HV 45%, NP 20%). The maximum eVAS scores recorded in these responding patients to tonic heat ranged between 2.5-3.7, compared to 1.7-4.5 with cold stimuli, above the sensory response intensity measured

with standard BST/QST techniques. In general, the application of tonic cold stimuli at the level of SCI and measurement of the early (10s) integrated e-VAS response appeared to provide the best differential diagnosis between SCI pain patients and volunteers without pain (NP=30; SYR=29 versus NoNP=5; HV=14 e-VAS.s), but these data should be interpreted cautiously due to the low number of pain responding volunteers included in this study. No pain responses to tonic thermal testing applied below the level of SCI were measured in this study.

At and above-level tonic thermal testing was valuable in identifying the effect of SCI physical factors on sensory responses in the NP group and in SYR patients. Specifically, at-level pain response slope to tonic heat stimuli was higher in thoracic NP patients than that reported by the cervical NP group. At-level testing with tonic cold stimuli in patients with SYR also indicated a higher early integrated (10s) e-VAS response compared to the sensory response in HV, associated with a higher above-level maximum e-VAS response to tonic heat stimuli. These thermal sensory modifications in the SYR group were also identified with standard BST/QST techniques, where an increase in response intensity to a 48°C test-tube applied at and above the injury was identified in the SYR compared to the healthy group.

3.5.2. *Afferent and dorsal horn dysfunction during SCI-NP development*

Finnerup et al. (2003a,b), examined sensory detection and pain thresholds in patients following SCI and described significantly higher heat detection and tactile detection thresholds in pain patients compared to pain free subjects but no difference in pain intensity or tolerance thresholds. With the current BST/QST procedures allodynia to activation of low-threshold A β mechanoreceptors by brush was not detected either at or below the level of injury in our SCI patients. Mechanical allodynia (“pain caused by non-noxious stimulation”) has been identified in previous studies in experimental pain (**Campbell et al., 1988; Price, 1991**), and has been explained by the presence of hyperexcitable dorsal horn neurons, that begin to respond to A β low-threshold mechanoreceptor input (**Price, 1991; Bennett et al., 1994**). At level mechanical allodynia as identified by **Finnerup et al. (2003a)** may only develop during the chronic phase of SCI which could explain the difference found in our acute SCI pain patients.

The failure to find a significant decrease in tactile detection and mechanical pain threshold in some patients with allodynic skin indicates the absence of a generalized sensitization, either peripherally or centrally. In **Gottrup’s et al. (1998)** study a correlation failed between mechanical pain difference and evoked pain, (assessed by punctuate or by pressure stimuli). This observation, however, does not exclude the possibility that peripheral input from mechanosensitive nociceptors drives dorsal horn neurons into a state of hyperalgesia, which manifests itself as a mechanical hyperalgesia. The universal lowering of mechanical threshold may simply preclude the possibility of finding a correlation between nociceptor excitability and evoked pain. We tested our patients on the painful site and signs as temporal summation (only below the level) may be seen in painful and non painful sites; this may be due to an implication of spinothalamic pathways and not only of local fibres. As the previous authors concluded, dynamic and static hyperalgesia are probably mediated by different mechanisms, but both the dynamic and the static type may be maintained or generated by activity in heat-sensitive nociceptors. Even when we tapped the skin with a stiff von Frey hair by stimuli above 0.3 Hz (**Price et al., 1989; Price, 1991**) and a coarse brush (1-2 cm/s) every 1.5 s, we could not evoke or increase pain intensity.

Our results using tonic thermal stimuli that A δ and C fibres excited by the noxious heat and cold (48°C tube and acetone) presented significantly higher intensity response below the level of the lesion in NP group of patients compared to HV, although SYR group was higher at any level compared to the other groups. Although it is known that the population of receptors with A δ fibres in human skin respond to more than one modality of noxious stimulation -mechanothermal unit (**Bromm et al. 1984**) and the responses to noxious heat can occur without prior heating and the discharge rate can be higher than that shown by C polymodal nociceptors (**Treede et al., 1998**), we have not seen C fibre mechanical

excitation in acute patients, only in SYR, either at or below the level of injury. Moreover, and as occurred in our results, **Van Hees and Gybels (1981)** could not prove that mechanical stimuli activate the C polymodal nociceptors, even when their high levels of activity correlated well with pain when the afferent fibres were activated by noxious heat or chemical stimuli. This is probably due to the activation of specific C-fibre effect, as C-fibres do not respond to mechanical stimuli, and we found an enhanced response to thermal stimuli. It seems like the C polymodal nociceptors could not be excited differentially between groups by our QST examination with von Frey filaments and 48°C heat tube (except SYR versus HV above and below), even when it is known that the skin of the human hand and foot respond to noxious mechanical, thermal and chemical stimuli (**Bromm et al., 1984**); cooling is rarely effective in activating these units (**Wasner et al., 2004**), and warming to 40-45 °C can excite some of them. Since A δ mechanoheat receptors have a higher threshold for noxious heat pulses than do C polymodal nociceptors, these must be responsible for the discrimination of heat pain from threshold (43-45°C) to levels that can damage the skin (above 50°C) (**Adriaensen et al., 1980**). Therefore, it may be that active C-fibres are easier to recruit with cold/heat stimuli after SCI.

We would like to add here further research about some studies that have already been able to detect new types of C fibres, some of them are maybe more involved than others specifically in the SCI processes, since we have seen in our results that we rather did not detected their activation by the QST, but we had enhanced response to thermal stimuli. In addition to mechano-heat-responsive C units also found in previous studies, novel classes of C nociceptors in human skin have been reported, units responding only to mechanical stimuli, units responding only to heating, and units that were insensitive to mechanical and heating stimuli and also to sympathetic provocation tests; they may contribute both to primary hyperalgesia to heat and pressure after chemical irritation, and to secondary hyperalgesia as a consequence of central sensitization (**Schmidt et al., 1995**). On the other hand, the vasomotor responses are mediated by nociceptor input and reflect the processing of this input mainly at a spinal level; demonstrated because the stimulus induced changes of the skin blood flow in the stimulated hand during stimulation on periods of 2 min to induce tonic pain perceptions, and estimated the pain level at 10-sec intervals on a VAS (**Magerl et al., 1990**). A subpopulation of C-polymodal nociceptors is sensitive to noxious low temperature and may thus contribute to the determination of cold pain, which is probably one mediator of the symptom cold hyperalgesia in peripheral nerve disease (**Campero et al., 1996**). Also there are insensitive branches in human mechanosensitive cutaneous C nociceptors that can be detected by transcutaneous electrical stimulation and sensitized by topical application of chemical irritants. Activation of those branches in the course of inflammatory processes may contribute to spatial summation at central synapses and hence to hyperalgesia (**Schmelz et al., 1994**).

Although no temporal summation was registered in our subjects and patients with QST, other studies in animals using electrophysiology have shown that repeated stimulation of C fibres causes hyperactivity and prolonged discharge in the dorsal horn nociceptive cells (**Davis et al., 1987**; **Dickenson et al., 1987**). In normal subjects repeated Ad and C nociceptor stimulation cause temporal summation with increasing second pain and pain that outlasts the stimulation (**Price, 1991**). Repeated stimulation of A β -low threshold mechanoreceptors never produce pain in normal subjects, but produces abnormal “wind-up”-like pain in patients with nerve injury pain (**Price et al., 1989**). In **Eide et al. (1996)** in a study with SCI patients, “wind-up”-like pain in 64% of the patients by repeated stimulation with a high intensity von Frey hair, normally activating Ad and C nociceptors, and in 22% of the patients by a low intensity von Frey hair, normally activating A β low threshold mechanoreceptors; the difference with our study could be in our better homogeneity and less chronicity in the patient groups.

3.5.3. Neuronal hyperexcitability at the level of SCI: The Central Pain Generator Hypothesis (CPG)

Thoracic SCI subjects with NP presented higher pain sensitivity to tonic heat stimulation (see below). This observation is in contrast to similar reductions in thermal or mechanical detection and pain thresholds and sensitive evoked potentials observed in patients with or without pain (**Finnerup et al., 2003a**), although patients with pain below the level of the lesion showed significantly more *sensitive*

hypersensitivity at level than non-pain patients (**Finnerup and Jensen, 2004**). At level changes in sensitivity to pain stimuli may be related to higher grey matter lesions at the rostral end of the injury, observed by magnetic resonance (**Finnerup et al., 2003a**). High frequency spontaneous activity was recorded in dorsal horn nociceptive cells at the level of the injury in a paraplegic patient with central pain (**Loeser et al., 1968**). This data, together with **Vierck and Light's** work (**1999, 2000**) suggest the presence of *neuronal hyperexcitability* caused by excitotoxic changes and injury to inhibitory neurons at the *rostral end* of the lesion, may be an important additional mechanism SCI pain. **Nathan and Smith (1979)** suggested that the factor which would trigger ongoing dysesthesias might be the afferent input from below the level of the lesion into dysfunctioning hyperexcitable relays at levels rostrally to the lesion. Indeed, SCI central pain may also result from supraspinal neuroplastic changes in response to both deafferentation and abnormal input from a spinal pain generator (see below, **Finnerup and Jensen, 2004**). However, not all the patients with SCI present signs of hyperexcitability (**Finnerup et al., 2003b; Finnerup and Jensen, 2004**), indicating that other mechanisms are present.

3.5.4. Ascending sensory tract dysfunction during SCI-NP development

Our results with reduced touch and two point discrimination thresholds, combined with deficits in vibratory stimuli at the level of lesion indicate that some patient groups (SYR versus NoNP) present sensory dysfunction of the dorsal column lemniscal system. The SYR group presented higher pain intensity at and below level (QST) and at level with tonic cold stimuli (TSAR) also explains, like **Defrin et al. (2001)**, that pain and temperature remain after SCI, although supraspinal changes in pain centre function could contribute to these changes (see below). Because pain and thermal sensory perception are primarily mediated to the brain via spinothalamic pathways, whereas the sensations of touch, vibration and joint position are primarily mediated by dorsal column-medial lemniscal pathways (**Boivie et al., 1994; Beric et al., 1988**), central pain following SYR may reflect an imbalance of function between these two pathways.

In other studies, QST with incomplete SCI by **Davidoff et al. (1987)** found that testing of temperature and thermal pain indicated an absence of sensation in 77% of the patients. Vibratory sensibility was also reduced in another 77% and touch perception was diminished but preserved in 69%. Common features of most of their patients was the presence of vibratory and touch perception in contrast to absence of temperature and pain, indicating relative preservation of the dorsal column function with virtual abolition of the classical anterolateral, spinothalamic system function. They found a high incidence (81 %) of dysesthesias in SCI patients with a combination of absent spinothalamic functions and preservation of dorsal column function. Furthermore, **Pagni (1976)** concluded that lesions of the spinothalamic system regardless of the level that occurred produced dysesthesias and pain while lesions of dorsal column system produce only paraesthesias. This suggested that an imbalance between the temperature and pain system and large fibre-touch system can contribute to the abnormal spontaneous sensations. **Beric et al. (1988)** proposed that dysesthesias may result from central misinterpretation of residual dorsal column system input in the absence of suppression via integrated spinothalamic system activity. We believe, as **Beric et al. (1988)**, that the fact that dysesthesia is usually not present immediately after the SCI emphasizes the crucial role of a central supraspinal dysfunction which takes some time to develop. The usual time interval between post-trauma and the return of dorsal column functions offers an opportunity for follow-up sensory evaluation and perhaps application of measures to prevent such sensory reorganization that would lead to development of dysesthesias and pain.

3.5.5. Modified sensory function above the level of SCI.

In our studies using standard BST and QST methods, changes in sensory function to pain stimuli were identified in the pain groups following application of 48°C tube stimuli at the C2 dermatomal level. These results were in contrast to those results obtained by **Finnerup et al. (2003b)**, where failed to evoke pain above level SCI. Changes in sensory function due to downstream deafferentation has been identified in several studies, where central deafferentation may produce hyperexcitability and spontaneous activity, that may produce spontaneous and abnormal stimulus-evoked pain (see **Chapter**

2, 2.1.3. and 2.5.2 sections). In patients with spinal cord injury and central pain, recordings in the ventroposterior thalamus disclosed increased receptive fields and increased spontaneous activity in the denervated cells, and electrical stimulation in the denervated region of the thalamus induced pain similar to the central pain (**Lenz et al., 1988**). Epileptiform discharge recorded in hyperactive neurons in the thalamus was also demonstrated in patients with central pain due to causes other than spinal cord injury (**Yamashiro et al., 1991**). This has recently been confirmed by studies in animal models of SCI (**Hains and Waxman, 2006**).

3.5.6. Thermal hyperalgesia during neuropathic pain

According to our results at and below the level of the lesion, the occurrence of abnormal evoked pain by thermal heat and cold stimulation was significantly more common in painful (below and at the level of the lesion) than in non-painful denervated areas (c.f. **Eide et al., 1996**). Although neither allodynia nor “wind-up” like pain was not observed in acute SCI NP patients, previous findings of abnormal evoked pain may be consistent with the experimental findings of hyperexcitability in nociceptive spinothalamic tract neurons, which may be involved in the pathogenesis of central pain (**Eide et al., 1996**). However, thermal hyperalgesia is not always evident, and in neuropathic pain patients’ hypoalgesia, hyperalgesia and normal sensitivity to thermal stimuli may all be demonstrated in the painful area (**Lindblom and Verrillo, 1979; Verdugo and Ochoa, 1992**). In amputees, hyperalgesia to mechanical stimuli can be demonstrated without associated thermal hyperalgesia (**Nikolajsen et al., 1996**). Furthermore, in experimental neuropathic pain models, hyperalgesia to mechanical stimuli may be seen in the absence of thermal hyperalgesia (**Bennett and Xie, 1988; Seltzer et al., 1990; DeLeo et al., 1994**). In **Gottrup’s et al. (1998)** patients with unilateral traumatic nerve injury and brush-evoked allodynia there was an inverse relationship between heat and cold pain difference and degree of mechanically evoked pain, which is consistent with results reported by **Rowbotham and Fields (1996)** in patients with post-herpetic neuralgia, which suggest that abnormal mechanically-evoked pain in traumatic nerve injury is in part maintained or generated by activity in thermosensitive nociceptors. They found an inverse relationship between thermal sensory threshold and spontaneous pain intensity, similar to the cold spontaneous pain correlations found by us, and a positive correlation between spontaneous pain intensity and severity of brush-evoked allodynia. The influence of thermosensitive nociceptors in maintaining or generating sensitization is supported by the parallel increase of touch-evoked pain and spontaneous pain following incremental increases of skin temperature which is observed in patients with traumatic nerve injury and heat hyperalgesia (**Koltzenburg et al., 1994**).

3.5.7. Heat and cold sensory channels

In our SCI patients tonic thermal testing at the level of the injury generated less response rate of pain with cold (except in SYR patients) but not with heat stimulation, possibly due to the longer time to activate deeper cold receptors (**Morin and Bushnell., 1998**). In general, although not significant, the integrated pain response to tonic cold stimuli revealed interesting differences between SCI with and without neuropathic pain. Interestingly a higher proportion of WDR neurons and high-threshold (HT) neurons respond to innocuous cold stimulation in NP SCI animals. These results suggest that the chronic pain-like behaviours in spinally injured rats may be generated and maintained by abnormalities and enhanced sensitivity to cold in dorsal horn neurons (**Hao et al., 2004**). In contrast, heightened sensitivity to tonic heats stimuli was noted at the level of thoracic SCI in NP patients.

A generalized response to cold stimuli in NP patients may be due to the wide distribution of cold receptors in the vascular system (**Fruhstorfer and Lindblom, 1983; Klement and Arndt, 1991; 1992**) whereas those for innocuous warm and cool are located in the skin (**Klement and Arndt, 1991**). Tonic stimulation of vascular thermal receptors may contribute to the continued increase in heat and cold pain perception observed throughout the 30s stimulus presentation used in **Morin and Bushnell’s (1998)**. Interestingly, larger temperature differences were needed in the noxious cold than noxious heat range to produce equal perceptual differences, which may reflect a longer activation time of deep cold receptors. This temperature-perception relationship is similar to that between temperature and response

rates of dorsal horn lamina I HPC (heat-pinch-cold) neurons that respond to noxious heat and cold (**Craig and Bushnell, 1994; Craig and Serrano, 1994**), suggesting that the activity of such neurons could subserve the perception of both heat and cold pain. Wide-dynamic-range (WDR) neurons in deeper layers of the dorsal horn that respond to both noxious heat and noxious cold (**Kenshalo et al., 1982**) could also participate in the perception of both heat and cold pain. **Chery-Croze and Duclaux (1980)** observed that when punctate skin areas are stimulated with extreme heat or cold, subjects reported no temperature sensation, but only a pricking sensation for both extremes. However, despite the lack of temperature perception and the similarity of the pricking sensation, subjects could distinguish noxious heat from noxious cold, suggesting differential processing somewhere within the CNS.

Electrophysiological and functional brain imaging studies indicate that higher level processing of noxious heat and cold may provide differential information regarding pain. In the monkey (**Craig et al., 1994**) and human thalamus (**Lenz et al., 1993**) some neurons responded exclusively to noxious heat whereas others also responded to cold. Positron emission tomography (PET) studies in humans show that noxious heat activates cortical regions, principally the primary and secondary somatosensory cortices (SI and SII), anterior cingulate area 24 (ACC) and regions of the insular cortex (IC, **Jones et al., 1991; Talbot et al., 1991; Coghill et al., 1994; Craig et al., 1996**). The same regions may be activated by noxious cold but SI is activated more by heat rather than by cold pain and interestingly the IC more by cold pain than by heat pain. The differential activity within these regions may partly explain the different perceptual qualities of heat and cold pain.

3.5.8. Sensitization to tonic heat stimulation

No evidence for abnormal pain processing could be identified in acute SCI NP patients with repeated pinprick stimulation (c.f. **Eide et al., 1996**) or with tonic thermal stimuli with the TSAR system (c.f. **Kleinböhl et al. 1999**). It is unlikely that the present tonic thermal method was insufficient to induce temporal summation, as a very rapid sensitivity to heat was revealed at the level of thoracic SCI. Although we cannot explain the differential response to thermal and mechanical stimuli, we would note that a similar difference has been noted in other neuropathic pain patients (**Price et al., 1989; Nikolajsen et al., 1996**). **Price et al. (1989)** found that the magnitude of temporal summation to repetitive heat stimuli to be the same in symptomatic skin as in contralateral normal skin, in patients with neuropathic pain, regardless of whether thermal hypoalgesia or hyperalgesia was present.

Kleinböhl et al (1999) used a tonic heat paradigm (the “dual sensitization” procedure which provides a subjective and behavioural index of sensitization, **Kleinböhl et al, 1993; Van Ackern et al., 1994; Kleinböhl, 1996**) to assess early sensitization (15-100s) in 30 chronic pain patients with musculoskeletal/back pain and headache pain and healthy controls. They found that the degree of sensitization was linearly related to stimulus temperature, and that the groups differed significantly in the “sensitization gradient”: musculoskeletal pain patients sensitized earlier and stronger than healthy subjects. Interestingly, this enhanced heat sensitization in musculoskeletal patients was largely independent of altered pain thresholds, which limits the original hypothesis that temporal summation to tonic noxious stimulation should be a general factor in the development of chronic pain as suggested by previous studies (**Kenshalo et al., 1979; Klepstadt et al., 1990; Ren, 1994**). Rather, it suggests a patient subgroup with heat sensitization, particularly prominent in chronic musculoskeletal pain patients, but not limited to them. Enhanced sensitization in musculoskeletal patients was reflected both by early sensitization below pain threshold and by the slope of the sensitization gradients. A small subgroup of “extreme sensitizers” could be distinguished lying outside the control range of gradients. Musculoskeletal pain appeared to be over-represented in this extreme group which also showed an extremely low tonic pain threshold.

Short-term sensitization could not be related to the duration of pain in the **Kleinböhl et al (1999)** study. The most practical finding of this study was the fact that different types of heat pain thresholds and gradients of tonic heat sensitization had a different validity in discriminating between chronic pain syndromes, and also in discriminating patients from healthy controls. This indicates that both pain

severity and pain sensitization may be combined with benefit in experimental clinical studies. The observation that pronounced heat sensitization appeared well below pain thresholds in patients while no impressive sensitization was found in controls up to clearly painful intensities, is at variance with earlier reports using repetitive stimulation in a temporal summation paradigm (**Price et al., 1994; Lautenbacher et al., 1995**) and subjective ratings which suggest pronounced temporal summation in healthy subjects. It is possible that an examination heat sensitization below clear pain threshold in our study may also have revealed central sensitization.

Tonic stimulation together with the bias-free psychophysical method of readjustment to apparent initial temperature used in their method addresses a different kind of temporal summation or sensitization to nociceptive input, possibly more closely related, as the authors said, to central sensitization which is assumed to be a relevant process for the development of chronic pain. This unbiased behavioural method may also simply provide a truer measurement of sensory temperature processing thus showing clearly specific sensory changes in patients, as in our study. The hypothesis that sensitization to tonic stimulation at the perceptual level in the range 15-100s is related to “central wind-up” would directly relate psychophysical and neurophysiological aspects of the process leading to chronic pain (**Tölle et al., 1996**). There are several arguments in favour of this relationship: firstly, intensity and duration of the tonic stimuli applied in the dual sensitization procedure are within the necessary range to trigger windup processes (**Price et al., 1994**). Second, windup is a characteristic and specific feature of nociceptive wide dynamic range (WDR) neurons which transfer afferent input, underlying heat pain perception (e.g. **Talbot et al., 1989**). Third, the temporal characteristics of subjective sensitization correspond to those of wind up: the response of WDR neurons gradually increases over 5–20 s (**Willis, 1990**) as does the intensity of sensation in the dual sensitization procedure (?E). This process is reversible while stimulus temperatures are between 48 and 50°C, and it can be repeated within relatively short time-intervals corresponding to the intertrial intervals of the present study. Therefore, later sensitization of the skin and induced “hyperalgesia” is not present. Sensitization at the perceptual level appears below pain threshold and increases systematically with higher temperatures, which is also known in central sensitization processes (**Willis, 1990**).

The fact that pronounced heat sensitization began far below pain threshold in those patients argues for additional processes to be involved in clinical populations (**Kleinböhl et al. 1999**). Central sensitization would be sufficient to explain their findings, if premature sensitization could be related to lowered critical frequencies for “wind-up” in patients, which lies normally in the range of 0.3 to 0.5 Hz (**Mendell, 1966; Price et al., 1977**). Alternatively, elevated tonic discharge rates of C-polymodal afferents below 45°C could be responsible for the difference in controls, but considering the unremarkable deviations in pain threshold per se, this seems less probable. Studies on the effects of specific NMDA-receptor antagonists on subjective and behavioural sensitization as compared with pain thresholds should clarify this question. They should also show which parameters of the sensitization characteristic differentiating between subgroups of pain patients are actually connected with “wind-up” or other NMDA-sensitive processes at higher levels and which are not. This would help to specify the meaning of clinical observations and pilot trials demonstrating positive effects of a number of NMDA-antagonists in adjuvant pain medication (**Quack, 1994; Persson et al., 1995**).

3.5.9. Relative role of central and peripheral sensitization after SCI

We found significant higher and very rapid heat sensitivity (2 units of VAS/s) at the level of thoracic SCI level in the NP group, but not when applied at any other body site, nor with the application of tonic cold stimuli. It is widely accepted that both peripheral and central processes may play a role in the pathophysiology of the NP symptoms after SCI (**Wall editors letter Pain, 2001**). Sensitization of nociceptor unit receptors, spontaneous or stimuli-induced ectopic impulse generation, “multiplication” of impulses, and ephaptic transmission are possible pathophysiological mechanisms that may be present at the peripheral level which may explain the patient's symptomatology (**Serra, 1999**). Despite the apparent disparity between perceptual temporal summation and nociceptor adaptation, using microneurographical techniques, central and peripheral sensitization mechanisms are proposed that can

reconcile the relationship between nociceptor activity and pain perception (**Andrew et al., 1999**). Furthermore, the role of peripheral mechanisms at the receptor level is alluded to by **Morin and Bushnell's (1998)** study. In fact, heat pain, cool and warmth appear to depend on surface temperature, whereas cold pain is related to subcutaneous temperature, suggesting that different receptors are activated at different skin depth for noxious heat and noxious cold. It has been observed in monkeys (**Tillman et al., 1995**) that receptor endings for CMH nociceptors are located in the epidermis and dermis, and data collected by **Morin and Bushnell (1998)** study suggest a similar receptor location in humans.

3.5.10. Neuropathic Pain in patients with Syringomyelia

Most of the patients with syringomyelia (64%) presented an atraumatic injury, while the traumatic cases were caused mainly by traffic accidents. All of these patients presented chronic cases of injury and 91% were medicated due to the presence of dysesthesia. Examination of fMRI images taken from these patients highlighted spinal cord cavities with associated white matter injury in 10 out of 11 patients (see example in **Appendix Picture 3.7 and 3.8**). These findings are consistent with **Vierck et al. (1990)**, who described that white matter injury may play a role in NP development after SCI, but that gray and white matter injury is required for full development of this pain. In contrast, some studies have indicated that gray matter injury slightly rostral to the SCI is required for central pain development after SCI (**Finnerup and Jensen, 2004**). However, the resolution of our magnetic resonance images does not permit us to speculate on the extent of gray matter damage in syringomyelia, although it is likely that ascending tracts are further compromised compared to NP patients, based on lower supraspinal responses to tonic cold stimuli (see above).

3.5.11. Thermal stimulation in Syringomyelia patients

Changes in sensory function at and above the level of syringomyelia were noted with BST and tonic thermal stimuli. At level, an enhanced sensory intensity in response to heat at 48°C (test-tube) and a higher early integrated (10s) pain response to tonic cold stimuli, was seen when compared to the healthy volunteer group. Importantly, the number of pain responding in SYR patients was the same as that observed in the HV group. Above level a higher VAS (48°C test-tube) and maximum pain e-VAS (tonic heat) score was obtained when compared to the HV group suggesting supraspinal changes in sensory function due to either spinothalamic or higher pain centre dysfunction. This hypothesis was further supported when a significantly reduced 10 and 30s integrated pain response to tonic heat stimuli was identified at the supraspinal level when compared to the SCI-NP patients.

However, **Ducreux et al. (2006)** found no significant difference in the magnitude of sensory deficits between patients with or without NP, suggesting that lesions of the spinothalamic pathways are not sufficient for the development of central pain. A different pattern of sensory deficit was observed between patients with spontaneous pain only (n=11) and patients with both spontaneous pain and allodynia (n=20), which was interpreted as a complex interaction of pathophysiological spinal mechanisms that may contribute to central NP during syringomyelia. Indeed both psychophysical and functional neuroimaging testing demonstrated that different central NP symptoms are sustained by distinct mechanisms. In patients with spontaneous pain only, the thermal sensory loss was significantly more asymmetrical and there was a direct relationship between the extent of thermosensory deficits (i.e. deafferentation) and the intensity of burning pain. In contrast, patients with allodynia had reduced thermal deficits, in terms of both intensity magnitude and body extension. In addition, the sensory deficits were different between patients with cold or tactile allodynia, suggesting distinct pathophysiological mechanisms related to the sub-modalities of allodynia. Their fMRI study further confirmed this, showing that different sub-types of allodynia were associated with distinct patterns of brain activity, which do not necessarily correspond to the “pain matrix” involved in acute physiological pain. The prefrontal cortex was the only area consistently activated by pathological evoked pain, suggesting that alteration of high-level pain modulatory mechanisms might play a major role in allodynia due to central lesion. From a clinical perspective, these data suggest that these symptoms should respond differently to treatment (**Attal et al., 2000; 2002**) and confirm the

importance of a mechanism-based classification of patients with neuropathic pain, including central pain.

3.5.12. Methodological issues associated with BST/QST measurement of SCI- NP

3.5.12.1. The Neuropathic pain diagnostic questionnaire (DN4)

The presence of neuropathic pain was successfully identified in both the NP and SYR patient groups (in mean values; =4/10 compared to the non-pain groups NoNP=2/10 and HV=0/10 respectively), although no differences were found between patient groups for either the sensory descriptors or BST examination of sensory function. The number of DN4 sensory descriptor items utilized by neuropathic pain patients (i.e. 9.82% in NP and SYR groups) was higher than that identified with examination of sensory function (i.e. 17-61% in NP and SYR groups), in agreement with the study by **Bouhassira et al. (2005)**. In our study “tingling” and “numbness” were the sensory descriptors most widely used by NP patients. Hypoaesthesia to touch and pin-prick were much more frequent in NP than in NoNP patients and are similar to other studies (**Carli et al., 2002; Giesecke et al., 2004; Petzke et al., 2003; Staud et al., 2003; Nielsen et al., 2005**). The presence of painful brush was also more frequent in NP in contrast to, although dynamic allodynia was not formally in NP pain patients based on VAS intensity scores.

Even though this study focused on NP after central SCI, the possible contribution of peripheral injury cannot be excluded. Interestingly, no difference between the frequency of the DN4 items was observed between patients presenting peripheral or central lesions, with the exception of pain increased by pressure which was more frequent in patients with a peripheral lesion (i.e. 54% vs. 31%, $p < 0.01$; **Bouhassira et al., 2005**). Consequently we may propose that the DN4 questionnaire may be valid in its application in the SCI population that include central and/or peripheral lesion. In conclusion, the DN4 Spanish version is an important tool for initially identify NP in the clinic, but is rather poor in differentiating between acute SCI-NoNP and NP patients based on sensory examination and the incidence of pain descriptors.

3.5.12.2. The importance of stimulation site in experimental pain studies

It is well known that critical variables such as the location, temperature, duration and surface area of the test stimuli affect the composition, dispersion and magnitude of the afferent volley, which in turn affects central temporal and spatial summation, ultimately modulating the timing of ascending activity to the cerebral cortex. When possible, mechanical and thermal sensory testing was performed on hairy skin in those subjects studied here. The dorsal aspect of the arm and hand, trunk and lower leg was selected for mechanical and thermal stimulation. Some studies indicate that mechanoreceptors in the human hairy skin do not differ considerably in their characteristics from those receptors in human glabrous skin (**Järvilehto et al., 1976**). In contrast, hairy skin presented a much lower heat pain threshold than glabrous skin (**Taylor et al., 1993**). **Granovsky et al. (2005)** found that on hairy skin of the hand, 41°C stimuli using a peltier device similar to the TSAR system, evoked an ultra-late evoked potential mediated by C fibres, whereas this potential was only registered with a 51°C stimuli mediated by Ad afferents. The most intense heat stimulus applied to glabrous skin (51°C) failed to evoke an Ad-mediated response suggested to be due to the low number of (if any) of AMH type 2 receptors (**Haimi-Cohen et al., 1983; Tillman et al., 1995**), but other psychophysical studies indicated that at moderate stimulus intensities to hairy skin the increment in VAS as a measure of sensitization is likely to be mediated by AMH type 2 fibres (**Treede et al., 1998; Kleinböhl et al., 2006**).

Recent studies have identified cerebral activation with specific afferent fibre stimulation. For instance, **Granovsky et al. (2005)** applied stimuli that were more selective for C fibres because of the low heat intensity employed (below the threshold for all receptors innervated by Ad fibres); the highest intensity was below the threshold for type 1 AMH nociceptors. Peltier contact heat stimulation is advantageous because of the more prolonged and spatially extensive excitation of C-innervated receptors with a

clearly defined evoked potential, similar to that observed with laser stimulation of **Towell et al. (1996)**, who found that painful stimulation of either hairy or glabrous skin evoked an ultra-late potential at shorter latencies.

3.5.12.3. Individual differences in pain sensitivity: Responders versus non-responders.

One of the most striking features of pain studies is the large range variation in response to identical noxious stimuli (**Nielsen et al., 2005**). Our experience with the peltier system was for a higher response rate to tonic heat applied in HV and NoNP at the level of injury. In addition, BST/QST techniques also revealed a wide range of variation in sensory response rate, depending on the site of stimulation relative to selected lesion level and the instrument used (see **Table 3.9**). Several chronic pain conditions are associated with increased individual sensitivity to experimentally induced pain (**Carli et al., 2002; Giesecke et al., 2004; Petzke et al., 2003; Staud et al., 2003; 2004; Nielsen et al., 2005**).

Recent studies indicate that individual differences in sensory responses to experimental stimuli are correlated with individual differences in pain-related brain activity (**Coghill et al., 2003**), and also partly influenced by genetic factors (**Diatchenko et al., 2005; Kim et al., 2004; Solovieva et al., 2004; Zubieta et al., 2003**). These findings provide crucial evidence that individual differences in *reported* pain intensity may reflect actual differences in *experienced* pain. Using a single fixed stimulus intensity is problematic for many stimulus modalities because the wide range in individual variation produces a “flooring and/or ceiling effect”, highlighting the difficulty in identifying a stimulus that is both tolerable and painful for all subjects. An alternative is to test each subject with temperatures that are painful but tolerable to that subject, and to extrapolate the measured scores (**Nielsen et al., 2005**), which is the method that we adopted for tonic thermal stimulation. The **Nielsen et al. (2005)** study indicates that the positively accelerating power function is an excellent model of individual stimulus–response functions evoked by painful contact heat.

Another major methodological problem encountered in this study was the low sensory response rate to either BST or tonic thermal stimuli clearly within the pain intensity range (2-10 on the VAS). Indeed many tonic thermal responses were below 1.5 and were not therefore analyzed. This occurred mainly with cold stimuli, but was also prevalent with tonic heat testing in both patients and healthy volunteers.

These problems were addressed by initially identifying the temperature required to produce a VAS score of 2/10 (pain threshold). These temperatures were usually in the range of 47-49°C for heat, but we were unable to lower the cold testing temperature to below 3°C for technical reasons. Consequently, the stimuli were painful in nature but were not tolerated up to 30s by healthy volunteers, and presented further tolerance problems in SCI patients. Thus, the probability of finishing a tonic thermal trial probably reflects the adoption of temperatures that do not always induce a painful response (1-2/10 on the VAS using a mean of 48°C for tonic heat stimulation and a mean of 3°C for tonic cold stimulation). Indeed analysis of non-painful sensory responses to thermal stimuli may also provide valuable information regarding sensory dysfunction during neuropathic pain conditions (see below, **Kleinböhl et al, 1999**).

Random order stimulus presentation would eliminate response bias due to expectations (**Petzke, et al. 2003**), however we decided to follow a fixed protocol due the technical limitations of the TSAR system, with cold stimuli requiring a longer preparation time than for tonic heat stimuli and thus being associated with different intertrial testing times. Indeed **Nielsen et al. (2005)** demonstrated that augmented pain ratings, flattened pain curves and a marked reduction in pain thresholds was present when stimuli were presented as a random series. It has been suggested that randomization may also introduce other methodological complications. For instance, if some of the stimuli given are perceived as painful, randomization may introduce the expectation that all the testing stimuli may be painful (**Nielsen et al., 2005**).

Another potential factor that contributes to individual pain response rate may be the presence of pharmacological treatment in some patients. Almost 70% of our patients were medicated with Amitriptyline and/or Gabapentin, especially this latter reduces tactile allodynia in a rat model of neuropathic pain (**Wallin et al., 2002**) and oral Gabapentin, administered to healthy volunteers in a regimen similar to that used in treating chronic neuropathic pain, reduces measures of central sensitization evoked by intradermal capsaicin (**Gottrup et al., 2004**). These unidentified treatment effects may have decreased sensitivity to nociception in our patient population and may explain why clear pain responses were not recorded in all patients in this study.

3.5.13. Non-painful and painful sensory responses to BST/QST

The visual analogue scale (VAS) has demonstrated to be the most used instrument to measure pain (**See Chapter 1**). In our studies a *unique and continuous VAS scale* was used to measure pain intensity, including the rating of non-painful sensations below the defined pain threshold of 2. We employed the VAS as a continuous all inclusive rating of non-painful sensory intensity, that became unpleasant and then finally painful until the end of the scale which was defined as unbearable pain.

Any sensory response to standard BST/QST methodology perceived higher than 0.5 on the VAS scale was analyzed (non-painful). However, clear pain sensations were scarce when measured in most of the patient groups, addressing the issue of whether the presence of pain signs to normally innocuous and noxious stimuli necessarily are associated with just painful (2/10) or obviously painful (>2/10) responses. The IASP's definitions of these terms (see Introduction Chapter 2) do not allude to any VAS threshold intensity score. Moreover, the IASP definitions pronounce that "the activity induced in the nociceptor and nociceptive pathways by a noxious stimulus is not pain, which is always a psychological state, even though we may well appreciate that pain most often has a proximate physical cause", highlighting that the local sensory responses may not be "painful" (see Psychological mechanisms in Chapter 4). It is possible that those responses measured with standard BST/QST methods may not be defined as allodynia or hyperalgesia, but we suggest that those sensations experienced by the patients are close to pain in quality, and may allow us to study the underlying pathophysiological mechanisms associated with changes in nociceptive function after central injury. In this study e-VAS scores of greater than 1.45 were analyzed, although in some cases the majority of subjects responded with sensory responses below 1/10 on the scale. The clinical interest of measuring such non-painful responses is currently under investigation.

Pain response intensities to tonic heat ranged between 2.5-3.7 (just above pain threshold) compared to 1.7-4.5 (from just below threshold to moderate pain intensity) with cold stimuli in those patients studied here, similar to those intensities measured in other studies in chronic neuropathic pain patients (**Gruener et al., 1994; Eide et al., 1996; Defrin et al., 2001**). The wide range of sensory intensity is exemplified by the recent study of **Granovsky et al. (2005)** where the stimulation of the glabrous thenar skin produced sensations of mild/strong but painless warmth when peak contact heat temperatures of 41 and 51°C were applied, respectively, in contrast to the response to 51°C applied to the hairy skin of the dorsum of the hand which was described as moderately painful with a pinprick-like sensation (VAS intensity between 5-6) compared to a warm sensation following 41°C stimuli.

3.5.14. Tonic thermal testing conditions

3.5.14.1. Temporal issues of thermal stimulation

In this study, a 30s thermal stimulus was sufficient to evoke, in pilot experiments, both a consistent pain and a prolonged e-VAS response that included several sub-components, such as a maximum pain score, sensory response slope, early 10s integral and a long 30s integral. Tonic thermal stimuli have been used widely by other authors (**Yarnitsky et al., 1992** used 40s stimuli while **Granot et al., 2003** used 30s). Unfortunately complete pain curve responses could not be obtained and compared between subject groups because of the heterogeneity between samples and the different individual tolerance to tonic thermal stimuli.

Some studies have already reported that tonic thermal/repetitive stimuli may increase or decrease perceived sensation (**Pertovaara and Kojo, 1985; Staud et al., 2001; Tillman et al., 1995; Yarnitsky and Ochoa, 1990**). It is to be expected that tonic/repetitive stimuli could sensitize sensory pathways and cause an increase in pain scores for subsequent stimuli. However, pain scores for phasic stimuli (47°C of 30s duration) were not changed by a preceding tonic stimulus (47°C of 70s duration) despite a high pain intensity (VAS) of 5.4 ± 2.3 in the **Granot et al. (2003)** study in healthy subjects. Furthermore, phasic and tonic pain scores were significantly correlated. These results support the concept that a strong sensitisation in pain patients can be measured using tonic thermal stimuli (**Eide and Rabben, 1998; Kleinböhl et al, 1999**).

In our study we used thermal stimuli that were already at noxious temperatures without a previous habituation process and was therefore considered to produce more reliable painful responses during the initial phase of thermal stimulation. In addition, lower temperatures for cold (usually 3°C) and slightly higher temperatures for heat (usually 48°C) than were applied in the **Granot et al. (2003)** study were adopted, as they represented better the pain thresholds for healthy subjects. **Morin and Bushnell (1998)** used various cold temperatures ranged from -5° to 23° °C and heat temperatures from 41° to 48° °C and found that 47° °C and 9° °C accurately defined heat and cold pain threshold respectively (VAS=5) in healthy subjects. However, their tonic thermal stimulation method included a ramp from neutral to desired noxious temperature, particularly as both volunteers and patients can habituate better to tonic noxious stimulation, including those fibromyalgia patients in the study by **Staud et al. (2004)**.

3.5.14.2. Analysis of pain response components: Slope, Maximum and Integrated e-VAS response.

In this study, the application of tonic thermal stimuli revealed significantly higher at-level sensory responses (higher slope to heat stimuli) between thoracic SCI NP patients compared to cervical injury while SYR patients described a higher early 10s integrated sensory response to cold stimuli relative to HV. Importantly, significant differences in integrated sensory responses were identified when no change in maximum pain response was observed. Above the injury subcomponent analysis revealed further interesting changes in sensory function. While lower integrated responses to cold stimuli were observed in the NP compared to SYR patients, the opposite was true when heat produced a higher maximum pain response in the SYR group suggesting that diagnostic identification of supraspinal changes in pain function are modality specific. Generally, the application of tonic cold stimuli at the level of SCI and measurement of the early (10s) integrated e-VAS response appeared to provide the best differential diagnosis between SCI pain patients and volunteers without pain (NP=30, SYR=29 versus NoNP=5, HV=14 e-VAS.s) and may provide some information into changes in supraspinal sensory function (NP=12 versus SYR=27 e-VAS.s), but these data should be interpreted cautiously due to the low number of subjects responding with pain sensations. In tonic thermal and mechanical stimuli study, **Arendt-Nielsen et al. (1996)** demonstrated an increase in central sensitization in hyperalgesic pain areas, suggesting a way in which temporal summation and hyperalgesia may be present and indeed modulated by similar common neural mechanisms.

Morin and Bushnell (1998) used the tonic thermal stimulation procedure, with a ramp from neutral to the noxious range, showing a positively accelerating stimulus-response function in the heat range and a negatively accelerating function in the cold range in a small sample of healthy volunteers, with a change in slope near pain threshold for both ranges. The slopes between innocuous warm and noxious heat were significantly different and had a similar tendency between innocuous cool and noxious cold. For example, the slope for heat pain was 69.7 ± 36.4 , and for cold pain was 2.1 ± 0.6 (absolute values). The steepest slope was found in the heat pain range. No difference in peak latency between heat pain ratings and cold pain ratings was identified, with latency times lying nearly at the end of the 30s stimulation period. The times of maximum warm and cool perception neither differed, but both of these latencies were observed well before the end of the tonic stimulation period. At the end of stimulation, subjects continued to feel heat or cold for a period of time. For noxious heat and innocuous warmth and cool, this delay was short (2.8-5.5 sec) but for painful cold stimulation, the

delay was significantly longer (13.7 sec). These results were explained by the hypothesis that heat pain, cool and warmth depend on activation of receptors at the surface, whereas cold pain was related to subcutaneous temperature, suggesting activation of different receptors for noxious heat and noxious cold.

Looking at our data results (see **Table 3.10 in section 3.4.5**), we observed that the medians for maximum e-VAS scores at-level testing with either tonic heat (VAS=3.7) or cold (VAS=3.7) stimuli were generally higher in HV than the sensory response obtained at the C2 dermatome (VAS=1.8-1.9), while the highest pain score was registered by the SYR group at level in response to cold stimuli (VAS=4.5). In contrast, the NP group generally presented higher pain scores during tonic at-level cold stimulation (VAS=3.2 in NP group) compared to heat stimulation (VAS=2.5 in NP group). Maximum VAS as a pain variable was sufficiently sensitive to distinguish between SCI-NP patients from the NoNP group (VAS=1.7), although the highest level of pain experienced was not greater than that identified in the HV group (VAS=3.8).

Analysis of the early integrated (10s) pain response to tonic cold stimulation provided better differential diagnosis between subject groups and SCI levels, including HV, than the max VAS pain variable. While tonic cold stimulation applied to healthy subjects produced the same integrated VAS score at or above the level of SCI (14.2 versus 14.0 VAS.s), tonic heat stimulation revealed a much higher pain response in the HV group when applied at the C2 dermatomal level (at level=2.4 versus above level=14.7 VAS.s). A better differential diagnosis was also reached with at-level tonic cold stimulation when NP patients (NP=29.8 and SYR=28.7 VAS.s) were compared with either the HV (14.2 VAS.s) or NoNP (5.2 VAS.s) groups, suggesting that NP after SCI is more readily detectable using cold stimuli. Furthermore, SYR patients presented no difference between the integrated 10s pain response applied either at level (28.7 VAS.s) or below level (27.0 VAS.s), in contrast to tonic cold stimulation testing in the NP group (at-level=29.8 versus above-level=12.3 VAS.s). Further evidence for a sensory dysfunction in SYR patients at the supraspinal level is supported by a sub-modality differences when the 10s integrated pain response to cold stimuli (27.0 VAS.s) is compared in response to tonic heat stimuli (above-level=0.0 and at-level=24.5 VAS.s).

Consistent with **Morin and Bushnell's study (1998)**, our data identified higher pain sensitivity slopes in response to tonic heat (1.4 VAS/s) compared to cold (0.1 VAS/s) in healthy controls. Furthermore heat sensitivity in the HV group was higher at the level of injury than that identified at the C2 dermatomal level (At-level=1.4 versus Above-level=0.3 VAS/s). Sensitivity to at-level tonic heat stimuli was significantly higher in thoracic NP (1.8 VAS/s) when compared to the cervical NP group (0.1 VAS/s). However in general, spinal cord injury presented reduced slope measures at-level tonic heat compared to the HV group but had increased sensitivity to cold stimulation in pain patients (HV=0.1, NP=0.7 and SYR=0.3 VAS/s) with the response in the NoNP group considerably lower (NoNP=0.05 VAS/s). Above level changes in sensory function to tonic thermal testing were similar to that described using the 10s integrated pain response, where patients with SYR presented higher sensitivity to tonic cold (SYR=0.2 versus HV=0.05 VAS/s) and a dramatic loss of sensitivity to tonic heat (SYR=0.02 versus HV=0.33 VAS/s).

3.5.14.3. *Qualitative sensory pain descriptors*

Sensory descriptors chosen to describe heat pain differed from those chosen to describe cold pain, with a wider range of words consistently chosen for cold (mainly “sharp”, “stinging”, “pricking” and “aching”) than for heat pain (only “burning”) were identified in **Morin and Bushnell's study (1998)**. Different qualities were found in our study. At the level of the lesion tonic heat stimuli was associated mainly with “punctate” and “burning” sensations and “punctate”, “cold” and “diffuse” sensations in response to cold stimuli. Interestingly, above lesion testing with either tonic heat or cold stimuli, the descriptors “punctate” and “cold” were the most present, and not “burning”.

3.5.14.4. Radiating pain

The prevalence of radiating pain did not depend on the level of the lesion, as it was present either with cervical or thoracic, incomplete or complete SCI lesions. Other methodological problems could include whether or not the subject responded to thermal stimulation, with radiating pain being more prevalent following 48°C presented at the site of stimulation. Therefore, no clear pattern of radiation was detected.

3.5.15. Relative advantage of standard BST/QST and tonic thermal stimulation.

In general, the application in our study of mechanical QST either at, below or above the level of lesion in NP patients suggested that light brush could not evoke any sensory response distinct to non-pain subjects, while significant changes in sensory function to vibration, von Frey stimulation, two-point discrimination and pin-prick was not identified when NP patients were compared to NoNP subjects, possibly due to the low number of subjects analysed. Indeed brush stimuli applied below the injury level produced lower sensory scores in NP, indicating this test may be complicated by a reduced mechanical detection threshold or by medication effects associated with Amytriptiline/Gabapentin. In contrast, at-level painful brush was detected with the DN4 in the NP probably due to an order effect, since the DN4 was always measured before the standard QST in the testing session. In contrast, at-level mechanical testing revealed that detection thresholds were worse in NP and SYR subjects. Vibratory stimuli at the level of lesion was significantly worse in NP than in the HV group, which is supported by **Bowsher (1999)** which suggested that deficits in low-intensity mechanical sensory modalities, such as touch and vibration, are common in patients with central pain due to spinal lesions although, as he continues, is rare in central pain patients due to SCI. In fact, an alteration in A β fibre function or dorsal column-medial lemniscal pathway function (vibratory stimuli) appear to be compromised during acute SCI patients with NP (**Boivie et al., 1994; Beric et al., 1998**). Some authors (**Eide et al., 1996**) did not find significant differences in the mechanical threshold values between painful and non-painful denervated areas (at, below and above the level of injury), which also occurred when reduced sensations to touch, vibration, joint position, and two point discrimination were compared together. We found that only at the level of the lesion that our subjects reported combined changes in pain intensities and mechanical thresholds, but not below or above the injury. The more likely explanation could reside in the hypothesis that the CPG is active at the level of SCI during the acute phase, disrupting A β fibre function mainly in view of the fact of the reduction in detection threshold and vibration. Two point discrimination at the level of injury was reduced in chronic SYR patients compared to NoNP patients, which may suggest either dorsal column dysfunction or indeed altered cortical representation (**Song et al., 1993; Ducreux et al., 2006**) in chronic SCI/SYR with NP patients. It appears therefore that a simple precision millimetre gauge seems to be a good tool to identify patients with chronic pain at the level of the lesion, although not for more acute SCI.

Application of the 48°C test-tube distinguished chronic pain patients (SYR) from NoNP and HV subjects at level of the lesion, which presented a higher sensory intensity. Below the level of the lesion this methodology was also useful. Acetone drop testing was also very useful in indicating higher sensory response in chronic pain patients (SYR) than NoNP at the level of the lesion. Below the level, HV and SYR subjects registered a higher significant response intensity than NoNP. **Wasner et al. (2004)** suggested that menthol acts to sensitize cold-sensitive peripheral vasoactive C nociceptors and activates cold-specific Ad fibres. Stimulation with acetone - as with menthol - may be also a form of achieve central sensitization based on the ongoing activity in the sensitised cold-sensitive peripheral C nociceptors. Taken together, BST and tonic thermal stimulation to test of thermal sensitivity indicates that C fibre dysfunction may mediate the changes in local sensibility after SCI.

Eide et al., (1996) study in SCI patients obtained more significant results in BST/QST than us, but the method was different, for example they used thicker von Frey filaments (6.65 units) for rating temporal summation. Several of the patients reported a stinging, pin prick-like sensation in denervated skin areas that was more prominent than the thermal sensation, which was demonstrated three times more

often in painful than non-painful denervated skin areas. Their tactile sensibility was more reduced in non-painful than in painful denervated areas, but the difference, as in our results, was not significant. No changes were observed for changes in sensory function to light touch, vibration, joint position or two point discrimination. In 22% of the patients wind up-like pain could be evoked using a von Frey of 1.65 units. The difference for temporal summation between non-painful and painful denervated areas was significant in their results.

3.5.16. Limitations of the tonic thermal pain testing methodology.

The main limitations of the BST/QST testing may be related to the lack of pain response in the patients, the limited VAS measure achieved (with no possibility to obtain integral or slope measures as in the peltier system), and the tonic thermal testing was not feasible due to temperature fluctuation after skin contact. Both healthy and SCI patients identified sensory responses below the level of the lesion with simple BST/QST but not with tonic thermal stimulation applied with the peltier system. *Habituation* in the form of cutaneous nociceptive fibre fatigue (Kleinböhl et al., 2006) is not probable because only a 7-10 minute inter-test period was observed since positive QST assessment below the injury, excluding the possibility of cutaneous fibre sensitization. Another explanation may be the cumulative effect of a repetitive *stress-induced anticipation of pain* reported by the majority of the patients, specifically to the tonic thermal testing, but this did not account for the reduced responses in healthy volunteers. In fact, below level testing was always applied first in patients, and the effect of anticipation was probably much higher at the beginning of the TSAR session. Anticipation, and stress could produce analgesia, which may have produced a higher threshold so that neither heat nor cold could be detected below the level of injury.

Other methodological design limitations were identified in the course of the study. The stimuli were not presented in at even inter-test periods, as we had to wait 40s in order to pre-cool or pre-heat the peltier thermode to reach the desired temperature required (3°C and 48°C). Observing a constant inter-trial period would have been excessive for the subject and tiredness would have affected the pain ratings. The low rate of pain response to tonic thermal stimulation presented another problem to the study, which was compounded by the low number of subjects recruited for each group and the possibility of pharmacological treatment effects. Finally, unpleasantness to tonic thermal testing was not rated as it was difficult for the patient to divide his attention to more than the three main tasks solicited (continuous pain intensity, and election of sensory descriptors and localization of the sensory response after tonic thermal stimulation).

3.5.17. Advances made by this study.

The three instruments studied here (DN4, standard BST/QST and tonic thermal stimulation) have demonstrated their utility in the present experimental pain study. Although standard BST/QST has been performed over the last 15-20 years in the pain clinic for NP diagnosis, the other two tools may well provide further information.

The DN4-Spanish version has recently been confirmed to be reliable, stable and valid for the differential diagnosis of neuropathic pain conditions, as it is able to differentiate the neuropathic and nociceptive component of pain, with the same cut-off value than in the original version. It is easy to answer by the patient and easy to calculate the total DN4 score, thanks to its scale of 10 questions. The psychophysical BST/QST measures introduced here have a potential application in routine clinical QST and may provide clinical markers of acute and chronic pain syndromes. Quantitative sensory testing has demonstrated its utility and reliability over several studies in the two decades, and is feasible and available for every clinical researcher, physician and in general for anyone working with NP patients, and no complicated training is needed. The tonic thermal stimulation method can provide stimulus-response characteristics of the pain curve, which BST cannot achieve. The computerized e-VAS system is easy to use and provides specific pain response characteristics that are normally not measured with standard QST techniques. Thus, more accurate data of pain responses can be analyzed

between different NP patients (eg. Differences in above-level responses to tonic heat stimuli) even when the maximum pain score was the same, providing an accurate neuropsychophysical assessment of implicated pain pathways.

3.5.18. Further research: Improvement in pain measurement systems.

There is a great need for further psychophysical studies of pain sensation in healthy pain-free people, to serve as a basis for a better understanding of pathological pain responses, to improve both diagnostic current pain treatment techniques (**Gracely, 1994; Granot et al., 2003**). Electrophysiological, and functional brain imaging studies combined with quantitative laser and contact thermal stimulation methods will provide the basis for more efficient pain studies. One of the applications of these new techniques could include the ability to assess C fibre function for the detection of small fibre polyneuropathies (**Krørup, 2003; Granovsky et al., 2005**).

Using magnetic resonance imaging (MRI) to assess brain function, **Koyama et al. (2005)** and **Coghill (2003)** found that study participants who reported tonic heat stimuli as intensely painful had pronounced activation of brain regions that were important in pain. In contrast, people who reported that the same stimulus was only mildly painful had minimal activation of these same areas. Healthy volunteers who reported higher levels of pain showed increased activation in important pain processing centres: the primary somatosensory cortex, which contributes to the perception of where a painful stimulus is located and its intensity, and the anterior cingulate cortex, which is involved in the processing of unpleasant feelings evoked by pain. Interestingly, there was little difference between subjects in thalamic activation, which is involved in transmitting pain signals from the spinal cord to higher brain regions. **Koyama et al. (2005)** and **Coghill (2003)** also confirmed that a mental representation of an impending sensory event can significantly shape neural processes that underlie the formulation of the actual sensory experience and provide an insight as to how positive expectations diminish the severity of chronic disease states. Indeed individual differences in pain sensitivity are probably due to a combination of cognitive factors, such as past experience with pain, emotional state at the time that pain was experienced, and expectations about pain.

Pain responses can also be studied with single infrared laser pulses, to measure individual sensory and pain thresholds. Radiant heat stimulation using a CO₂-laser selectively activates Ad and C fibres in hairy skin and minimizes mechanoreceptive influences with precise control of stimulus intensity and frequency. Subsequent to the stimulus, subjects are asked if the stimulus was detected as warm, hot, stinging, unpleasant or painful. Using the method-of-limits, each ascending series terminates at the first “painful” rating and pain threshold and sensory thresholds are calculated as the average of the following three series. Single laser pulses are perceived as “stinging heat” in the non-painful intensity class or as painful “pinpricks” for higher intensity, thus indicating nociceptive first pain sensations (**Kleinbohl et al., 2006**). Laser application as a methodology is not exempt from problems derived from the changes in baseline temperature by changes in haemodynamic thermoregulation and passive surface heat flux in the skin (**Brugmans et al., 1991**) and may therefore mimic “perceptual sensitization” during stimulus repetition (**Kleinbohl et al., 2006**).

Contact thermal stimulation produce larger evoked potential amplitudes at shorter latencies when evoked from hairy compared to glabrous skin, an effect which is greater for high intensity stimuli (**Granovsky et al., 2005**). The average C-fibre mediated potential latency recorded was shorter than that obtained by brief laser stimulation of very small skin areas associated with laser stimulation (**Bragard et al., 1996; Kakigi et al., 2003; Opsommer et al., 1999**). In addition, the average latencies for the Ad-mediated contact heat potentials are slightly longer than those reported for the Ad-mediated potential evoked by brief laser stimulation of a larger skin area (**Bromm and Lorenz, 1998; Kakigi and Shibasaki, 1991; Kakigi et al., 2000; Lorenz and Garcia-Larrea, 2003**). Compared to most laser stimulation techniques, the advantages of contact thermal stimulation techniques are that peak temperature can be easily controlled and that more skin thermoreceptors are activated over a longer duration.

3.5.19. Conclusions

Although neuropathic pain was identified using the DN4 questionnaire in the NP and SYR recruited in this study, detailed analysis of sensory responses to standard bedside and quantitative sensory testing provides further information into the presence of pain signs and mechanisms at, below and above the SCI. Tonic thermal testing provides important information associated with pain responses at and above the level of injury while standard BST/QST techniques adequately assessed non-painful sensory function at all levels relative to the SCI. At the level of the lesion, both BST/QST and tonic thermal testing techniques differentiated between thoracic and cervical NP patients, and between SYR and HV subjects. Importantly, tonic thermal stimulation techniques applied above the level of injury also detected changes in sensory function between SYR and healthy volunteers. We suggest that further development of tonic thermal testing techniques combined with detailed sub-component e-VAS analysis (maximum e-VAS score, early integrated e-VAS response, and e-VAS slope) will be instrumental in assessing sensory function and spinothalamic/supraspinal pain centre pathophysiology after SCI, when combined with standard BST/QST procedures.

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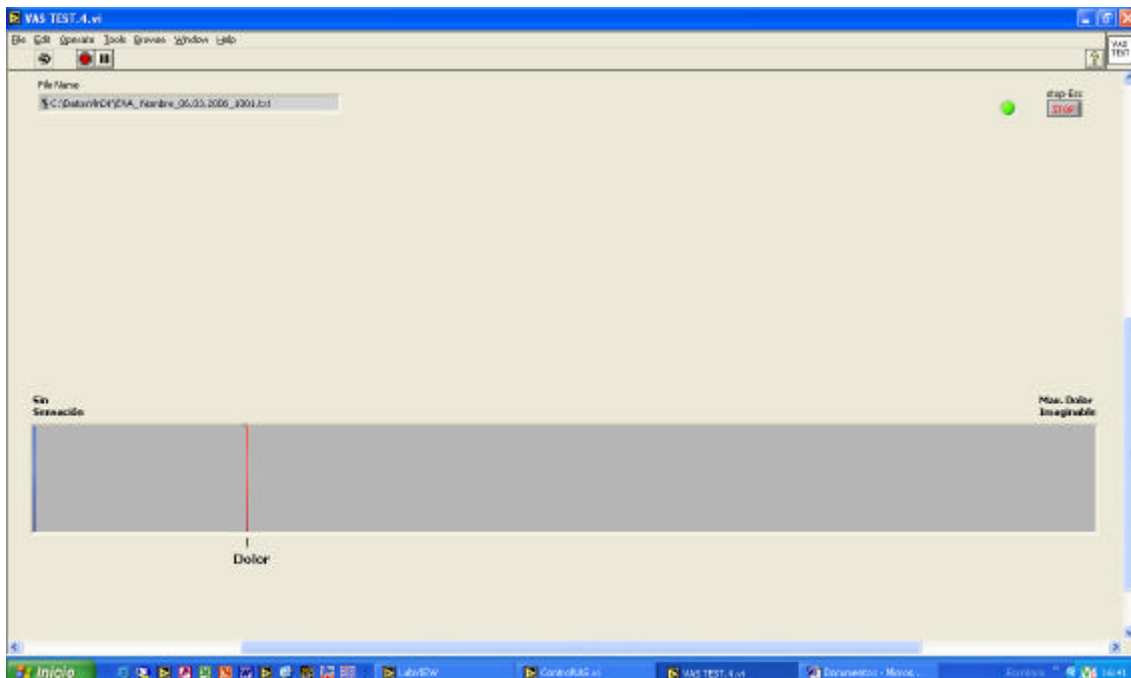
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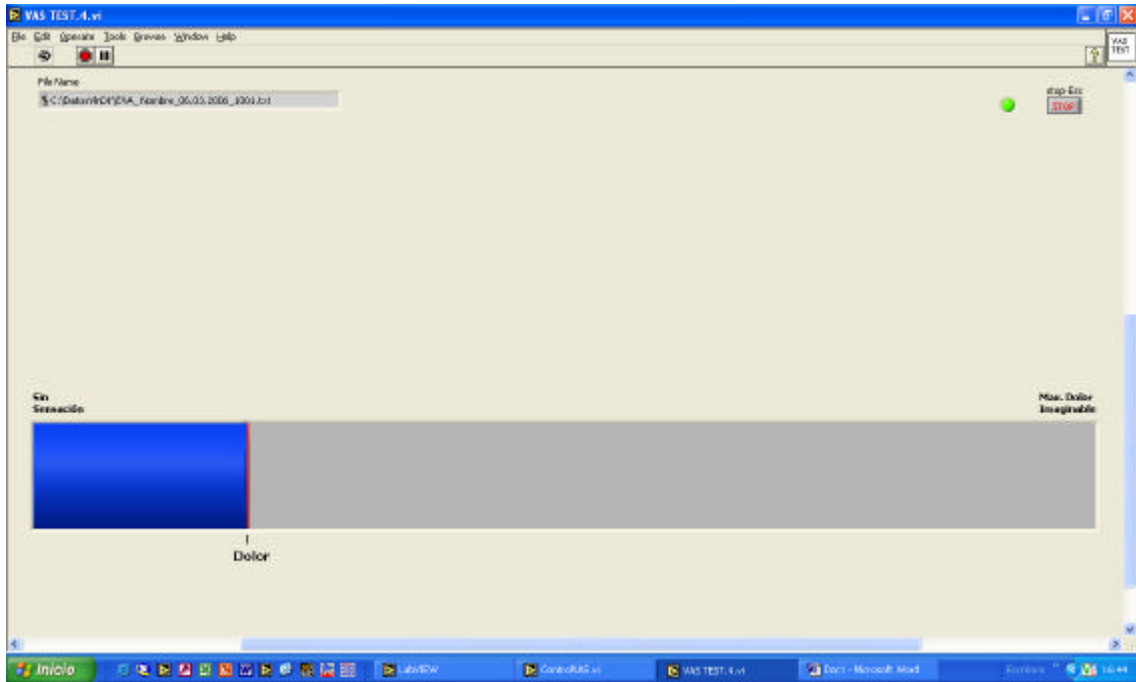
APPENDIX CHAPTER 3



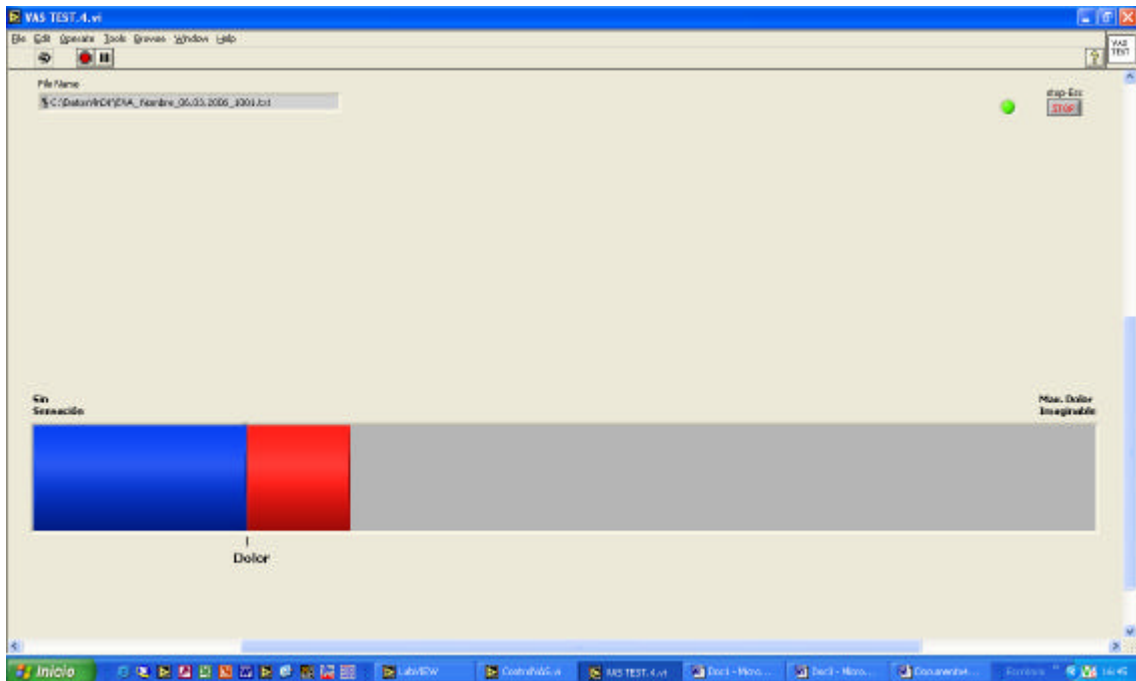
Appendix Picture 3.1. Bedside and Quantitative Sensory Testing (up to down): precision millimetre gauge, drop of acetone, Tip Therm®, von Frey filament, coarse brush (No.10 “Pappel” 113 Germany), Rydel-Seiffer graduated tuning fork.



Appendix Picture 3.2. Electronic VAS screen used to present the subject’s continuous pain rating unpleasantness and painful intensity. In this example, the blue horizontal cursor rate indicates an e-VAS score of 0/10 indicating that neither sensations or unpleasantness nor pain are present.



Appendix Picture 3.3. Electronic VAS screen, as Picture 3.2, indicating an e-VAS score of “2/10” representing unpleasantness and sensations that are just painful (pain threshold).

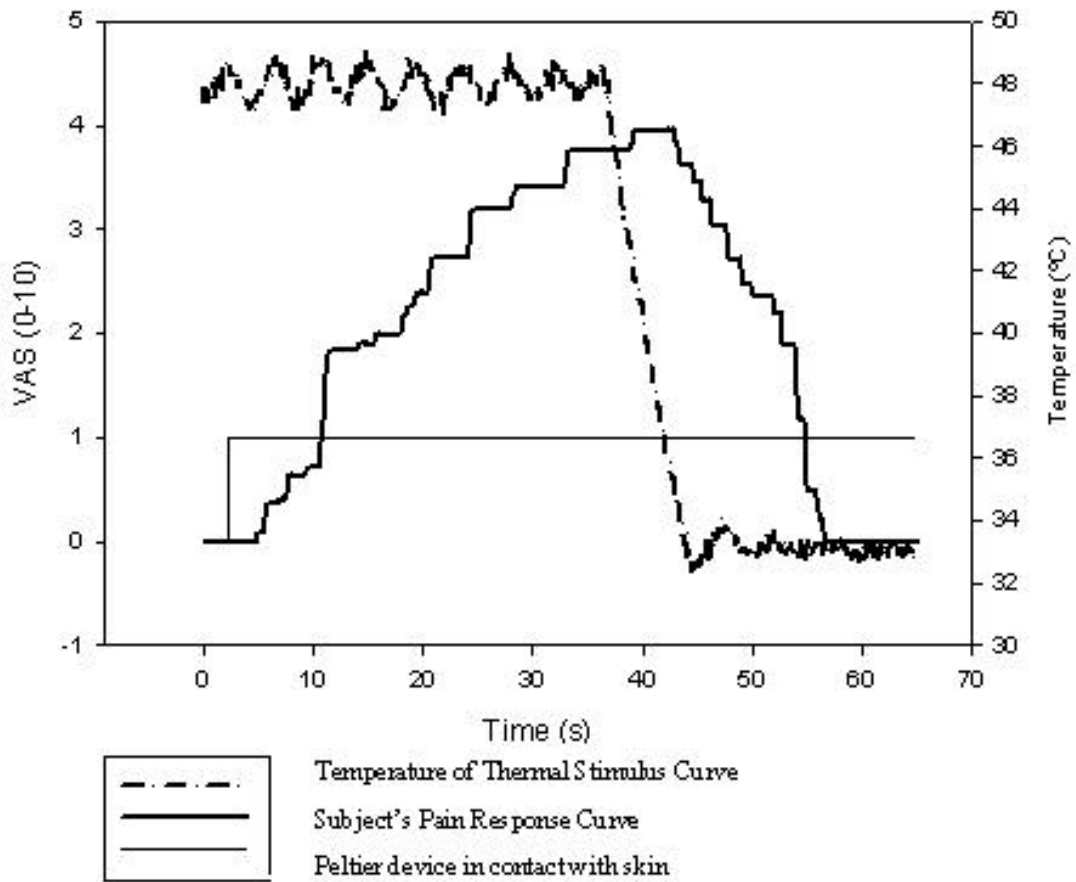


Appendix Picture 3.4. Electronic VAS screen, as Picture 3.2, indicating that the subject rate unpleasant sensations and a clear pain sensation. In this example, the cursor indicates an e-VAS score of 3/10 (pain sensation to the stimulus).

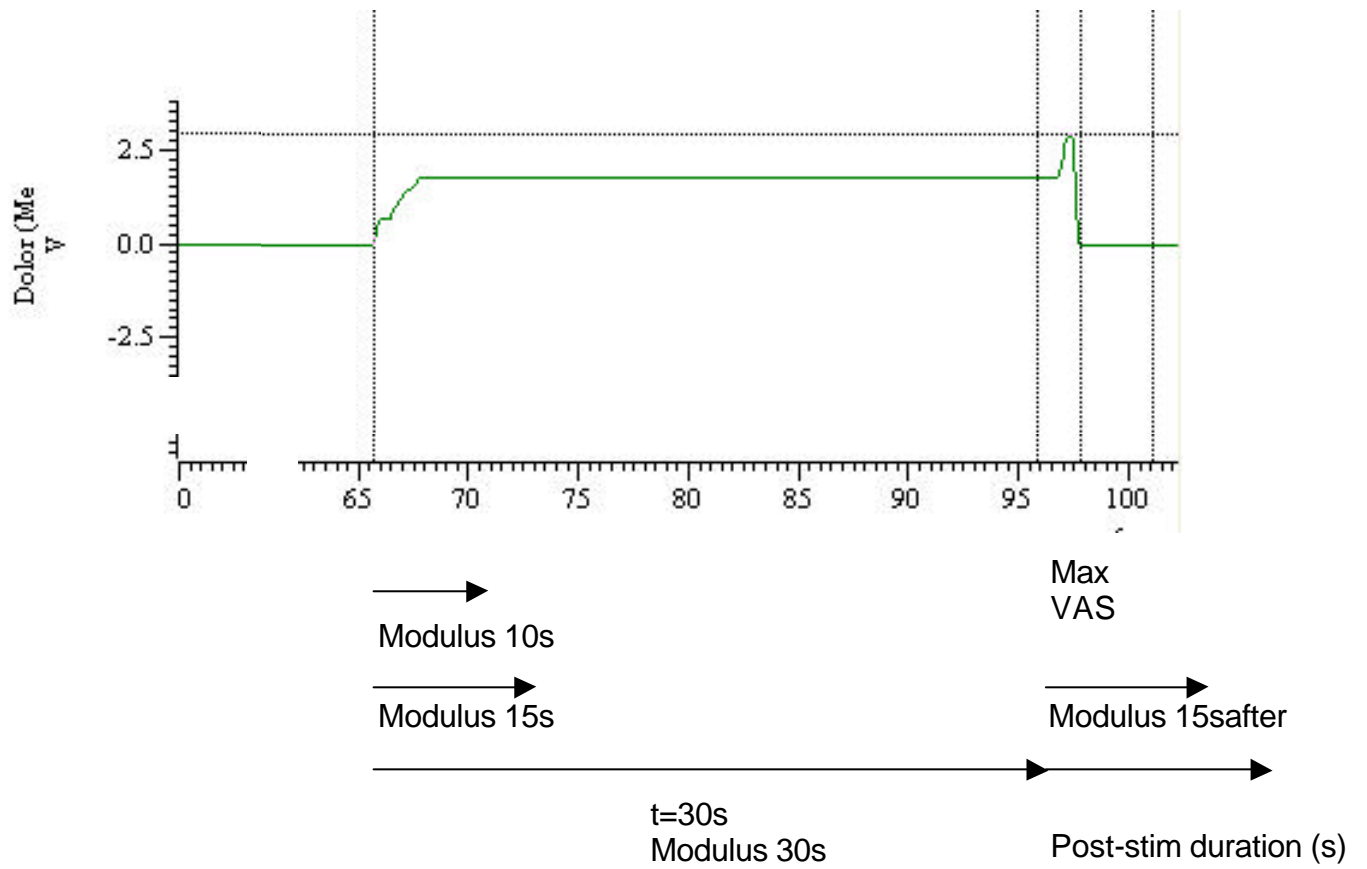


Appendix Picture 3.5. Tonic thermal psychophysics equipment used to rate pain intensity using the eVAS system and the board used to provide sensory descriptors and a dermatomal map to localize their evoked pain. The TSAR peltier system was attached to a supporting frame that facilitated at, above and below level testing in SCI patients in wheelchairs.

Example Thermal stimulation (HV subject)



Appendix Picture 3.6. Illustration representing the applied temperature (48°C), contact of the heated Peltier with the skin of the HV subject and the continuous pain intensity reported by the subject using the eVAS device.



Appendix Picture 3.7. Subject's example of e-VAS response to a 30 s thermal stimuli, indicating the different pain response components calculated after data collection.

HOJA DE CONSENTIMIENTO INFORMADO PARA EL PACIENTE

Para satisfacción de los Derechos del Paciente, como instrumento favorecedor del correcto uso de los Procedimientos Diagnósticos y Terapéuticos, y en cumplimiento de la Ley General de Sanidad.

Yo D/Dña....., como paciente (o D./Dª....., como su representante), en pleno uso de mis facultades, libre y voluntariamente, EXPONGO: que he sido debidamente INFORMADO/A por el Dr....., realizada el día, de que entro a formar parte de un estudio clínico para el diagnóstico del dolor neuropático. El objetivo es llevar a cabo un control de la evolución temporal de las medidas neurológicas y psicofísicas que se utilizan para la evaluación del dolor.

El estudio consiste en diagnosticar dolor neuropático por debajo y al nivel de la LM. Para ello se consultará la historia clínica, tanto en archivo como en planta, y se realizarán entrevistas personales y pruebas psicofísicas (de sensibilidad) para la evaluación del dolor. El número de sesiones se determinará en cada caso, pero no será superior a 6 en cada seguimiento. La duración de cada sesión será aproximadamente de una hora. Los días de citación se adaptarán a su comodidad, comprometiéndose usted a asistir a las sesiones en esas citas. Si no pudiera asistir le agradeceríamos lo comunicara previamente y le asignaremos otro día de citación a su conveniencia. La medicación será controlada por los facultativos de planta y por la Unidad del Dolor del hospital, con objeto de mantenerla controlada y estable en la medida de lo posible. Si no es posible, los facultativos de la Unidad del Dolor pueden proponerle salir del estudio.

Si presenta dolor, primero se le preguntará por la localización de su dolor, que iremos dibujando en un mapa humano. Después

caracterizaremos su dolor y la calidad de vida actual mediante las preguntas de diversos cuestionarios. La intensidad del dolor se medirá en una escala analógica y después electrónica. La prueba de calor-frío (tanto si tiene o no dolor) consiste en que durante 2-3 minutos usted tendrá que determinar el nivel de sensación que de manera continua o intermitente durante un máximo de 30 segundos le produce un dispositivo y durante este periodo se le aplicará un estímulo (caliente o frío) en una o más de las siguientes localizaciones alternativamente: la cara, antebrazo, palma de la mano, planta del pie y/o gemelo. Siempre se puede apartar del dispositivo cuando se desee si le resulta desagradable, ya sea comunicándolo o por usted mismo, por lo que no sufrirá ningún perjuicio.

El riesgo de efectos indeseados en la piel es mínimo, aunque en pieles extremadamente sensibles no se descarta que pueda producirse cierta rojez y sensación de quemazón, que desaparecerá a las pocas horas. Afirmo que he recibido explicaciones sobre la naturaleza y propósitos del procedimiento, beneficios, riesgos, alternativas y medios con que cuenta el Hospital para su realización, habiendo tenido ocasión de aclarar las dudas que me han surgido. (Si desea más información puede contactar con el teléfono del hospital 925 24 77 00 Extensión 47112 (Isocinéticos) y /o se la proporcionaremos personalmente el día de la prueba).

MANIFIESTO: que he entendido y estoy satisfecho de todas las explicaciones y aclaraciones recibidas sobre el proceso médico citado. Y OTORGO MI CONSENTIMIENTO para que me sea realizado este seguimiento del tratamiento del dolor por parte de la Unidad del Dolor y Unidad de Neurología Experimental (Grupo Función Sensitivomotora) del Hospital Nacional de Paraplégicos de Toledo (SESCAM)

Entiendo que este consentimiento puede ser revocado por mí en cualquier momento antes de la realización del procedimiento. Y, para que así conste, firmo el presente documento:

Toledo, a, dede 200....

Firma del paciente y N° D.N.I. (O representante legal en caso de incapacidad)	Firma Médico de la Unidad del Dolor	Firma del investigador principal

Protocol Appendix 3.1.a. First page of the Psychophysics Protocol, with the consent form signed by each subject/patient, explaining the objectives of the study, the methodology and the free will of abandon the study at any time.

PSYCHOPHYSICS PROTOCOL
(Dr Julian Taylor and Silvia Huelbes)

Name: Birth/age: Date:
 SCI level: Syringomyelia level
 Spontaneous pain: Actual VAS Intensity:, Actual VAS Unpleasantness: 7 Day VAS Intensity
 Paroxysm Present at Study Time (Yes/No) and where: above: at: below:
 Allodynia present?.....
 Hyperalgesia present?.....

Full Clinical Case History: cause of Inflammation, MR and ASIA:

.....

SESSION #1: CLINICAL PAIN, QUANTITATIVE SENSORY TESTING AND PSYCHOPHYSICS TRAINING

Min.estimated time: 20'+30'=50'

Psychophysics Training and Clinical Pain History (5 min)

- 1) Training the patient on electronic VAS 0-10, 2 as threshold: Intensity and Unpleasant sensation.
- 2) Learning the descriptors of Evoked Pain (4 groups):
 - a) No sensation at all
 - b) Hot, Warm, Burning, Cool, Cold
 - c) Acute, Dull
 - d) Diffuse, Tingling, Pricking, Pressure
- 3) Explain to the patient concepts of paraesthesias, dysesthesia and radiation during and after pain stimulation and express on the correct dermatomes with the descriptors above on the diagram.
- 4) Locate areas

	Control Area (face)	At level	Below level (Calf)
Dermatomes /site			

- 5) Locate areas of hyposensitivity and allodynia in the legs

Below level (legs) applied at different areas of sensibility
Normal Sensitivity..... Allodynia..... Hypersensitivity.....

Protocol Appendix 3.1.b. Second page of the Psychophysics Protocol, consisting in the subject's clinical history, the brief training and the location of painful areas.

DN4 Questionnaire- Spanish Version

Cuestionario DN4- Versión en español

Por favor complete este cuestionario marcando una respuesta para cada número en las 4 preguntas de abajo:

ENTREVISTA AL PACIENTE

Pregunta 1 : ¿Tiene el dolor una o más de las siguientes características?

	SI	NO
1- Quemazón		
2- Frío doloroso		
3- calambres eléctricos		

Pregunta 2 : ¿Está asociado el dolor con uno o más de los siguientes síntomas en la misma zona?

	SI	NO
4- Hormigueo		
5- Alfileres y agujas		
6- Entumecimiento		
7- Picazón		

EXAMEN AL PACIENTE

Pregunta 3 : ¿Está el dolor localizado en una zona donde el examen físico puede mostrar una o más de las siguientes características?

	SI	NO
8- Hipoestesia al tacto		
9- Hipoestesia con pinchazos		

Pregunta 4 : En la zona dolorosa, el dolor puede estar causado o incrementado por:

	SI	NO
10- Cepilladura		

Protocol Appendix 3.1.c. Third page of the Psychophysics Protocol, the DN4 questionnaire consisting in 10 questions: sensory descriptors and signs related to bedside sensory examination.

Clinical Pain Examination (20 min)

- 1) Complete DN4 Questionnaire (Dr.Bouhassira)
- 2) Dermatome mapping (See page below) of
 - a) Spontaneous Pain,
 - b) Hyposensitivity,
 - c) Evoked Pain in Normal and Hypersensitivity areas

Quantitative Sensory Testing- Evoked Pain

- 1) Mechanical Thresholds (Tactile Sensation by Von Frey filaments) → (mN)

	Control (Face)	At level	Below level
1 Ascendant			
1 Descendent			
2 Asc (“dummy”)			
2 Desc (“dummy”)			
3 Ascendent			
3 Descendent			
Mean Asc			
Mean Desc			

- 2) Heat and Cold pain (Heat 48°C and Acetone/Thermtip) → Intensity VAS

	Control	At level	Below level
Heat 48°C			
Cold			

- 3) Vibration sensation (Tuning fork) → Perception (Yes/No), 0-8 units Rydell Seiffer

	Control	At level	Below level
Percept (Yes/No)			

Protocol Appendix 3.1.d. Fourth page of the Psychophysics Protocol, the Quantitative Sensory Testing- Evoked Pain consisting in assessing the mechanical thresholds, heat and cold pain and vibration sensation.

4) Dynamic Allodynia

a) 5 strokes with brush → VAS

	At level	Below level
coarse brush		
soft brush		

b) Wind up-like pain (Temporal Summation, 50 strokes) → VAS

No. strokes	At level	Below level
10		
20		
30		
40		
50		

5) Static Allodynia (Punctate Allodynia) → VAS

a) 5 pokes → VAS

	Control	At level	Below level
No. vF used			
VAS			

b) Wind-up like pain (Temporal Summation, 50 pokes) → VAS

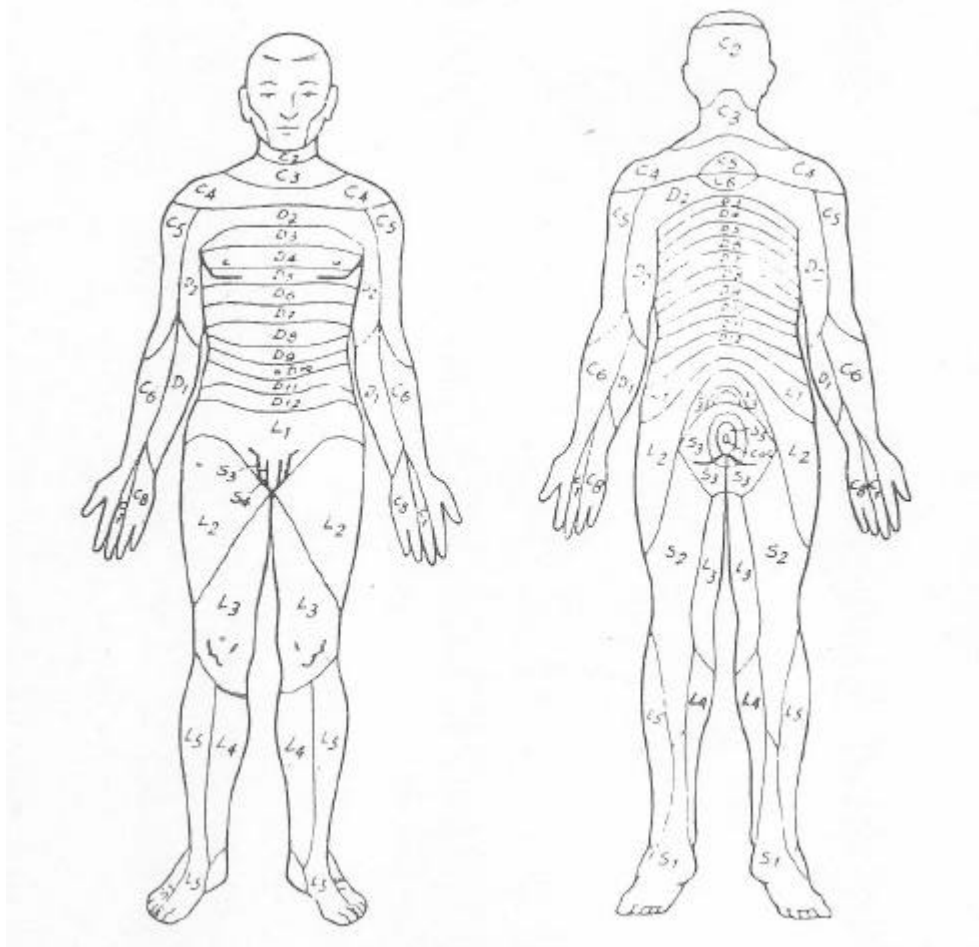
Nº pokes	At level	Below level
10		
20		
30		
40		
50		

6) Two-point discrimination → Perception(Yes/No)

	Control	At level	Below level
Min separation detected (in mm)			
Percept(Yes/No)			

Protocol Appendix 3.1.e. Fifth page of the Psychophysics Protocol, the Quantitative Sensory Testing-Evoked Pain consisting in assessing the dynamic and static allodynia, Wind up-like pain and Two-point discrimination

Map of dermatomes



Protocol Appendix 3.1.f. Map of dermatomes used to paint/place the painful and unpleasant sensations by the subject/patient, part of the Psychophysics Protocol.

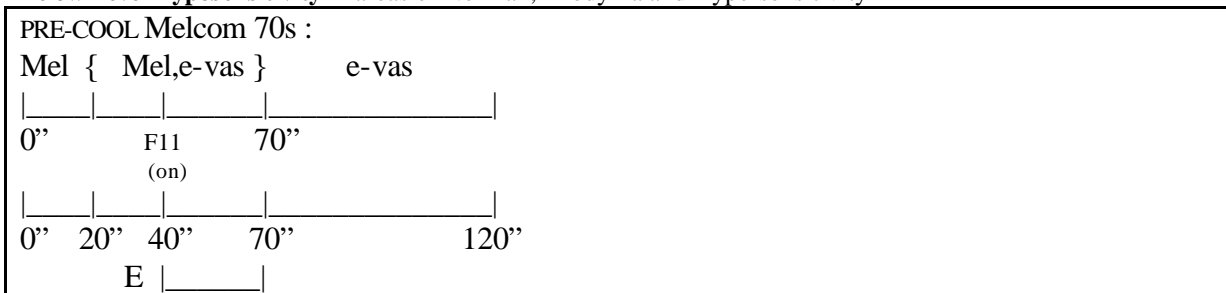
Psychophysics Protocol for Thermal Stimulation with the TSAR system

Order of sessions: **WATER BATH AT 10°C / 20°C**

Min.estimated time: 30'

Session 1A) BELOW LEVEL HEAT & COLD: Temporal Summation with long pulse (30s)

Below Level Hyposensitivity in areas of Normal ,Allodynia and Hypersensitivity



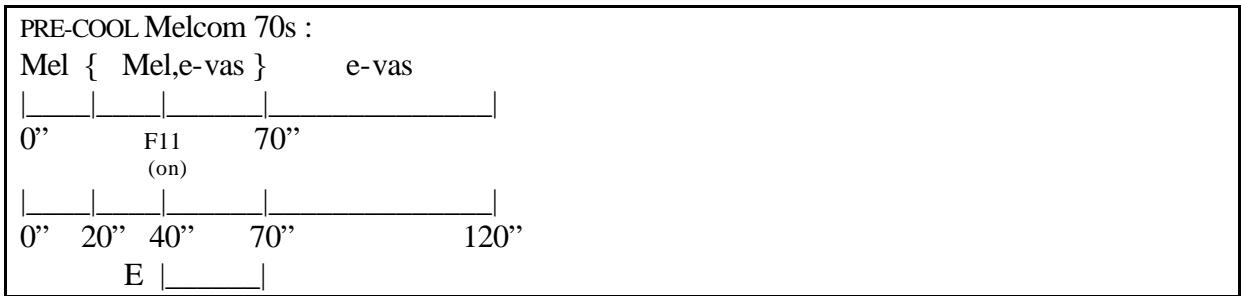
Real Time VAS Intensity

	Below level (legs) applied at different areas of sensibility	Pain Experience DURING STIMULUS Dermatomes Descriptores (1 de cada 3 grupos):	Pain Experience AFTER STIMULUS Dermatomes Descriptores (1 de cada 3 grupos):
3°C IF NOT TOLERATED AT LEVEL SKIP TO 13°C	Hyposensitivity (calf) 0..... Normal Sensitivity 0..... Allodynia 0..... Hypersensitivity 0.....
13°C opt	Hyposensitivity (calf) 0..... Normal Sensitivity 0..... Allodynia 0..... Hypersensitivity 0.....
Dummy 33°C	Hyposensitivity (calf) 0..... Normal Sensitivity 0..... Allodynia 0..... Hypersensitivity 0.....
OPTIONAL 48°C	Hyposensitivity (calf) 0..... Normal Sensitivity 0..... Allodynia 0..... Hypersensitivity 0.....

Protocol Appendix 3.1.g. Psychophysics Protocol for Thermal Stimulation with the TSAR system below the level of the lesion.

Session 1B) AT LEVEL HEAT & COLD: Temporal Summation with long pulse (30s)

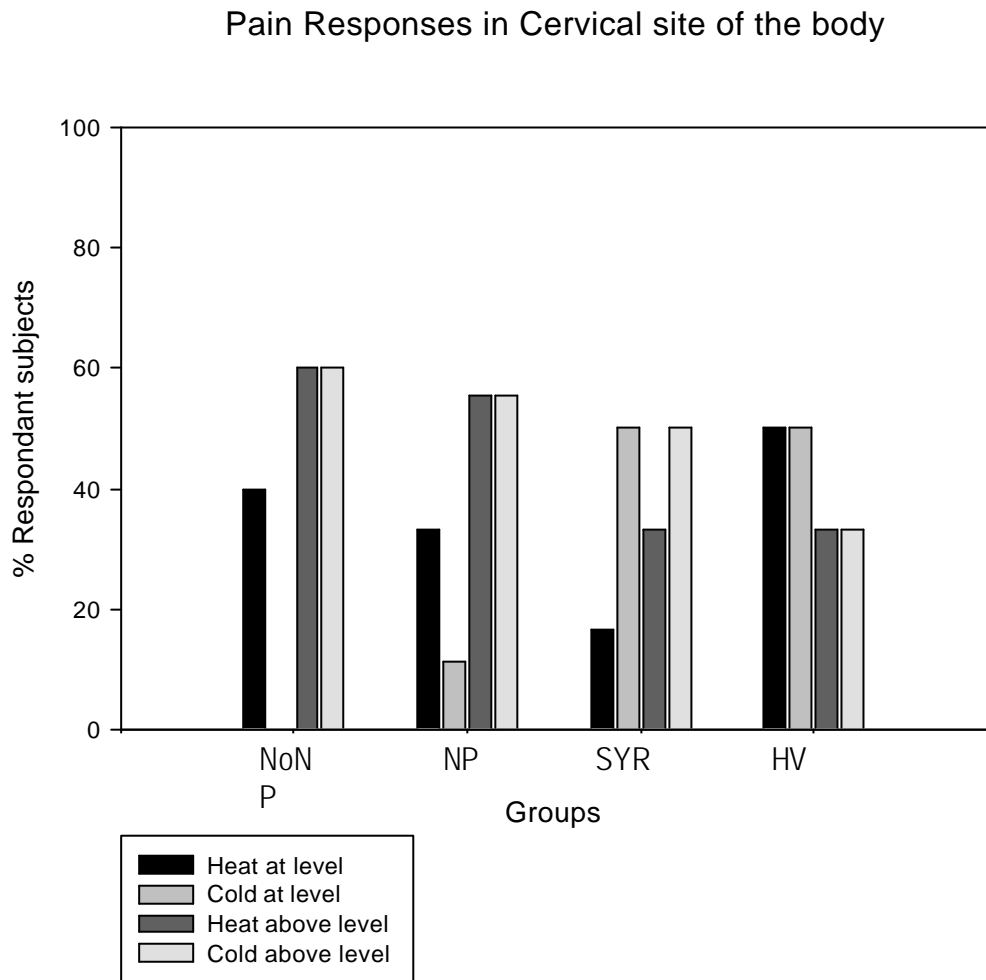
At Level



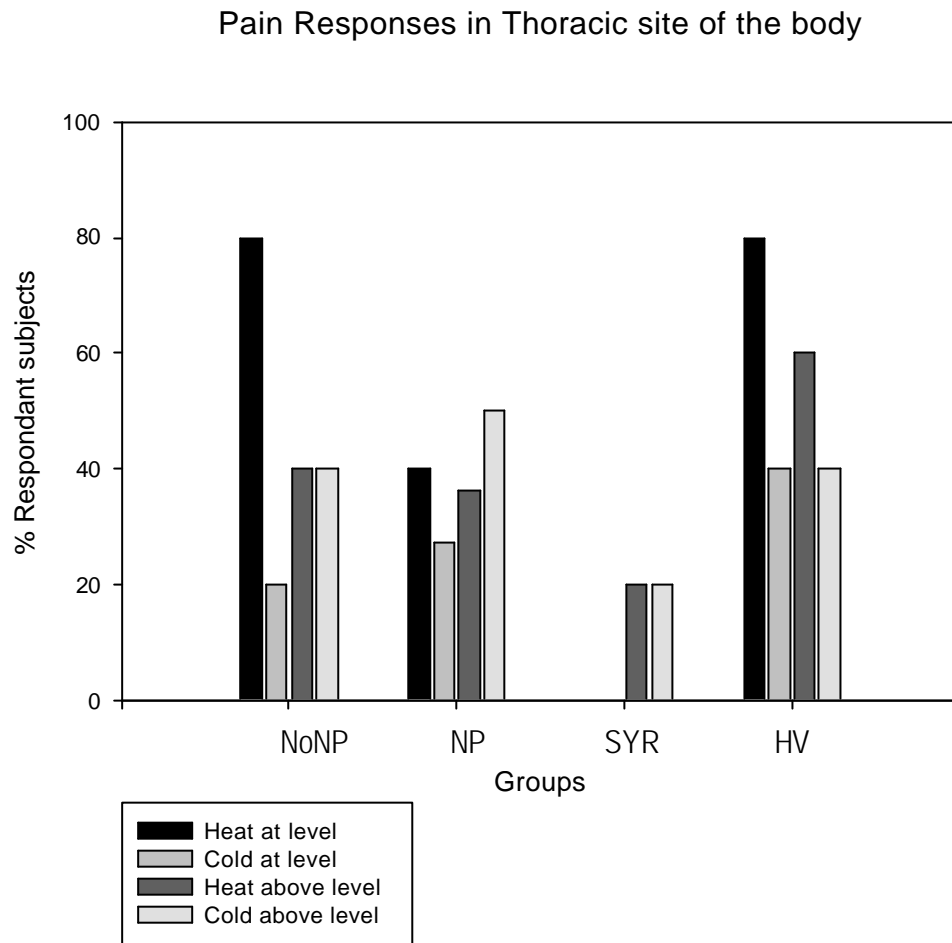
Real Time VAS Intensity

	At level (his level)	Pain Experience DURING STIMULUS -Dermatomes map (changes in paraesthesia,disaesthesia, radiation) -Descriptors (1 of each 3 groups):	Pain Experience AFTER STIMULUS -Dermatomes map (changes in paraesthesia,disaesthesia, radiation) -Descriptors (1 of each 3 groups):
3°C IF NOT TOLERATED AT LEVEL SKIP TO 13°C	0-----		
13°C opt	0-----		
Dummy 33°C	0-----		
OPTIONAL 48°C	0-----		

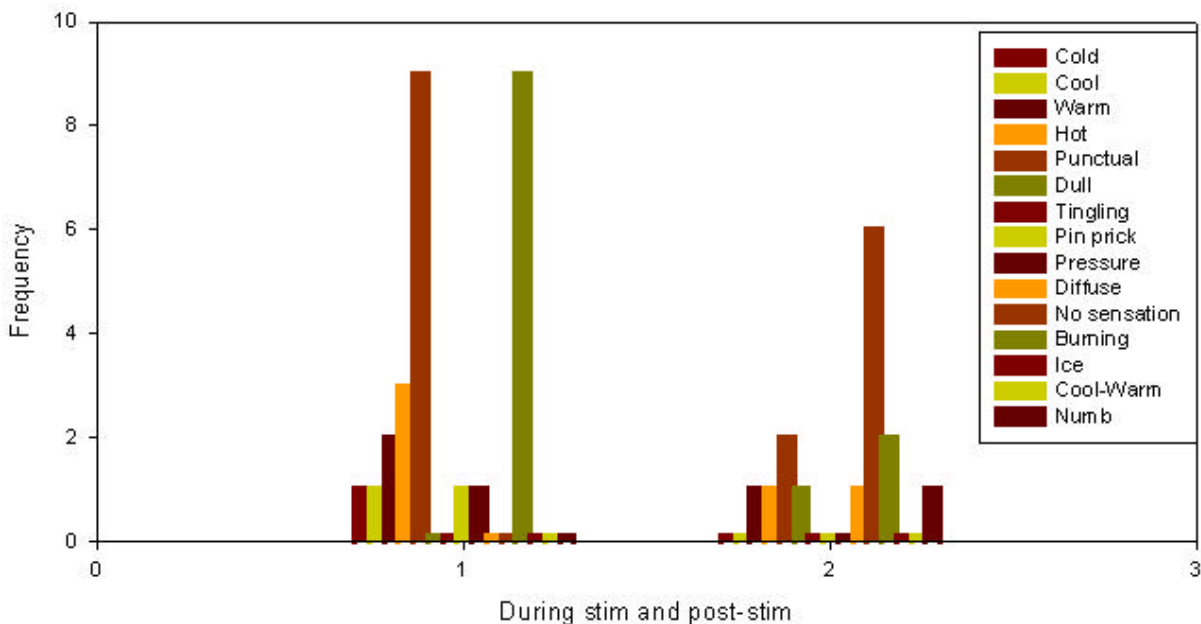
Protocol Appendix 3.1.h. Psychophysics Protocol for Thermal Stimulation with the TSAR system at the level of the lesion.



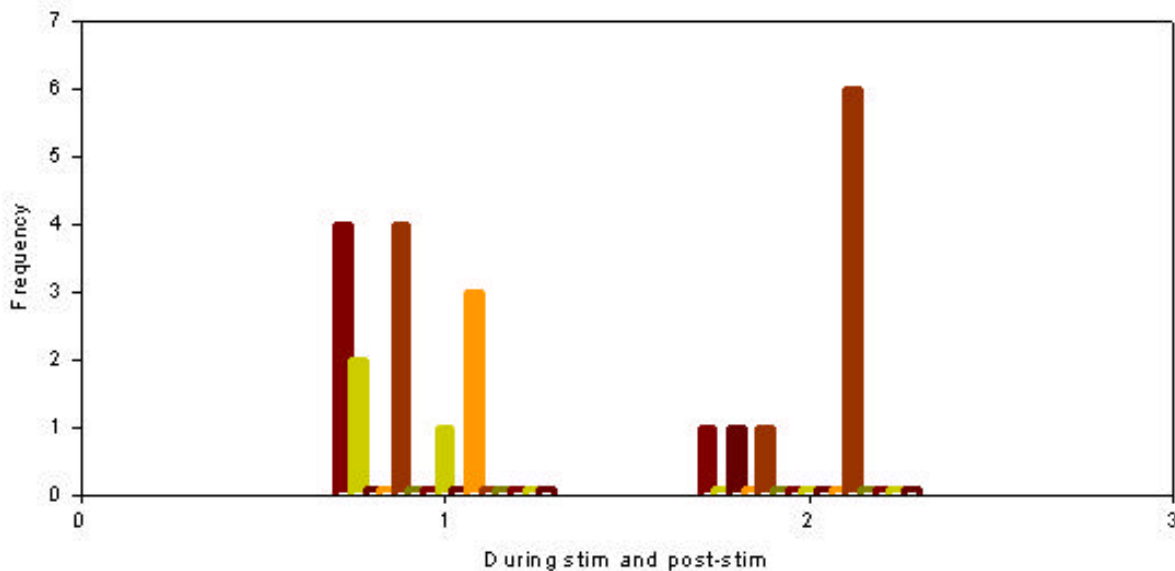
Appendix Fig 3.1. Percentage of pain responding subjects in response to cold and heat 30s stimuli applied at cervical dermatomes. The experimental subject groups were Non Neuropathic Pain group (NoNP); Neuropathic Pain group (NP); Syringomyelia group (SYR) ; Healthy volunteers group (HV)



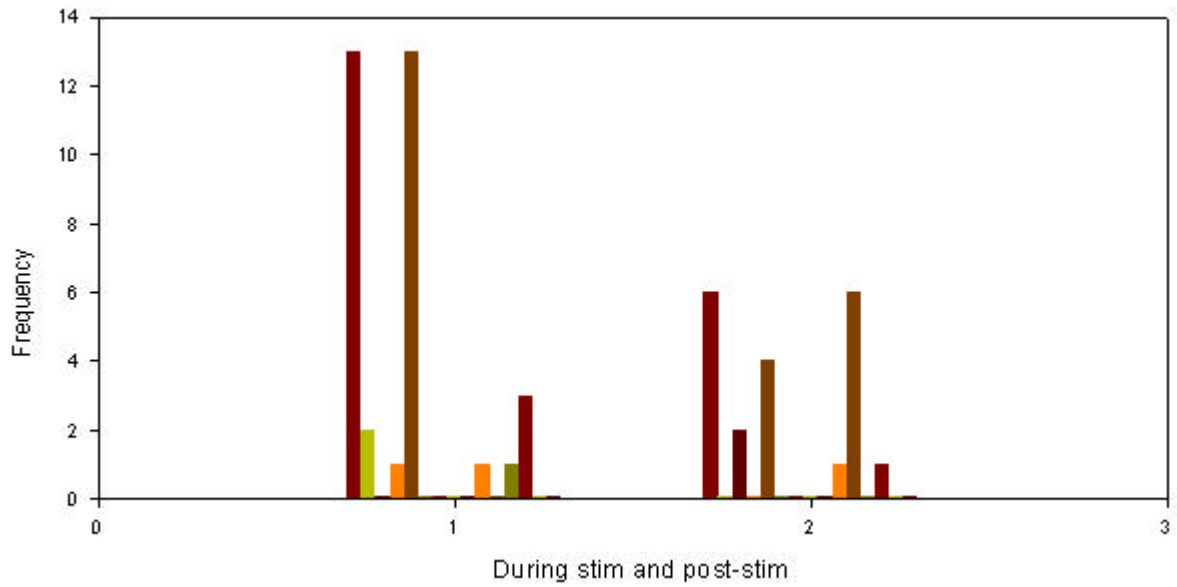
Appendix Fig 3.2. Percentage of pain responding subjects in response to cold and heat 30s stimuli applied at thoracic dermatomes. The experimental subject groups were Non Neuropathic Pain group (NoNP); Neuropathic Pain group (NP); Syringomyelia group (SYR) ; Healthy volunteers group (HV)



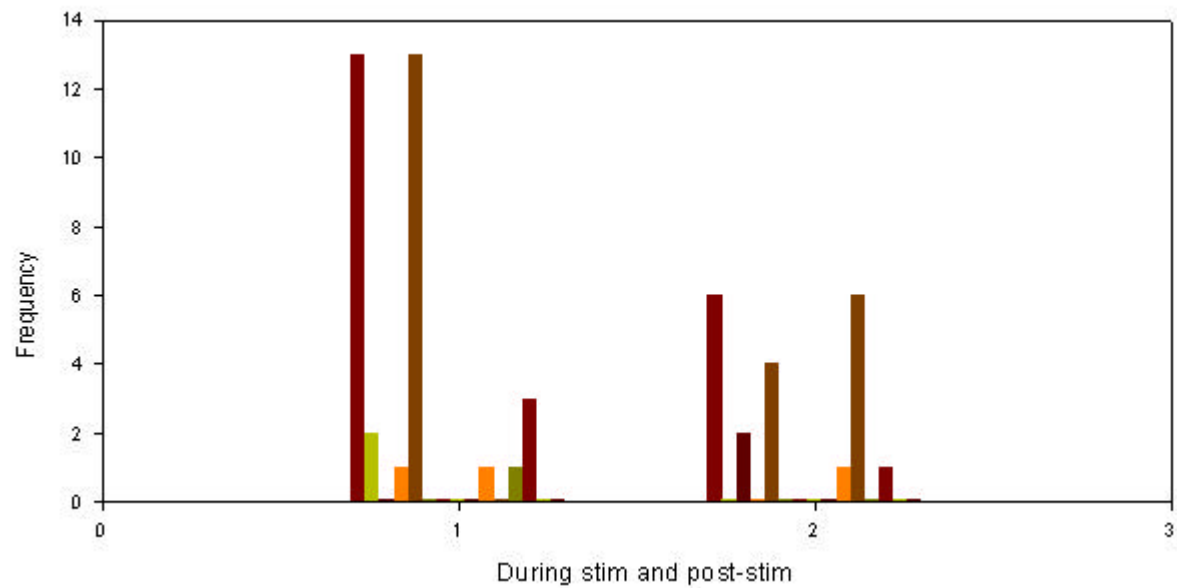
Appendix Fig 3.3. Descriptors reported by groups NoNP, NP and SYR At level of the lesion with Heat stimulation.



Appendix Fig 3.4. Descriptors reported by groups NoNP, NP and SYR At level of the lesion with Cold stimulation



Appendix Fig 3.5. Descriptors reported by groups NoNP, NP and SYR Above the level of the lesion with Heat stimulation



Appendix Fig 3.6. Descriptors reported by groups NoNP, NP and SYR Above the level of the lesion with Cold stimulation

NON PARAMETRIC STATISTICAL ANALYSIS (MANN-WHITNEY U) FOR DIFFERENCES BETWEEN GROUPS IN THERMAL STIMULATION

-HEAT AT LEVEL

	max	slope	time	modulus30	modulus10	modulus15	Duration post	Modulus 15after
Mann-Whitney U	17,000	18,000	16,500	10,000	8,000	6,000	7,000	3,00
Wilcoxon W	45,000	39,000	37,500	31,000	18,000	27,000	13,000	9,00
Z	-,571	-,429	-,733	-1,281	-,853	,000	-,149	-1,06
Asymp. Sig. (2-tailed)	,568	,668	,464	,200	,394	1,000	,881	,28
Exact Sig. [2*(1-tailed Sig.)]	,628	,731	,534	,240	,476	1,000	1,000	,40

Table App 3.1. Statistical analysis for differences between pain responses to tonic heat stimulation at 48°C for 30s between NoNP and NP subject groups

	max	slope	time	modulus30	modulus10	modulus15	Duration post	Modulus 15after
Mann-Whitney U	12,000	12,000	6,000	5,000	5,000	4,000	5,000	6,000
Wilcoxon W	22,000	22,000	27,000	26,000	15,000	14,000	11,000	16,000
Z	,000	,000	-1,574	-1,492	-,866	,000	-,354	,000
Asymp. Sig. (2-tailed)	1,000	1,000	,116	,136	,386	1,000	,724	1,000
Exact Sig. [2*(1-tailed Sig.)]	1,000	1,000	,257	,171	,486	1,000	,857	1,000

Table App 3.2. Statistical analysis for differences between pain responses to tonic heat stimulation at 48°C for 30s between NoNP and SYR subject groups

	max	slope	time	modulus30	modulus10	modulus15	Duration post	Modulus 15after
Mann-Whitney U	9,000	8,000	13,500	7,000	5,000	1,000	4,000	,000
Wilcoxon W	30,000	29,000	28,500	28,000	11,000	7,000	10,000	6,000
Z	-1,095	-,853	-,299	-,516	-,354	-1,155	-,218	-1,732
Asymp. Sig. (2-tailed)	,273	,394	,765	,606	,724	,248	,827	,083
Exact Sig. [2*(1-tailed Sig.)]	,329	,476	,792	,714	,857	,400	1,000	,200

Table App 3.3. Statistical analysis for differences between pain responses to tonic heat stimulation at 48°C for 30s between NoNP and HV subject groups

	max	slope	time	modulus30	modulus10	modulus15	Duration post	Modulus 15after
Mann-Whitney U	13,000	10,000	10,000	8,000	9,000	10,000	8,000	5,000
Wilcoxon W	41,000	20,000	38,000	29,000	30,000	31,000	23,000	15,000
Z	-,189	-,758	-1,121	-,853	-,640	-,426	-,490	-,866
Asymp. Sig. (2-tailed)	,850	,449	,262	,394	,522	,670	,624	,386
Exact Sig. [2*(1-tailed Sig.)]	,927	,527	,527	,476	,610	,762	,730	,486

Table App 3.4. Statistical analysis for differences between pain responses to tonic heat stimulation at 48°C for 30s between NP and SYR subject groups

	max	slope	time	modulus30	modulus10	modulus15	Duration post	Modulus 15after
Mann-Whitney U	10,000	11,500	15,500	6,000	5,000	6,000	7,000	3,000
Wilcoxon W	38,000	39,500	30,500	12,000	11,000	12,000	13,000	13,000
Z	-1,218	-,475	-,386	-,775	-1,033	-,775	-,149	-,463
Asymp. Sig. (2-tailed)	,223	,635	,699	,439	,302	,439	,881	,643
Exact Sig. [2*(1-tailed Sig.)]	,268	,648	,755	,548	,381	,548	1,000	,800

Table App 3.5. Statistical analysis for differences between pain responses to tonic heat stimulation at 48°C for 30s between NP and HV subject groups

	max	slope	time	modulus30	modulus10	modulus15	Duration post	Modulus 15after
Mann-Whitney U	8,000	4,000	6,000	3,000	3,000	3,000	4,000	2,000
Wilcoxon W	18,000	14,000	21,000	9,000	9,000	9,000	10,000	12,000
Z	-,490	-1,155	-1,342	-1,061	-1,061	-1,061	-,707	-,926
Asymp. Sig. (2-tailed)	,624	,248	,180	,289	,289	,289	,480	,355
Exact Sig. [2*(1-tailed Sig.)]	,730	,343	,413	,400	,400	,400	,629	,533

Table App 3.6. Statistical analysis for differences between pain responses to tonic heat stimulation at 48°C for 30s between SYR and HV subject groups

-COLD AT LEVEL

	max	slope	time	modulus30	modulus10	modulus15	Duration post	Modulus 15after
Mann-Whitney U	1,000	1,000	,000	1,000	,000	1,000	1,000	1,000
Wilcoxon W	2,000	2,000	10,000	2,000	1,000	11,000	7,000	2,000
Z	-,707	-,707	-1,581	-,707	-1,414	-,707	-,447	-,707
Asymp. Sig. (2-tailed)	,480	,480	,114	,480	,157	,480	,655	,480
Exact Sig. [2*(1-tailed Sig.)]	,800	,800	,400	,800	,400	,800	1,000	,800

Table App 3.7. Statistical analysis for differences between pain responses to tonic heat stimulation at 3°C for 30s between NoNP and NP subject groups

	max	slope	time	modulus30	modulus10	modulus15	Duration post	Modulus 15after
Mann-Whitney U	,000	1,000	,000	1,000	,000	1,000	1,000	,000
Wilcoxon W	1,000	2,000	6,000	7,000	1,000	7,000	7,000	1,000
Z	-1,342	-,447	-1,342	-,471	-1,342	-,471	-,471	-1,342
Asymp. Sig. (2-tailed)	,180	,655	,180	,637	,180	,637	,637	,180
Exact Sig. [2*(1-tailed Sig.)]	,500	1,000	,500	1,000	,500	1,000	1,000	,500

Table App 3.8. Statistical analysis for differences between pain responses to tonic heat stimulation at 3°C for 30s between NoNP and SYR subject groups

	max	slope	time	modulus30	modulus10	modulus15	Duration post	Modulus 15after
Mann-Whitney U	,000	1,000	,000	1,000	,000	1,000	1,000	,000
Wilcoxon W	1,000	2,000	15,000	2,000	1,000	7,000	2,000	1,000
Z	-1,464	-,707	-1,555	-,447	-1,464	-,447	-,447	-1,464
Asymp. Sig. (2-tailed)	,143	,480	,120	,655	,143	,655	,655	,143
Exact Sig. [2*(1-tailed Sig.)]	,333	,800	,333	1,000	,333	1,000	1,000	,333

Table App 3.9. Statistical analysis for differences between pain responses to tonic heat stimulation at 3°C for 30s between NoNP and HV subject groups

	max	slope	time	modulus30	modulus10	modulus15	Duration post	Modulus 15after
Mann-Whitney U	2,000	4,000	4,500	3,000	6,000	3,000	4,000	3,000
Wilcoxon W	12,000	10,000	10,500	9,000	12,000	9,000	10,000	9,000
Z	-1,414	-,707	-,585	-1,070	,000	-1,061	-,734	-,696
Asymp. Sig. (2-tailed)	,157	,480	,558	,285	1,000	,289	,463	,487
Exact Sig. [2*(1-tailed Sig.)]	,229	,629	,629	,400	1,000	,400	,629	,700

Table App 3.10. Statistical analysis for differences between pain responses to tonic heat stimulation at 3°C for 30s between NP and SYR subject groups

	max	slope	time	modulus30	modulus10	modulus15	Duration post	Modulus 15after
Mann-Whitney U	8,000	6,000	9,500	5,000	5,000	4,000	3,000	3,000
Wilcoxon W	18,000	16,000	24,500	11,000	20,000	19,000	13,000	9,000
Z	-,490	-,577	-,146	-,354	-1,225	-1,470	-1,061	-,655
Asymp. Sig. (2-tailed)	,624	,564	,884	,724	,221	,142	,289	,513
Exact Sig. [2*(1-tailed Sig.)]	,730	,686	,905	,857	,286	,190	,400	,700

Table App 3.11. Statistical analysis for differences between pain responses to tonic heat stimulation at 3°C for 30s between NP and HV subject groups

	max	slope	time	modulus30	modulus10	modulus15	Duration post	Modulus 15after
Mann-Whitney U	2,000	4,000	4,500	3,000	,000	5,000	3,000	2,000
Wilcoxon W	17,000	14,000	10,500	9,000	15,000	20,000	9,000	8,000
Z	-1,640	-,707	-,953	-,664	-2,236	-,745	-,664	-1,107
Asymp. Sig. (2-tailed)	,101	,480	,341	,507	,025*	,456	,507	,268
Exact Sig. [2*(1-tailed Sig.)]	,143	,629	,393	,700	,036	,571	,700	,400

Table App 3.12. Statistical analysis for differences between pain responses to tonic heat stimulation at 48°C for 30s between SYR and HV subject groups

-HEAT ABOVE LEVEL

	max	slope	time	modulus30	modulus10	modulus15	Duration post	Modulus 15after
Mann-Whitney U	22,000	17,500	11,000	17,000	10,000	5,000	10,000	,000
Wilcoxon W	77,000	27,500	17,000	32,000	46,000	8,000	38,000	3,000
Z	-,367	-,354	-,260	-,733	-,408	-,586	-,756	-1,732
Asymp. Sig. (2-tailed)	,713	,723	,795	,463	,683	,558	,450	,083
Exact Sig. [2*(1-tailed Sig.)]	,768	,733	,921	,518	,776	,667	,527	,200

Table App 3.13. Statistical analysis for differences between pain responses to tonic heat stimulation above 48°C for 30s between NoNP and NP subject groups

	max	slope	time	modulus30	modulus10	modulus15	Duration post	Modulus 15after
Mann-Whitney U	6,000	4,000	4,000	3,000	1,000	1,000	4,000	2,000
Wilcoxon W	21,000	10,000	10,000	9,000	7,000	2,000	10,000	8,000
Z	-,447	-,707	-,258	-1,350	-1,550	,000	-,734	-1,107
Asymp. Sig. (2-tailed)	,655	,480	,796	,177	,121	1,000	,463	,268
Exact Sig. [2*(1-tailed Sig.)]	,786	,629	1,000	,250	,200	1,000	,629	,400

Table App 3.14. Statistical analysis for differences between pain responses to tonic heat stimulation above 48°C for 30s between NP and SYR subject groups

	max	slope	time	modulus30	modulus10	modulus15	Duration post	Modulus 15after
Mann-Whitney U	7,000	7,000	6,000	9,000	6,000	4,000	7,500	1,000
Wilcoxon W	22,000	17,000	12,000	24,000	21,000	7,000	22,500	7,000
Z	-1,163	-,738	-,586	-,733	-,450	-,391	-,618	-,447
Asymp. Sig. (2-tailed)	,245	,461	,558	,463	,653	,696	,537	,655
Exact Sig. [2*(1-tailed Sig.)]	,310	,556	,786	,548	,786	,857	,556	1,000

Table App 3.15. Statistical analysis for differences between pain responses to tonic heat stimulation above 48°C for 30s between NoNP and HV subject groups

	max	slope	time	modulus30	modulus10	modulus15	Duration post	Modulus 15after
Mann-Whitney U	4,000	10,000	10,000	2,000	,000	,000	7,000	2,000
Wilcoxon W	59,000	16,000	16,000	8,000	6,000	1,000	13,000	8,000
Z	-1,859	-,845	-,519	-2,130	-2,455	-1,528	-,800	-,592
Asymp. Sig. (2-tailed)	,063	,398	,604	,033*	,014*	,127	,424	,554
Exact Sig. [2*(1-tailed Sig.)]	,077	,469	,776	,036	,012	,250	,517	,800

Table App 3.16. Statistical analysis for differences between pain responses to tonic heat stimulation above 48°C for 30s between NP and SYR subject groups

	max	slope	time	modulus30	modulus10	modulus15	Duration post	Modulus 15after
Mann-Whitney U	12,000	24,000	18,000	18,000	10,000	7,000	8,000	,000
Wilcoxon W	27,000	79,000	54,000	33,000	25,000	22,000	23,000	3,000
Z	-1,596	-,123	-,396	-,601	-1,466	-1,708	-1,546	-1,225
Asymp. Sig. (2-tailed)	,110	,902	,692	,548	,143	,088	,122	,221
Exact Sig. [2*(1-tailed Sig.)]	,129	,953	,833	,606	,171	,106	,149	,667

Table App 3.17. Statistical analysis for differences between pain responses to tonic heat stimulation above 48°C for 30s between NP and HV subject groups

	max	slope	time	modulus30	modulus10	modulus15	Duration post	Modulus 15after
Mann-Whitney U	,000	4,000	6,000	3,000	2,000	,000	5,000	,000
Wilcoxon W	15,000	10,000	12,000	9,000	8,000	1,000	11,000	6,000
Z	-2,249	-1,050	-,586	-1,358	-1,660	-1,485	-,769	-1,414
Asymp. Sig. (2-tailed)	,024*	,294	,558	,174	,097	,137	,442	,157
Exact Sig. [2*(1-tailed Sig.)]	,036	,393	,786	,250	,143	,333	,571	,500

Table App 3.18. Statistical analysis for differences between pain responses to tonic heat stimulation above 48°C for 30s between SYR and HV subject groups

-COLD ABOVE LEVEL

	max	slope	time	modulus30	modulus10	modulus15	Duration post	Modulus 15after
Mann-Whitney U	25,000	20,500	17,000	6,500	1,000	2,000	14,000	1,000
Wilcoxon W	80,000	35,500	32,000	9,500	4,000	5,000	50,000	4,000
Z	,000	-,554	-,980	-,404	-1,886	-1,650	-,342	-1,549
Asymp. Sig. (2-tailed)	1,000	,580	,327	,686	,059	,099	,732	,121
Exact Sig. [2*(1-tailed Sig.)]	1,000	,594	,371	,711	,073	,145	,808	,190

Table App 3.19. Statistical analysis for differences between pain responses to tonic heat stimulation above 3°C for 30s between NoNP and NP subject groups

	max	slope	time	modulus30	modulus10	modulus15	Duration post	Modulus 15after
Mann-Whitney U	4,000	8,000	3,500	8,000	2,000	4,000	5,000	3,000
Wilcoxon W	19,000	23,000	13,500	18,000	5,000	14,000	15,000	6,000
Z	-1,470	-,490	-,235	-,492	-,926	,000	-,887	-,492
Asymp. Sig. (2-tailed)	,142	,624	,814	,623	,355	1,000	,375	,623
Exact Sig. [2*(1-tailed Sig.)]	,190	,730	,800	,730	,533	1,000	,486	,800

Table App 3.20. Statistical analysis for differences between pain responses to tonic heat stimulation above 3°C for 30s between NoNP and SYR subject groups

	max	slope	time	modulus30	modulus10	modulus15	Duration post	Modulus 15after
Mann-Whitney U	5,000	10,000	2,000	6,000	1,000	2,000	8,000	1,500
Wilcoxon W	15,000	20,000	5,000	21,000	4,000	5,000	18,000	4,500
Z	-1,230	,000	-1,414	-,980	-1,389	-,926	,000	-1,174
Asymp. Sig. (2-tailed)	,219	1,000	,157	,327	,165	,355	1,000	,240
Exact Sig. [2*(1-tailed Sig.)]	,286	1,000	,533	,413	,267	,533	1,000	,267

Table App 3.21. Statistical analysis for differences between pain responses to tonic heat stimulation above 3°C for 30s between NoNP and HV subject groups

	max	slope	time	modulus30	modulus10	modulus15	Duration post	Modulus 15after
Mann-Whitney U	11,000	19,000	13,500	14,000	17,000	11,000	13,000	6,000
Wilcoxon W	66,000	74,000	23,500	24,000	62,000	21,000	23,000	16,000
Z	-1,273	-,142	-,432	-,849	-,154	-1,082	-,519	-,984
Asymp. Sig. (2-tailed)	,203	,887	,666	,396	,877	,279	,604	,325
Exact Sig. [2*(1-tailed Sig.)]	,240	,945	,683	,454	,940	,330	,683	,413

Table App 3.22. Statistical analysis for differences between pain responses to tonic heat stimulation above 3°C for 30s between NP and SYR subject groups

	max	slope	time	modulus30	modulus10	modulus15	Duration post	Modulus 15after
Mann-Whitney U	11,000	13,000	10,000	19,000	18,000	16,000	11,000	7,000
Wilcoxon W	21,000	23,000	46,000	29,000	28,000	26,000	47,000	17,000
Z	-1,274	-,999	-1,136	-,141	,000	-,309	-,851	-,735
Asymp. Sig. (2-tailed)	,203	,318	,256	,888	1,000	,758	,395	,462
Exact Sig. [2*(1-tailed Sig.)]	,240	,374	,368	,945	1,000	,825	,461	,556

Table App 3.23. Statistical analysis for differences between pain responses to tonic heat stimulation above 3°C for 30s between NP and HV subject groups

	max	slope	time	modulus30	modulus10	modulus15	Duration post	Modulus 15after
Mann-Whitney U	2,000	6,000	6,000	6,000	6,000	6,000	4,000	8,000
Wilcoxon W	12,000	16,000	16,000	16,000	16,000	16,000	14,000	18,000
Z	-1,742	-,581	-,661	-,581	-,577	-,581	-1,162	,000
Asymp. Sig. (2-tailed)	,081	,561	,508	,561	,564	,561	,245	1,000
Exact Sig. [2*(1-tailed Sig.)]	,114	,686	,686	,686	,686	,686	,343	1,000

Table App 3.24. Statistical analysis for differences between pain responses to tonic heat stimulation above 3°C for 30s between SYR and HV subject groups



Appendix Picture 3.8. Magnetic resonance image which power taken from the site of the SCI from a patient with Syringomyelia with quistic cavities at the cervical level (C3-C6).



Picture Appendix 3.9. Magnetic resonance image which power taken from the site of the SCI from a patient with Syringomyelia with quistic cavities thoracic level (T10-T11).

Group	At Level			Below Level			Above Level		
	1HV	2NoNP	3NP	1HV	2NoNP	3NP	1HV	2NoNP	3NP
Tactile detection threshold (mN)	.111 ² .029^{3*} .864 ⁴	.335 ³ .050^{4*}	.009^{4*}	1.00 ² .282 ³ .402 ⁴	.640 ³ .097 ⁴	.718 ⁴	.283 ² .076 ³ 1.000 ⁴	.121 ³ .283 ⁴	.076 ⁴
Tuning fork (0-8 AU)	.473 ² .037^{3*} .966 ⁴	.089 ³ .651 ⁴	.111 ⁴	.475 ² .248 ³ .126 ⁴	.853 ³ .244 ⁴	.437 ⁴	.959 ² .350 ³ .502 ⁴	.186 ³ .338 ⁴	.757 ⁴
10-50 von Frey pokes 2-3 times higher than threshold (VAS)	.230 ² .906 ³ .683 ⁴	.335 ³ .230 ⁴	.550 ⁴	.312 ² .447 ³ .317 ⁴	.696 ³ .033^{4*}	.049⁴	NT	NT	NT
Millimetre gauge (cm)	.080 ² .720 ³ .539 ⁴	.231 ³ .044^{4*}	.472 ⁴	.311 ² 1.000 ³ .376 ⁴	.174 ³ .453 ⁴	.344 ⁴	.098 ² .128 ³ .219 ⁴	.753 ³ .667 ⁴	.422 ⁴
5 von Frey pokes 2-3 times higher threshold (VAS)	.357 ² .874 ³ .303 ⁴	.816 ³ 1.000 ⁴	.432 ⁴	.146 ² .284 ³ .706 ⁴	.429 ³ .083 ⁴	.134 ⁴	NT	NT	NT
48°C Tube (VAS)	.661 ² .292 ³ .016^{4*}	.735 ³ .043^{4*}	.087 ⁴	.029^{2*} .025^{3*} .515 ⁴	1.000 ³ .007^{4*}	.003^{4*}	.189 ² .050^{3*} .054^{4*}	.584 ³ .535 ⁴	.798 ⁴
Drop of Acetone/ Tip Therm (VAS)	.519 ² .755 ³ .118 ⁴	.735 ³ .043^{4*}	.156 ⁴	.013^{2*} .102 ³ .844 ⁴	1.000 ³ .017^{4*}	.099 ⁴	.495 ² .067 ³ .183 ⁴	.584 ³ .546 ⁴	.762 ⁴
Coarse brush (VAS)	.383 ² .074 ³ .867 ⁴	.502 ³ .600 ⁴	.145 ⁴	.084 ² .010^{3*} .223 ⁴	.816 ³ .563 ⁴	.307 ⁴	NT	NT	NT

Table Appendix 3.25. QST analysis (Mann-Whitney U analysis) for the four groups: NoNP= non Neuropathic Pain and SCI patients; NP= Neuropathic Pain and SCI patients; SYR=Syringomyelia and SCI patients; HV= Healthy volunteers. *: p = 0.05

¹=HV; ²=NoNP ; ³= NP ; ⁴= SYR; NT= Not tested

--VERSIÓN RESUMIDA EN ESPAÑOL--

CAPÍTULO 3.

EVALUACIÓN SENSORIAL CUANTITATIVA
Y PSICOFÍSICA TÉRMICA
EN LA VALORACIÓN DE LA NOCICEPCIÓN Y DOLOR
EN LA LESIÓN MEDULAR**3.1. Introducción**

En este capítulo exponemos el completo estudio diagnóstico del DN en pacientes lesionados medulares con DN agudos (de 46 meses después de la lesión) y crónicos con Siringomielia versus sin DN y voluntarios sanos usando diferentes métodos: el cuestionario DN4, la Evaluación Sensorial Cuantitativa (QST) y el sistema TSAR (Sistema de Estímulo y Respuesta Térmicos), para revelar qué mecanismos pueden encontrarse presentes en los pacientes que sufren de DN, e investigar más el papel del CPG local (Generador de Dolor Central) en su generación.

3.1.1. Cuestionario de Diagnóstico de Dolor Neuropático: Discriminación entre DN y nociceptivo.

Clínicamente, el DN es generalmente caracterizado por la asociación de síntomas sensitivos inespecíficos positivos y negativos, aunque aún no existe un consenso de criterio diagnóstico en DN (**Jensen et al., 2001, Hansson, 2002, Woolf and Mannion, 1999 and Dworkin et al., 2003**). Tradicionalmente, el diagnóstico de DN ha recaído ampliamente en la evaluación sensorial más que en descriptores de dolor, los cuales se pensó que no eran suficientes para el diagnóstico de DN (p.e. **Baron, 2000, Jensen et al., 2001, Hansson, 2002, Dworkin, 2002 and Rasmussen et al., 2004**). Sin embargo, **Bouhassira et al. (2005)** ha desarrollado un cuestionario, útil como herramienta diagnóstica para la identificación de pacientes con DN comparados con dolor nociceptivo, e identifica varios síntomas de dolor presentó expresados preferentemente en estos pacientes con un valor discriminante claro (“quemante”, “descargas eléctricas” y “cosquilleo”). En concreto, la asociación de síntomas dolorosos y parestesia/ disestesia posee una alta especificidad y valor diagnóstico, y las buenas propiedades discriminantes de las 7 cuestiones basadas sólo en la entrevista (entrevista DN4) sugieren que este cuestionario podría usarse en una amplia variedad de estudios clínicos incluyendo, por ejemplo, encuestas telefónicas y hacerlo apropiado para estudios epidemiológicos (**Bouhassira et al., 2005**).

3.1.2. Estimulación con Pruebas Sensoriales Cuantitativas (QST): LM y otras patologías.

Finnerup et al. (2003b) examinó la detección sensitiva y los umbrales de dolor por encima del nivel de la lesión en pacientes con LM central y DN, sin DN y 20 controles. Los pacientes con LM con dolor presentaban mayores umbrales de detección comparados con los LM sin dolor. Estos datos sugieren cambios en la función somatosensorial (hiperexcitabilidad) en dermatomas rostrales al nivel segmental de la lesión unidos a la presencia de DN central en estos pacientes, y también cambios en los sistemas inhibitorios y facilitatorios. Exámenes neurológicos estándar de los signos de dolor (**Finnerup et al., 2003b**) permiten una aproximación a los mecanismos centrales presentes después de la LM e incluyen signos como la alodinia dinámica, hiperalgesia mecánica e hiperalgesia al frío presentes al nivel de la lesión aunque la sumación temporal no estuvo presente (**Finnerup et al., 2003b, Eide et al., 1996**). Es notable que la mayoría de los pacientes de DN incluidos en el estudio de **Finnerup et al. (2003b)** fueron pacientes LM con lesiones completas y por tanto procesos fisiopatológicos que provocan sensibilización central no estuvieron tan intactos como en aquellos con lesión incompleta. Basado en esta investigación, los pacientes con dolor central presentaron hiperactividad más frecuentemente en los dermatomas correspondientes al nivel de lesión que aquellos sin dolor y encontraron una correlación significativa entre la intensidad de la disestesia evocada por la cepilladura al nivel de la LM y el dolor espontáneo por debajo del nivel de lesión.

El QST por estímulos térmicos nociceptivos se considera un modelo útil para la valoración de la percepción de dolor en individuos sanos así como en pacientes de dolor (**Gruener and Dyck, 1994; Kalman et al., 1999; Khalili et al., 2001; Meier et al., 2001; Verdugo and Ochoa, 1992; Yarnitsky et al., 1995; Granot et al., 2003**). El diagnóstico incluiría no sólo una descripción y la evolución de la dolencia, sino también una evaluación de la función del sistema espinotalámico y dorsal y evaluación neurofisiológica clínica de los nervios periféricos y de las funciones de la médula espinal por debajo del nivel de lesión (**Beric et al., 1988**). El QST

incluye a menudo herramientas fiables y no costosas muy útiles clínicamente, como el vibrómetro graduado Rydel–Seiffer para medir los umbrales vibratorios (Whitton et al., 2005). En el uso de valores umbral para la detección de estimulación térmica y táctil, Eide et al. (1996) encontró que cambiaron significativamente en las áreas denervadas de la piel aunque no había diferencias en los umbrales entre áreas con y sin dolor, ni tampoco en las reducciones en sensaciones táctiles, de vibración, de posición y discriminación entre dos puntos en áreas denervadas y dolorosas de la piel. La alodinia y dolor tipo sumación temporal fueron significativamente más comunes en áreas denervadas dolorosas.

La fisiopatología de la pérdida sensorial que acompaña a este tipo de dolor crónico se dirigió hacia varias hipótesis (Defrin et al., 2001). Un caso informado por Browder and Gallagher (1948) sugirió que el dolor crónico podría desarrollarse tras una lesión de la columna dorsal, pero no obtuvo apoyo ya que posteriores observaciones mostraron que las lesiones discretas del sistema lemniscal aumentan sólo las parestesias pero no el dolor crónico (Cassinari and Pagni, 1969; Pagni, 1977). En un estudio posterior, Beric et al. (1988) examinó 13 pacientes con LM y DN; estos sujetos presentaron una casi completa pérdida de las sensaciones térmicas por debajo de la lesión, mientras que las sensaciones de vibración y táctiles se hallaban significativamente menos dañadas.

3.1.3. Psicofísica de la Evaluación Sensorial Térmica Cuantitativa y el Sistema TSAR.

El Sistema Térmico de Estímulo y Respuesta (TSAR), desarrollado por algunos autores (Mauderli et al., 2003; Vierck et al., 1997) proporciona características estímulo-respuesta mediante la combinación de intensidad y frecuencia de estímulo. Estudios previos, como Morin y Bushnell (1998) usaron varios rangos de temperaturas entre -5° y 23° C y temperaturas de calor desde 41° a 48° C y encontró que 47° C y 9° C fueron los umbrales de calor y de frío respectivamente (VAS=5) en los sujetos sanos. Su método fue más gradual para tolerar estímulos dolorosos ya que la tasa de temperaturas es continua y el área del cuerpo puede habituarse mejor a la estimulación nociva, como en el estudio de Staud et al. (2004) con pacientes con fibromyalgia. Defrin et al. (2002) sugirió que la integridad de los sistemas térmicos no nociceptivos es esencial para la percepción normal del dolor térmico, y que la sensación subjetiva de dolor depende de la integración de información desde los canales nociceptivos y no nociceptivos. Beric et al. (1988) encontró con pruebas térmicas que, en pacientes con lesión incompleta mayoritariamente, había ausencia de sensación en el 77% de ellos y la percepción táctil aún se preservaba en un 69% de los pacientes, habiendo diferencias significativas entre estas percepciones.

3.1.4. La Hipótesis del Generador Central de Dolor (CPG) y el DN con LM.

Los pacientes con LM con y sin dolor presentaron similares reducciones en detección térmica y mecánica y umbrales de dolor y potenciales evocados sensitivos (Ver Capítulo 2, sección 2.1.3), aunque los pacientes con dolor por debajo del nivel de lesión mostraron significativamente más *hipersensibilidad* al nivel que los pacientes sin dolor (Finnerup et al., 2003b), y presentaron mayores lesiones de la sustancia gris en el extremo rostral de la lesión, visto con resonancia magnética (Finnerup et al., 2003a). Este dato, junto con los de Vierck y Light's (1999, 2000) sugieren que la lesión vía espinotalámica por sí misma no explica el dolor central en pacientes, y la *hiperexcitabilidad neuronal* causada por cambios excitotóxicos y por lesión en las neuronas inhibitorias en el *extremo rostral* de la lesión pueden ser un importante mecanismo adicional para el dolor por debajo del nivel de lesión. Así, el dolor central de la LM puede ser el resultado de cambios neuroplásticos supraespinales en respuesta a la desaferentación y estímulo anormal procedente de un generador espinal (Finnerup et al., 2004). Por otra parte, no todos los pacientes con LM presentan signos de *hiperexcitabilidad* (Finnerup et al., 2003a,b y 2004), indicando que otros mecanismos deben estar presentes también. El DN en LM representa condiciones de dolor heterogéneas que dependen de diferentes mecanismos (Finnerup et al., 2004).

3.1.5. La Sensibilización Central medida con estímulos tónicos de calor y frío

Aunque se asume que el proceso de la sumación temporal a estímulos repetidos no puede explicar plausiblemente los cambios perceptivos a largo plazo en el dolor crónico (e.g. Woolf, 1996) y que no es central para el desarrollo de dolor crónico, la observación clínica de la sensibilización como marcador clínico en algunos síndromes de dolor crónico permanece. De hecho se ha observado en estudios con potenciación a largo plazo (LTP) en neuronas nociceptivas espinales (Li et al., 1999) y cerebrales (Chen et al., 2000; Kleinböhl et al., 2002). Más aún, los efectos a medio y largo plazo como la hiperalgesia y habituación interactúan con la sensibilización a corto plazo.

Existe una falta de procedimientos experimentales psicofísicos de dolor que proporcionen una base para la caracterización de aspectos dinámicos de plasticidad de dolor como cambios en sensibilización. Hasta la fecha, la sensibilización perceptiva ha sido mostrada en modelos de sumación temporal para calor de contacto y radiante (Nielsen and Arendt-Nielsen, 1998; Price et al., 1977), eléctrico (Arendt-Nielsen, 2000) y de estímulos mecánicos (Magerl et al., 1998).

Kleinböhl et al (1999) utilizaron un paradigma de calor tónico (el procedimiento de “sensibilización dual” que proporciona un índice subjetivo y comportamental de sensibilidad (Kleinböhl et al, 1993; Van Ackern et al., 1994; Kleinböhl, 1996)) para evaluar una sensibilización temprana (15-100 seg.), encontrando que el grado estaba linealmente relacionado con la temperatura estimular, y el grupo de pacientes con dolor musculoesquelético se sensibilizó antes que los controles sanos. Pero la sensibilización a corto plazo en humanos no se había investigado en pacientes crónicos hasta que Kleinböhl et al. (2006) propuso un método psicofísico basado en un paradigma de sumación temporal, que permite una valoración concurrente de sensibilización a corto plazo y habituación a medio plazo, asumida la relación al “wind-up” espinal y fatiga de fibras nociceptivas cutáneas, respectivamente.

3.1.6. Pacientes con Dolor Neuropático y Siringomielia

Existe una falta de estudios para esta enfermedad de la médula espinal que se caracteriza por la presencia de cavidades llenas de fluido que conducen a alteraciones sensitivas y de la espasticidad. Attal et al., (1999) encontró DN central en el 66% de sus pacientes y evidencia de déficit en vibración y sensibilidad táctil, similar en áreas de dolor y no dolor. Los potenciales evocados somatosensoriales mostraron buena correlación con los déficit vibratorios. Sus resultados confirman que el QST es útil en la práctica clínica para cuantificar los resultados quirúrgicos en estos pacientes. Bouhassira et al. (2006) no encontró diferencias en magnitud de DN/no dolor, pero un patrón déficit diferente fue observado entre pacientes con dolor espontáneo y éste con alodinia, sugiriendo que el DN central debido a Siringomielia no puede ser considerado como simple amplificación del dolor normal. Los datos psicofísicos y funcionales de neuroimagen demostraron que diferentes síntomas de DN central son mantenidos por distintos mecanismos. Quizá destacar que el papel del CPG, como ha sido identificado en DN y LM (Finnerup et al., 2003b), no se piensa que sea un mecanismo muy importante en pacientes con dolor tras la Siringomielia.

3.2. Objetivos

3.2.1. Objetivos del Estudio

1. Examinar las diferencias entre pacientes con LM y Dolor Neuropático (NP) y sujetos sin DN (Siringomielia-SYR, LM sin DN-NoNP y Voluntarios Sanos-HV) usando pruebas estándar QST y evaluar el posible papel del CPG actuando al nivel, por debajo y por encima del nivel de lesión.
2. Identificar las diferencias entre los pacientes LM con dolor y sujetos sin dolor (NP, SYR vs NoNP, HV) con estimulación térmica nociceptiva medida con el sistema TSAR, e identificar el papel del CPG que actúa al nivel, por debajo y por encima del nivel de lesión.
3. Evaluar si los pacientes con Siringomielia (SYR) son distintos de otros grupos de sujetos (NP, NoNP, HV) en sensibilidad y respuesta a estimulación térmica nociceptiva (QST and TSAR).
4. Examinar la utilidad del Cuestionario DN4 en la discriminación entre pacientes con DN y sin DN (SYR vs NoNP) y relacionado con descriptores de dolor previamente identificados en otros estudios de LM.

3.2.2. Hipótesis de Estudio

El CPG y el daño asociado a los tractos ascendentes principales (espinotalámicos y de la columna dorsal) son responsables en el desarrollo del DN al nivel y por debajo del nivel de lesión en la mayoría de los pacientes, y BST/QST y el sistema TSAR son instrumentos válidos para esta evaluación.

3.3. Métodos

3.3.1. Criterios de Selección

Los pacientes fueron reclutados en el Hospital Nacional de Paraplégicos de Toledo (España), y cubren toda la población del territorio español. Revisamos un total de 1630 historias clínicas y 30 pacientes con LM con y sin dolor fueron apropiados para el estudio, además de 11 pacientes con LM y Siringomielia. Pacientes con dolor neuropático (sensación de quemazón y/o presión principalmente, a cualquier nivel dermatómico) y lesión medular completa o incompleta sensitivo-motora (según la escala ASIA A-C) con un nivel por encima del cono medular (D10) evaluado a partir de los 4-6 meses después del trauma, es decir, en su fase aguda.

Similar a los criterios de los capítulos 2 y 4, los pacientes con DN central inicialmente descrito como de “quemazón” y/o “presión”, con una intensidad mayor que 3 en la Escala Analógica Visual VAS (EVA) con lesión medular completa o incompleta sensitivo-motora (según la escala ASIA A-C) con un nivel por encima del cono medular (D10) evaluado de los 4-6 meses después del trauma, es decir, en su fase aguda. La etiología de la LM fue traumática o atraumática (enfermedad). Las edades estaban comprendidas entre los 18 y los 75 años. Comprenden y hablan Español. Los espasmos relativos al dolor neuropático se permitieron, independientemente del nivel de LM. Todos los pacientes fueron voluntarios y firmaron un informe de consentimiento. La mayoría de los pacientes recibieron tratamiento analgésico estándar que fue prescrito en nuestro hospital en el momento del diagnóstico (36.7 % con Amitriptilina y/o Gabapentina, y 42.9 % describieron alguna “desagradabilidad” o disestesia/dolor pero no estaban medicados. Un total de 11 voluntarios sanos se eligieron en un ratio hombre-mujer de 60/40.

3.3.1.2. Criterios de Exclusión

Se excluyeron los pacientes con dolor psicógeno, esclerosis múltiple, neuropatías periféricas, “síndrome de dolor complejo regional (CRPS)”, daño cerebral, incapacidad para la comunicación verbal, hipoacusia severa o demencia, así como los pacientes que no pudieron ser examinados en la primera evaluación (antes del tratamiento farmacológico). Los pacientes con espasmos no relativos al dolor neuropático también se excluyeron del estudio.

3.3.1.3. Grupos Experimentales de Estudio

Los sujetos fueron asignados a unos de los siguientes grupos: pacientes con LM (Sin Dolor Neuropático “NoNP”, Con Dolor Neuropático “NP”, Siringomielia “SYR”) y voluntarios sanos “HV”. También se realizaron comparaciones en aquellos con lesión cervical y dorsal, de acuerdo con las tendencias observadas en el Capítulo 2. El grupo NoNP (n=10) fue constituido por 5 pacientes con lesión cervical y 5 con lesión dorsal. El NP (n=19), por 9 con lesión cervical y 10 con lesión dorsal. El SYR NP (n=10), por 5 con lesión cervical y 5 con lesión dorsal. Finalmente, el HV (n=11), por 6 con examen en el sitio cervical y 5 en el sitio dorsal.

3.3.1.4. Diseño general de estudios con pacientes.

Todos los procedimientos fueron aprobados por el Comité Ético de Investigación Clínica del “Complejo Hospitalario de Toledo-SESCAM” y se informó al paciente de la naturaleza del estudio, permitiéndole abandonar a voluntad.

3.3.1.5. Procedimiento Experimental

Se llevó a cabo la misma conducta tanto con pacientes como con los voluntarios sanos. Tras obtener el consentimiento informado del paciente y haberle explicado el procedimiento, se les hicieron las preguntas del cuestionario DN4 y el examen QST. El sujeto sentado fue situado con la parte del cuerpo elegida en contacto con la placa. Un breve entrenamiento de 10 min. consistió en practicar con el eVAS y la lista de descriptores verbales. Estimulamos el sitio cervical o dorsal más desagradable o doloroso para el paciente, y cuando fue posible utilizó su mano dominante. Los sujetos fueron examinados en una sesión, con pequeños descansos de 1 min. entre las diferentes temperaturas aplicadas y 5-10 entre los diferentes cambios en las partes del cuerpo. Los sujetos recibieron 30 seg. de estimulación con calor primero (normalmente 48°C en caso de ser bien tolerado durante los primeros 10 seg. o 43°C en caso contrario) seguidos del descanso de 1 min., un estímulo control de 33°C, descanso de 1 min. y 30 seg. de estimulación con frío (normalmente 3°C en caso de ser bien tolerado durante los primeros 10 seg. o 13°C en caso contrario). Cada una de las temperaturas fue presentada en tres sitios del cuerpo: por debajo del nivel de lesión (usualmente L4 o L5), al nivel de lesión (en un dermatoma coincidente

con su propio nivel de lesión) y por encima del nivel de lesión (la cara es C2 y fue el sitio control para todos los sujetos). En los voluntarios sanos estimulamos los mismos sitios, y elegimos C6 (el dorso del brazo) como dermatoma para la estimulación cervical y D6-7 para la estimulación dorsal. Durante el estímulo de 30 seg, y los 120 seg. después, el sujeto evaluó las sensaciones térmicas usando el e-VAS y al mismo tiempo eligió uno o más descriptores de la lista. Después se le preguntó por las sensaciones post-estímulo con la ayuda del mapa de dermatomas en la pizarra. La placa térmica fue situada más arriba o más abajo dentro del mismo dermatoma para evitar la estimulación repetitiva en el mismo sitio.

3.3.2. Cuestionario Diagnóstico y QST

3.3.2.1. Cuestionario DN4

El cuestionario “douleur neuropathique 4 questions” por el Dr. Bouhassira, es un cuestionario de administración clínica que ha sido reducido y simplificado a 10 preguntas, siendo la puntuación de 4 de 10 el corte para un diagnóstico de DN. Puede ser usado fácilmente por especialistas y no especialistas en la práctica diaria clínica como herramienta exploratoria. Presenta buenas propiedades discriminantes de las 7 cuestiones basadas en la entrevista sólo. Su formulación y relevancia clínica fueron considerados como buenos por el 90-95 % de pacientes e investigadores (**Bouhassira et al., 2005**). Este cuestionario incluye cuatro cuestiones consistentes en descriptores sensoriales y signos relacionados con la “Pruebas semi-cuantitativas de sensibilidad” (BST) (Basado en **Bouhassira et al., 2005**) (**Ver Appendix Protocol 3.1c.**). La versión española del DN4 (incluida en **Appendix Protocol 3.1.**) acaba de ser desarrollada por nosotros en colaboración con otros tres hospitales nacionales españoles y el apoyo del Dr. **Bouhassira** y la compañía farmacéutica **Pfizer**. Mediante dos análisis de una muestra de 164 pacientes se pudo concluir que la versión española del cuestionario es fiable, estable y válida para el diagnóstico diferencial de las condiciones de DN, ya que es capaz de diferenciar los componentes neuropáticos y nociceptivos del dolor, con el mismo punto de corte que en la versión original (**Huelbes S, Pérez C, Gálvez R, Insausti J, Bouhassira D, Díaz S, Rejas J, to publish**)

3.3.2.2. Evaluación Sensorial Cuantitativa (QST)

La evaluación se llevó a cabo por el mismo examinador (S.H.A), y se tuvo cuidado en evitar el estrés del paciente durante la evaluación. Se condujo el examen somatosensorial en el área cervical o dorsal más dolorosa para el paciente, estimulando dermatomas situados por debajo del nivel de lesión (L4 o L5), al nivel de su lesión y por encima de ésta (C2 como control). En los voluntarios sanos se eligió el nivel C6 o D6-7.

Los signos de dolor fueron puntuados en una escala VAS (la misma usada en el **capítulo 1**) para la evaluación del dolor con estímulos de frío y calor (mediante un tubo de ensayo a 48°C para el calor y acetona y Tip Therm® para el frío), Alodinia Mecánica/sensibilidad (Alodinia Dinámica) mediante 5 pinceladas con un pincel, Sumación Temporal al pincel (mediante 50 pinceladas), Alodinia Estática/sensibilidad (Alodinia Puntual) (mediante 5 toques con el filamento von Frey), Sumación Temporal a filamento de von Frey 3 veces más fuerte que su umbral (mediante 50 pinceladas). Las siguientes pruebas se evaluaron mediante “sí o no” por el sujeto para encontrar si el estímulo fue o no percibido: umbrales mecánicos (sensación táctil mediante filamentos von Frey), sensación de vibración (mediante vibrómetro) y discriminación entre dos puntos (por la mínima separación detectada en mm) (**Ver foto en Appendix Picture 3.1.**)

Basados en los resultados de **Eide et al. (1996)** y **Gottrup et al. (1998)**, la metodología fue adquirida por el examinador (S.H.A) gracias a la supervisión del **Professor Nurmikko** y el **Professor Bowsher** en la **Pain Relief Foundation** de Liverpool (Gran Bretaña) y los comentarios de Dr. Schweinhardt (Oxford, Gran Bretaña).

3.3.2.3. El Sistema TSAR

Basado en **Vierck et al. (1997)** y **Morin y Bushnell (1998)**, este método simula las condiciones naturales de la estimulación térmica nociceptiva. Usamos una placa de contacto tipo Peltier de 2.56 cm² con la temperatura controlada por ordenador ($\pm 0.1^\circ\text{C}$), y la rampa de cambios siendo constante a 0.5°C/s para el calor y 1°C/s para el frío, muestreando los datos a 10 Hz. Se pre-enfrió y pre-calentó el Peltier durante 40 seg. Estudios piloto en sujetos sanos produjeron una intensidad de dolor (VAS) de 2-3, así la temperatura más usada para el calor fue de 48°C y 3°C para el frío. También se usó un estímulo de control en cada zona de 33°C. (**Ver foto en Appendix Fig 3.6**). Estudios piloto en voluntarios sanos produjeron una intensidad de dolor de entre “2-3” en la escala VAS, donde “2” representaba el umbral de dolor, en respuesta a estímulos de frío y calor. Sin embargo, algunos voluntarios no pudieron tolerar la temperatura de 48°C (se usaron también 47 y 43°C) durante los 30s o no

identificaron dolor después del estímulo térmico. Se utilizó una temperatura “dummy” de 33°C durante 30s que no produjo sensación en los voluntarios sanos.

3.3.2.4. *Electronic VAS (e-VAS)*

La intensidad de dolor evocado que siguió a la estimulación térmica con el Peltier fue continuamente por el paciente mediante una VAS electrónica (e-VAS) que siempre podían ver en una pantalla (o en la escala manual de 100 mm) y recibían retroalimentación cada segundo. El color de la línea se mostró en azul desde 0 hasta 2/10, significando sensación desagradable pero no dolorosa, y en rojo desde ese punto hasta el final de la escala, significando sensación dolorosa hasta un máximo sufrible. Las palabras “sin sensación” y “dolor máximo” se situaron a ambos extremos de la escala (**Ver dibujos Appendix Pictures 3.2.-3.4**). Una vez que el estímulo de 30 seg. paró, se siguió valorando el e-VAS hasta 120 seg. después.

3.3.2.5. *Descripción de Calidad del Dolor y Localización: Lista de Descriptors Térmicos de Dolor y Mapa de dermatomas.*

Presentamos al sujeto una lista de descriptores verbales (**Ver Tabla 3.1.**) y un mapa de dermatomas (como el incluido en el **Protocol Appendix 3.1.**) en una pizarra portátil donde podía verla en todo momento. La lista consistió principalmente en 13 palabras extraídas del Cuestionario de dolor de McGill (**Melzack, 1975**). Pedimos al sujeto que comunicara cualquier sensación experimentada antes, durante o después de la presentación del estímulo y este podía mirar el mapa de dermatomas para ayudar a localizar las áreas del cuerpo implicadas.

3.3.3. *Análisis Estadístico de los Datos.*

Los datos se evaluaron usando tests no paramétricos (Mann Whitney y Cochran) con un 5% de significación aceptada, con el programa informático SPSS versión 13.0.

3.4. Resultados

3.4.1. *Datos Demográficos y Características*

Un total de 52 pacientes fueron reclutados. Los pacientes y voluntarios sanos fueron divididos en los siguientes grupos: grupo de Dolor No-Neuropático (NoNP) (N=10; n cervical = 5 ; n dorsal= 5); grupo de Dolor Neuropático (NP) (N=20; n cervical = 9 ; n dorsal = 11); grupo de voluntarios sanos (HV) (N=11; n examinado en el sitio cervical = 6; n examinado en el sitio dorsal = 5); grupo con Siringomielia (SYR) (N=11; n cervical = 6; n dorsal = 5). El rango de edad fue de 21 a 51 años (30.4 ±8.9) en el grupo NoNP; de 19 a 64 años (39.33±14.1) en el grupo NP; de 35 a 73 años (53.73±13.7) en el grupo SYR; y de 22 a 57 años (32.40±9.4) en el grupo HV. La LM traumática fue la causa más frecuente en nuestro hospital (100% en NoNP, 94 % en NP) excepto en el grupo de SYR (sólo 36%). Los pacientes con lesión dorsal estuvieron más presentes en el grupo NP (56%), después en el grupo NoNP (50%) y SYR (27%). La lesión completa (ASIA A) fue identificada en el 67% de los pacientes en el grupo NP, 60% en NoNP, y sólo en el 27% en SYR. (**Ver Tabla 3.2**). El grupo de pacientes se encontraba en su mayoría medicado: el 67% del grupo NP y el 82% del grupo SYR. El tratamiento fue una combinación de agentes analgésicos (Amitriptilina, Clonazepam o Gabapentina/Pregabalina) siguiendo un diagnóstico inicial o posterior de dysesthesias (94% en NP y 91% en SYR). El tiempo de comienzo de LM en el grupo NoNP fue de 4.45±0.91 (rango 4-6.5) y de 6.5±0.91 (6-6.5) para el cervical y 4.20±0.4 (4-5) para el dorsal. En el grupo NP la media fue de 5.44±1.83 (4-9) meses desde el comienzo de lesión para el grupo cervical y 4.18±0.60 (4-6) para el dorsal.

En el grupo SYR fue de 4.28±2.05 (1-8) años en el cervical, 14±10.61 (7-29) años en el grupo dorsal y un paciente con Siringomielia lumbar de 6 años de lesión. Los resultados descriptivos en **Appendix Fig. 3.1. and 3.2** muestran la tasa de respuesta dolorosa a los estímulos de calor y frío para los grupos NoNP, NP, SYR y HV que respondieron con un e-VAS mayor que 2/10 (umbral de dolor).

3.4.1.1. *Tasa de Respuesta de dolor a las Pruebas QST.*

Los resultados de la estimulación QST al nivel de lesión en los pacientes que responden mostró que en la prueba de umbral de detección táctil el 100% de los sujetos HV pudieron determinar su umbral, pero sólo el 60% de NoNP, el 55% de SYR y el 28% de NP pudieron determinar el umbral de sensibilidad (más sensible en sitios cervicales). El vibrómetro mostró bajas tasas de respuesta por debajo del nivel de lesión en pacientes (27% in

SYR); aunque al nivel en el grupo NP respondieron en el 78% de los casos, el más bajo comparado con los otros grupos. Por encima del nivel, el de SYR es el grupo que más bajo responde con el 91%. El test de 10-50 toques de von Frey (2-3 veces más alto que el umbral) mostró una respuesta disminuida al nivel en los grupos de LM (SYR fue el más bajo con sólo el 36% de respondientes). Sin embargo, SYR presentó las tasas más altas por debajo del nivel (36%). La prueba con el calibre milimétrico mostró una tasa baja de respondientes en NP (89%) y SYR (73%) al nivel y por debajo del nivel de LM; todos los grupos respondieron bien en el sitio control. La prueba con 5 toques de von Frey (2-3 veces más alto que el umbral) mostró la respuesta más baja en los pacientes con Siringomielia (9%) y el máximo en el grupo NP al nivel (77%). Por debajo del nivel de lesión el grupo de SYR es el que más responde. La prueba del tubo de 48°C indicó que los pacientes con SYR fueron los que más respondieron a todos los niveles de estimulación (91% al nivel, 55 por debajo y 80% por encima). Similares respuestas fueron obtenidas con la gota de acetona/ Tip Therm® excepto en el sitio control con el grupo NP (78%) con la tasa más alta de respondientes. El cepillo grueso mostró al nivel más respondientes en el grupo NoNP (50%); HV (50%) presentó al nivel y por debajo del nivel más sensibilidad que en otros grupos.

3.4.1.2. Tasa de Respuesta de Dolor a Estímulos de Calor y Frío.

Los resultados de estimulación al calor al nivel de la lesión en los pacientes que responden (**Ver Tabla 3.4 y Appendix Fig. 3.1. y 3.2**) mostró que en el grupo NoNP, sólo 2 (40%) de los pacientes en el grupo de LM cervical respondieron comparados con 4 (80%) con lesión dorsal. En el grupo NP, 3 pacientes (33.3%) con LM cervical y 4 (40%) con dorsal mostraron respuesta. En el grupo SYR sólo 1 paciente lo hizo en el grupo cervical (16.6%) mientras que ninguno de los pacientes del dorsal respondió. Entre el grupo HV, 3 (50%) respondieron a la estimulación cervical comparados con 4 (80%) a la estimulación dorsal.

A la estimulación al *frío* al nivel de la lesión respondieron en general menos que con al calor. En el grupo NoNP, ninguno del grupo cervical respondió y sólo 1 (20%) en el grupo de lesión dorsal. En el grupo NP, 1 paciente (11.1%) con lesión cervical y 3 pacientes con lesión dorsal (27.3%) mostraron respuesta. En el grupo SYR 3 pacientes con lesión cervical (50%) mientras que ninguno lo hizo en el grupo dorsal. En el grupo HV, 3 sujetos (50%) respondieron a la estimulación de dermatomas cervicales y 2 de ellos (40%) a los dorsales.

La estimulación al *calor* por encima de la LM en los pacientes que respondieron mostraron que 3 (60%) lo hicieron del grupo NoNP cervical mientras que fueron 2 (40%) en el grupo dorsal. En el grupo NP, 5 pacientes (55.5%) con lesión cervical y 4 con dorsal (36.3%) mostraron respuesta. El grupo SYR presentó 2 pacientes en el grupo cervical (33.3%) y 1 (20%) en el dorsal. Entre el grupo HV, 2 (33.3%) respondieron a la estimulación del sitio cervical y 3 de ellos (60%) lo hicieron en el sitio dorsal del cuerpo.

Los resultados de la estimulación al *frío* al nivel de lesión en los pacientes respondientes mostraron que en el grupo NoNP hubo 3 (60%) del grupo de lesión cervical y 2 (40%) del dorsal. En el grupo NP, 5 pacientes (55.5%) con lesión cervical y 5 (50%) con dorsal mostraron respuesta. El grupo de SYR presentó 3 pacientes (50%) en el grupo cervical y 1 (20%) en el dorsal. Entre los HV, 2 (33.3%) respondieron a la estimulación en el sitio cervical y 2 de ellos (40%) en el dorsal. El sitio de estimulación cervical presentó más respuestas en el grupo HV para el calor y el frío al nivel mientras que por encima del nivel (el control fue la cara), NoNP y NP lo hicieron para calor y frío. El grupo de SYR presentó las respuestas más bajas al calor al nivel comparado con los otros grupos. Como observamos, el grupo NP es similar al NoNP en este sitio, pero en el grupo dorsal presentó menores respuestas en calor que los grupos NoNP y HV. La estimulación dorsal presentó más respuestas en los grupos NoNP y HV para el calor, HV para el frío al nivel y también por encima del nivel para el calor mientras que para el frío por encima de la lesión lo hizo el NP. Los del grupo de SYR presentaron las respuestas más bajas a cualquier temperatura y nivel comparado con los otros grupos y es notable la ausencia total de respuestas al nivel de la lesión en el sitio dorsal.

3.4.1.3. Análisis del Cuestionario DN4

Las medianas, los percentiles 25 y 75 para el cuestionario DN4 mostraron similares valores en los grupos NP y SYR, entre 4 y 6 puntos del total de 10, mientras que el máximo obtenido para el grupo NoNP es sólo de 4.75 puntos (**Ver Tabla 3.6**). Llevamos a cabo análisis no paramétricos para varias muestras relacionadas (test de Cochran, distribución asintótica de dos colas) entre los grupos NoNP, NP y SYR. La pregunta 9 (Hipoestesia al pinchazo de alfiler) fue significativa entre NoNP y SYR ($P=.046$; presentada en todos los pacientes NoNP), y también entre los grupos NP y SYR ($P=.046$; más presente en los pacientes con SYR). La pregunta 10 (Cepilladura) fue significativa entre los grupos NoNP y NP ($P=.025$; más presente en pacientes NP) (**Ver Tabla 3.7**). Cuando el DN4 fue considerado en el total de puntos (test de Mann-Whitney U, distribución asintótica de

dos colas) no se vio significación entre los grupos: NoNP y NP ($P=.410$); NoNP y SYR ($P=.071$) ; NP y SYR ($P=.964$).

3.4.1.4. Dolor Irradiado

Estuvo más presente en la estimulación al calor al nivel de la lesión, con un total de 2 pacientes (40%) con lesión cervical y 1 (20%) con dorsal en el grupo NoNP; y 3 pacientes (33%) con lesión cervical y 2 (18%) con lesión dorsal en el grupo NP. En la estimulación al frío al nivel de la lesión sólo 2 pacientes (40%) con lesión cervical en el grupo NP lo presentaron. En la estimulación al calor por encima de la lesión, 1 paciente (20%) con lesión dorsal en el grupo NP y otro dorsal en el NoNP. En la estimulación al frío por encima de la lesión, hubo sólo 1 paciente (20%) con lesión dorsal en el grupo NP (**Ver Tabla 3.5**).

3.4.2. Análisis de las Respuestas al QST

La Sumación Temporal provocada por repetitivas cepilladuras en el sitio con un pincel grueso medidas cada 10 veces no produjo el deseado efecto de prevalencia en la respuesta, siendo sólo un paciente el que respondió a esta prueba. Por lo tanto no lo consideramos para los análisis, ya que no podemos comparar los valores, excepto el NP comparado con mayor n, pero tampoco fue significativo con el test de Mann-Whitney: 0.418 al nivel; 0.264 por debajo; 0.807 por encima ($n= 4$ cervical y $n=3$ dorsal); y también pudimos comparar el grupo SYR, (test de Mann-Whitney: 0.813 al nivel; 0.513 por debajo del nivel; 0.626 por encima del nivel ($n= 4$ cervical y $n=3$ dorsal). Y para los grupos NP y SYR, test de Mann-Whitney: 0.275 al nivel; 0.287 por debajo; 0.289 por encima ($n= 4$ cervical y $n=3$ dorsal). Las medianas y percentiles 25 y 75 se muestran en la **Tabla 3.8**.

Realizamos tests no paramétricos para el resto de pruebas para dos muestras independientes (test de Mann-Whitney U, distribución asintótica de dos colas, $P = 0.05$) al nivel, por debajo y por encima del nivel de lesión (**Ver Tabla 3.9**).

Se encontraron resultados significativos *al nivel* de lesión en Umbrales (mN) presentando el grupo NP peor detección sensitiva que el HV ($P=0.029$); NoNP más bajos que SYR ($P=0.050$) y SYR más bajos que NP ($P=0.009$). La sensación de vibración (0-8 AU) fue mejor detectada en sujetos HV que en NP (0.037). La discriminación entre dos puntos (mm) fue mejor detectada en el grupo NoNP que en SYR ($P=0.044$). El calor (tubo de 48°C) presentó mayor puntuación en la escala VAS en SYR que en HV ($P=0.016$) y SYR que NoNP ($P=0.043$). El frío (gota de acetona) mostró la misma respuesta alta en el VAS en SYR que NoNP ($P=0.043$).

Por debajo del nivel de lesión algunas diferencias fueron encontradas entre los grupos. La Sumación Temporal (mN) mostró mayor nivel de intensidad en NoNP que en SYR ($P=0.033$). El grupo NP y SYR tiene también significación ($P=0.049$) pero no se sabe claramente qué grupo presenta niveles más altos observando las medianas (presumiblemente el de SYR ya que $P75=2$). El calor (tubo de 48°C) presentó mayor puntuación en la escala VAS en SYR que en NoNP ($P=0.007$) y SYR que NP ($P=0.003$). El frío (gota de acetona) mostró respuestas más altas en VAS en HV y SYR que NoNP ($P=0.017$). La Alodinia Dinámica (cepilladura) presentó puntuaciones más altas en HV que en NP ($P=0.010$).

Por encima del nivel de lesión sólo pudimos encontrar diferencia significativa en calor (tubo de 48°C) entre NP con VAS más alto que el grupo HV ($P=0.050$) y cercano a significativo entre mayor VAS en SYR que en HV ($P=0.054$).

3.4.3. Descriptores Informados en la Realización durante la Prueba Térmica.

Los descriptores informados por los sujetos de los grupos NoNP, NP y SYR al nivel de la lesión en la estimulación con calor mostraron que “puntual” y “quemante” fueron los más presentes antes de la estimulación, mientras que “sin sensación” lo fue después del estímulo (**See Appendix Fig 3.4**).

Los descriptores informados al nivel de lesión con la estimulación al frío mostraron que “puntual”, “frío” y “difuso” fueron los más presentes antes de la estimulación, mientras que “sin sensación” lo fue después del estímulo (**See Appendix Fig 3.5**).

Los descriptores informados por encima del nivel de lesión tanto con calor como con frío mostraron que “puntual” y “frío” fueron los más presentes antes de la estimulación, mientras que “sin sensación” y “frío” lo fue después del estímulo (See **Appendix Fig 3.6 and 3.7**).

3.4.4. Análisis de las Respuestas de la Curva de Dolor.

No encontramos respuestas por debajo del nivel de lesión en pacientes, excepto en un paciente del grupo NoNP, por lo que no pudieron hacerse análisis con ello.

Realizamos tests no paramétricos para dos muestras independientes (test de Mann-Whitney U, distribución asintótica de dos colas) al nivel y por encima del nivel de lesión para la estimulación con calor y frío. Ver **Tablas App 4.1-4.25 en Appendix** para todos los análisis realizados. Los resultados significativos se muestran en los **Gráficos 3.1-3.6**. La **Tabla 3.10** muestra las medianas a cada nivel y la significación (complementario a los gráficos).

En el **gráfico 3.1**, la rampa de respuesta inicial para la estimulación de calor al nivel para los cuatro grupos se muestra en los sitios cervicales y dorsales, siendo significativo ($P=0.032$) en pacientes del grupo NP. En el **gráfico 3.2**, la respuesta inicial del Modulus de 10 seg. para estimulación de calor por encima del nivel es significativa entre los grupos NP y SYR ($P=0.014$). El **gráfico 3.3** muestra la respuesta inicial significativa en el VAS Máximo para la estimulación de calor por encima del nivel ($P=0.024$) para HV y SYR. En el **gráfico 3.4** se muestra la respuesta inicial significativa de Modulus 30 seg. para la estimulación por encima del nivel ($P=0.033$) para los grupos NP y SYR. En el **gráfico 3.5**, la respuesta inicial del Modulus 10s para la estimulación con frío al nivel muestra significación ($P=0.025$) para el grupo de SYR y HV. En la **Fig.3.1** podemos observar un ejemplo de curva de dolor en un paciente de SYR y un sujeto HV con frío al nivel de la estimulación mostrando los primeros 10 seg. de respuesta. Es de interés el **gráfico 3.6**, que con una respuesta inicial del Modulus de 10 seg. para la estimulación con frío por encima del nivel de lesión no muestra diferencia significativa, pero está cerca ($P=0.059$) para los grupos NoNP y NP.

3.5. Discusión

3.5.1. Resumen

El DN, basado en la identificación de descriptores comunes y exámenes sensoriales obtenidos con el cuestionario DN4, se identificó en ambos grupos de dolor con puntuaciones entre 4 y 6 sobre 10, con la presencia de “cepilladura dolorosa” en el grupo NP e “hipoestesia al pinchazo” en el de SYR. Los métodos BST/QST estándar fueron asociados con una reducción en la detección táctil y vibratoria, con un incremento asociado en la intensidad de respuesta a 48°C (por debajo y por encima del nivel) y cepilladura (por debajo). Sin embargo, en general no se observaron diferencias significativas en la función sensorial al nivel entre los pacientes NoNP y NP con exámenes estándar de dolor o con métodos térmicos, lo que puede reflejar el limitado número de pacientes reclutados en este estudio o la exclusión de respuestas no dolorosas a los estímulos térmicos en el análisis final. De hecho, la intensidad de respuesta sensorial al nivel a estímulos inocuos y nociceptivos en los pacientes SYR y NP usando tests estándar BST/QST sólo puntuaron 1/10 en el VAS, claramente por debajo de nuestro umbral definido de 2. Más aún, la tasa de respuesta de dolor al nivel a estímulos térmicos usando el método TSAR fue baja, con respuestas al calor (HV 64%, NP 35%) siendo ligeramente más altas que para los estímulos tónicos de frío (HV 45%, NP 20%). Las tasas máximas de puntuaciones e-VAS

Registradas en estos pacientes respondiendo al calor tónico estuvieron entre 2.5-3.7, comparado con 1.7-4.5 con estímulos de frío, por encima de la intensidad de respuesta sensorial medida con técnicas BST/QST. En general, la aplicación de estímulos tónicos de frío al nivel de la LM y la medida de una temprana respuesta (10s) e-VAS proporcionó el mayor diagnóstico diferencial entre los pacientes de LM y voluntarios sin dolor (NP=30; SYR=29 versus NoNP=5; HV=14 eVAS.s), pero estos datos deben ser interpretados cautelosamente debido al bajo número de voluntarios incluido en el estudio. No se midieron respuestas de dolor al test tónico térmico aplicadas por debajo del nivel de LM en este estudio.

Al nivel y por encima el examen térmico fue valorado para identificar el efecto de los factores físicos de LM en las respuestas sensoriales en el grupo NP y SYR. Específicamente, la pendiente de respuesta de dolor al nivel a los estímulos tónicos de calor fue más alto en pacientes NP con lesión dorsal que con cervical. El examen al nivel con estímulos de frío en pacientes con SYR también indicó una más alta respuesta integrada temprana (10s) comparada con la respuesta sensorial en HV, asociada con una más alta respuesta e-VAS máxima a estímulos térmicos de calor. Estas modificaciones térmicas en el grupo SYR fueron también identificadas con técnicas

BST/QST estándar, donde se identificó en SYR comparado con HV, un incremento en la intensidad de respuesta a 48°C de aplicación del tubo al nivel y por encima de la lesión

3.5.2. Disfunción aferente y del asta dorsal durante el desarrollo del DN-LM.

Finnerup et al. (2003a,b) examinó la detección sensorial y los umbrales de detección en pacientes tras la LM y describió significativamente mayor detección de calor y umbral de detección táctil en pacientes con dolor comparado con sujetos sin dolor pero sin diferencia en intensidad de dolor o umbrales de tolerancia. No pudimos observar activación de mecanorreceptores de bajo umbral A β en umbrales de vibración y umbrales táctiles; sin embargo, la alodinia mecánica (“dolor causado por estimulación no nociceptiva”) resultó de su activación en estudios previos (**Campbell et al., 1988; Price, 1991**). Una explicación tentativa de la alodinia mecánica es que las neuronas del asta dorsal hiperexcitables que normalmente responden a estimulación nociceptiva (nociceptores de alto umbral Ad y C) empiezan a responder a la actividad en mecanorreceptores de bajo umbral A β (**Price, 1991; Bennett et al., 1994**). Por lo tanto, en áreas denervadas dolorosas, la activación de mecanorreceptores de bajo umbral A β puede activar neuronas del tracto espinotalámico hiperexcitables.

El fallo al encontrar un decremento significativo en detección táctil y umbral mecánico de dolor en algunos pacientes con alodinia indica la ausencia de sensibilización generalizada, tanto periférica como centralmente. El estudio de **Gottrup's et al. (1998)** no excluye la posibilidad de que el input periférico de los nociceptores mecanosensitivos conduzca a las neuronas del asta dorsal a un estado de hiperalgesia. Nuestros resultados usando estímulos térmicos que excitaron las fibras A δ y C por calor y frío nociceptivos presentaron más intensidad de respuesta por debajo del nivel de lesión en los pacientes NP comparado con HV, aunque en SYR fue más alta comparada con la de otros grupos. Aunque la población de receptores con fibras A δ en la piel humana que responden a más de una modalidad de estimulación nociceptiva – la unidad mecanotérmica (**Bromm et al. 1984**) y las respuestas al calor nociceptivo pueden ocurrir primeramente al calor y la tasa de descarga puede ser más alta que la mostrada por los nociceptores C polimodales (**Treede et al., 1998**), no hemos visto excitación mecánica de fibras C en pacientes agudos, sólo en SYR, al o por debajo del nivel de LM. Más aún, y como ocurrió con nuestros resultados también, los altos niveles de actividad en estos receptores correlacionan bien con el dolor cuando las fibras aferentes fueron activadas por estímulos nociceptivos de calor o químicos, pero no mecánicos (**Van Hees and Gybels, 1981**). Parece que los nociceptores C polimodales no pudieron ser excitados diferencialmente entre grupos por nuestro examen QST con los filamentos de vF y el tubo de 48°C, incluso cuando se sabe que la piel de la mano y pies humanos responden a estímulos mecánicos, térmicos y químicos (**Bromm et al. 1984**); el enfriamiento es raramente efectivo en su activación (**Wasner et al., 2004**), y el calentamiento a 40-45°C pueden excitar algunos de ellos. Ya que los receptores A δ mecanotérmicos al calor tienen un umbral más alto para los pulsos nociceptivos al calor que los C polimodales, estos deben ser responsables de la discriminación del dolor al calor desde el umbral (43-45°C) a niveles que pueden dañar la piel (por encima de 50°C) (**Adriaensen et al., 1980**).

No se obtuvieron resultados positivos para la alodinia dinámica ni sumación temporal en la detección de áreas denervadas dolorosas y no dolorosas a cualquier nivel, contrariamente a autores como **Eide et al., (1996)**, y la percepción sensorial mediada por las vías espinotalámicas o dorso-mediales no pudieron ser más afectadas en áreas denervadas dolorosas en los pacientes con dolor central.

Aunque no fue registrada sumación temporal en nuestros sujetos y pacientes con QST, estudios más fuertes usando electrofisiología han mostrado que la estimulación repetida de fibras C causa hiperactividad y descarga prolongada (“wind-up”) en las células nociceptivas del asta dorsal (**Davis et al., 1987; Dickenson et al., 1987**). En personas normales la estimulación repetida de los nociceptores Ad y C causan sumación temporal con incremento de dolor secundario y dolor que se prolonga después de la estimulación (**Price, 1991**). La estimulación repetida de mecanorreceptores de bajo umbral A β nunca produce dolor en sujetos normales, pero produce “wind-up” en pacientes con dolor por lesión en los nervios (**Price et al., 1989**). En el estudio de **Eide et al. (1996)** se demostró “wind-up” en el 64% de los pacientes por estimulación repetida con un von Frey de alta intensidad, activando normalmente los nociceptores Ad y C, y en el 22%, mecanorreceptores de bajo umbral A β . El dolor evocado mediado por A β y Ad/C tenía la misma cualidad y casi la misma severidad y tendencia a la irradiación.

3.5.3. *Hiperexcitabilidad Neuronal al nivel de la LM: Hipótesis del Generador de Dolor Central (CPG)*

Basado en nuestros resultados con la estimulación tónica de calor (el grupo dorsal presentó mayor sensibilidad) y el calor y el frío al nivel y por encima del nivel, y el estudio de **Finnerup et al. (2003a)**, que examinó detección sensorial y umbrales de dolor por encima del nivel en pacientes con LM y DN, con LM y sin DN y HV; en ambas muestras los pacientes de los grupos de dolor presentaban altos umbrales de detección significativos comparados con sujetos sin dolor y altos umbrales de detección comparados con el grupo de LM sin dolor y no hubo diferencia en umbrales de tolerancia entre pacientes con LM con y sin dolor.

Nuestros pacientes con y sin dolor mostraron reducciones significativas en la estimulación al calor y al frío ente niveles de lesión. Así, la *hiperexcitabilidad neuronal* (**Finnerup and Jensen, 2004**) causada por cambios excitotóxicos y lesión en las neuronas inhibitorias en el extremo rostral de la lesión puede ser un mecanismo adicional importante para el dolor por debajo del nivel, pudiendo ser el resultado de cambios neuroplásticos supraespinales en respuesta a la desaferentación y al estímulo anormal desde un generador espinal (**Finnerup and Jensen, 2004**). Sin embargo, no todos nuestros pacientes con LM presentaron signos de hiperexcitabilidad (**Finnerup et al., 2003a,b; Finnerup and Jensen, 2004**), indicando que otros mecanismos están presentes, como los tractos espinotalámicos o vías de la columna dorsal.

3.5.4. *Disfunción del tracto sensorial ascendente durante el desarrollo de LM-DN*

Nuestros resultados con umbrales táctiles y discriminación de dos puntos, combinados con los déficit en estímulos vibratorios al nivel de lesión indican que algunos grupos de pacientes (SYR versus NoNP) presentan disfunción sensorial al sistema de la columna dorsal lemniscal. El grupo SYR presentó mayor intensidad de dolor al y por debajo del nivel (QST) y al nivel con estímulos tónicos de frío (TSAR) lo que también explica **Defrin et al. (2001)**, el dolor y la temperatura permanecen tras la LM, aunque los cambios supraespinales en la función del centro de dolor pudieron contribuir a estos cambios. Debido a que la percepción dolorosa y térmica están primariamente mediadas por la vía espinotalámica, mientras que las sensaciones de tacto, vibración y posición lo están por la vía de la columna dorsal medial lemniscal (**Boivie et al., 1994; Beric et al., 1988**), el dolor central tras la SYR puede reflejar un desequilibrio de la función entre estas dos vías.

3.5.5. *Función modificada sensorial por encima del nivel de LM.*

En nuestros estudios usando BST y QST estándar, se identificaron cambios en la función sensorial a estímulos en los grupos de dolor seguido de aplicación del tubo de 48°C al nivel C2 dermatómico; estos resultados son contrarios a los de **Finnerup et al., (2003b)**. Varios experimentos han proporcionado evidencia de que la desaferentación central puede producir hiperexcitabilidad y actividad espontánea en las neuronas centrales, que puede resultar en dolor central espontáneo, continuo e intermitente y evocado por estímulos. La actividad espontánea de alta frecuencia fue registrada en las células nociceptivas del asta dorsal al nivel de la lesión en pacientes parapléjicos con dolor central (**Loeser et al., 1968**). En pacientes con LM y dolor central, los registros en el tálamo ventroposterior revelaron campos receptivos incrementados así como actividad espontánea aumentada en las células denervadas (**Lenz et al., 1988**). La estimulación eléctrica en la región denervada del tálamo indujo dolor similar al dolor central (**Lenz et al., 1988**). La descarga epileptiforme registró en neuronas hiperactivas del tálamo fue también demostrada en pacientes con dolor central debida a causas distintas de la LM (**Yamashiro et al., 1991**), y en animales (**Hains and Waxman, 2006**).

3.5.6. *Hiperalgesia térmica durante el DN*

De acuerdo con nuestros resultados al y por debajo del nivel de lesión, la ocurrencia de dolor anormal evocado por calor y frío fue más común en áreas dolorosas que en no dolorosas (c.f. **Eide et al., 1996**). La hiperalgesia térmica no es siempre evidente, y en los pacientes con DN la hipoalgesia, hiperalgesia y sensibilidad normal a los estímulos térmicos pueden todas demostrarse en el área dolorosa (**Lindblom and Verrillo, 1979; Verdugo and Ochoa, 1992**). En amputados, la hiperalgesia mecánica puede no estar asociada con hiperalgesia térmica (**Nikolajsen et al., 1996**). Más aún, en modelos experimentales de DN, la hiperalgesia a estímulos mecánicos puede ser vista en ausencia de hiperalgesia térmica (**Bennett and Xie, 1988; Seltzer et al., 1990; DeLeo et al., 1994**).

3.5.7. Canales sensoriales de calor y frío

En nuestros pacientes con LM los exámenes al nivel de la lesión generaron menos respuestas de dolor con frío (excepto el grupo de SYR) pero no con calor, probablemente sus resultados pueden explicarse por la hipótesis de que el dolor al calor dependía de la temperatura de superficie, mientras que el dolor al frío estuvo relacionado con la temperatura subcutánea, sugiriendo diferentes receptores para el calor y frío nociceptivos (**Morin and Bushnell, 1998**) ya que las temperaturas nociceptivas usadas se comportaron diferentemente para los sujetos.

En el estudio de **Morin y Bushnell (1998)** se sugieren ambas similitudes y diferencias en el procesamiento periférico y central del calor y frío nociceptivo en el SNC. Ellos mostraron que sus resultados podrían ser explicados por la ya nombrada hipótesis de que el dolor al calor, la sensación de frescor y al calor inocuo parecen depender de la temperatura de superficie, mientras que el dolor al frío fue relacionado con la temperatura subcutánea, sugiriendo diferentes receptores para el calor nociceptivo y para el frío nociceptivo. Además, una explicación periférica indicaría que la sensación de frío es mediada por receptores a lo largo de las paredes venosas (**Fruhstorfer and Lindblom, 1983; Klement and Arndt, 1991; 1992**) mientras que para la sensación de frescor y calor inocuo están situados en la piel (**Klement and Arndt, 1991**). Se ha observado en monos (**Tillman et al., 1995**) que las terminaciones del receptor para los nociceptores C mecanotérmicos al calor están localizados en la epidermis y dermis, y los datos recogidos por **Morin y Bushnell (1998)** sugieren una similar localización receptiva en humanos. Por otra parte, la estimulación vascular de los receptores puede contribuir al aumento continuo en la percepción del dolor al calor y frío observada a través de la presentación del estímulo de 30 seg. Se necesitaron diferencias más amplias de temperatura en el frío nociceptivo que en el calor nociceptivo para producir diferencias perceptuales equivalentes (**Morin y Bushnell, 1998**). Esta relación de la percepción de temperatura es similar a la existente entre temperatura y tasas de respuesta de las neuronas de la lámina I del asta dorsal HPC (Frío-pinchazo-calor) que responden al calor y frío (**Craig and Bushnell, 1994; Craig and Serrano, 1994**), sugiriendo que la actividad de dichas neuronas podría favorecer la percepción del dolor al calor y al frío. Las neuronas de rango dinámico ancho (WDR) en las capas más profundas del asta dorsal que responden al calor y frío nociceptivos (**Kenshalo et al., 1982**) podrían participar también en la percepción del dolor al calor y al frío. **Chery-Croze y Duclaux (1980)** observaron que cuando un área cutánea de pinchazo es estimulada con calor o frío extremos, los sujetos no informaban de sensación de temperatura, sino sólo de sensación de pinchazo a ambos extremos. Sin embargo, a pesar de la falta de sensación de temperatura y de la similitud de la sensación de pinchazo, los sujetos pudieron distinguir el calor del frío nociceptivos, sugiriendo un diferencial procesamiento en algún lugar dentro del SNC.

3.5.8. Sensibilización a la estimulación tónica al calor

Kleinböhl et al (1999) utilizaron el paradigma de calor tónico (el procedimiento de “sensibilización dual” que proporciona un índice subjetivo y comportamental de sensibilización (**Kleinböhl et al, 1993; Van Ackern et al., 1994; Kleinböhl, 1996**)) para evaluar sensibilización temprana (15-100 seg) en 30 pacientes con dolor musculoesquelético/ de espalda y dolor de cabeza y voluntarios sanos. Ellos encontraron que el grado de sensibilización estaba linealmente relacionado con la temperatura del estímulo, y los grupos difirieron significativamente en el “gradiente de sensibilización”: los pacientes con dolor musculoesquelético se sensibilizaron antes y más fuertemente que los sujetos sanos)).

La sensibilización aumentada en los pacientes de dolor musculoesquelético era ampliamente independiente de los umbrales de dolor alterado. Esto parece limitar la hipótesis original de que el “wind-up” nociceptivo debería ser un factor general en el desarrollo de dolor crónico como sugirieron estudios previos (**Kenshalo et al., 1979; Klepstadt et al., 1990; Ren, 1994**). Esto sugiere un subgrupo sensibilizado, particularmente prominente en pacientes con dolor musculoesquelético crónico, pero no se limita a ellos. La sensibilización aumentada en pacientes con dolor musculoesquelético se reflejó tanto en sensibilización temprana por debajo del umbral como en la pendiente de gradientes de sensibilización. Un pequeño subgrupo de “sensibilizadores extremos” podría distinguirse, fuera del rango de control de los gradientes. El dolor musculoesquelético apareció sobre-representado en este grupo extremo el cual también mostró umbral de dolor tónico extremo. Sin embargo, la sensibilización a corto plazo pudo no estar relacionada con la duración del dolor en ese estudio. El hallazgo más práctico es el hecho de que diferentes tipos de umbrales de dolor al calor y gradientes de sensibilidad al calor tónico tienen diferente validez para discriminar entre síndromes crónicos de dolor, y también en la discriminación de pacientes de los voluntarios sanos. Esto indica que ambos, la severidad del dolor y la sensibilidad al dolor pueden combinarse con beneficios en medidas de dolor experimental en poblaciones clínicas. La observación de que la sensibilización pronunciada apareció por debajo del umbral de dolor de pacientes mientras que no se encontró gran sensibilización en controles hasta intensidades de dolor claramente dolorosas, es una variante con

informes anteriores usando estimulación repetitiva en un paradigma de sumación temporal (**Price et al., 1994; Lautenbacher et al., 1995**) y tasas subjetivas que sugieren sumación temporal pronunciada en voluntarios sanos. Parece que la estimulación continua junto con el método psicofísico libre de prejuicios de reajuste a la temperatura inicial aparente usada en su método, conduce a diferentes clases de sumación temporal o sensibilización al estímulo nociceptivo, posiblemente más cercanamente relacionada, como dijeron los autores, a la sensibilización central la cual es asumida por un proceso relevante para el desarrollo de dolor crónico.

La hipótesis de que la sensibilización a la estimulación tónica al nivel perceptiva en el rango de 15-100 seg relacionada con el “wind-up central” se relacionaría directamente con los aspectos psicofísicos y neurofisiológicos del proceso que conduce al dolor crónico (**Tölle et al., 1996**). Existen varios argumentos en favor de esta relación: primero, la intensidad y duración de los estímulos tónicos aplicados en el procedimiento de la sensibilización están dentro del rango necesario de desencadenamiento de los procesos de “wind-up” (**Price et al., 1994**); segundo, el “wind-up” es una característica de las neuronas de rango dinámico ancho (WDR) que transfieren el estímulo aferente, bajo la percepción del dolor al calor (e.g. **Talbot et al., 1989**); tercero, las características temporales de la sensibilización nociceptiva corresponden a las del “wind-up”: la respuesta de las neuronas WDR gradualmente se incrementa por encima de 5-20 seg (**Willis, 1990**) como lo hace la intensidad de la sensación en el procedimiento de sensibilización dual (?E). Este proceso es reversible mientras las temperaturas estímulo estén entre 48 y 50°C, y puede estar repetido entre relativamente cortos intervalos de tiempo correspondiente a los intervalos entre ensayos del presente estudio. Por tanto, la hiperalgesia tardía no está involucrada hasta exámenes prolongados a altas temperaturas. La sensibilización al nivel perceptiva aparece por debajo del umbral de dolor y se incrementa sistemáticamente con temperaturas más altas, lo que se conoce como “wind-up” (**Willis, 1990**). El hecho de que la sensibilización pronunciada empezó muy por debajo de los umbrales de dolor en aquellos pacientes expone procesos adicionales involucrados en poblaciones clínicas. Los efectos del “wind-up” serían suficientes para explicar sus hallazgos, si la prematura sensibilización pudiera ser relacionada a frecuencias críticas más bajas para el “wind-up” en pacientes, que normalmente se sitúa en el rango de 0.3 a 0.5 Hz (**Mendell, 1966; Price et al., 1977**). Alternativamente, las tasas de descargas tónicas elevadas a los aferentes polimodales C por debajo de 45°C pudieron ser los responsables para la diferencia en los controles, pero considerando las desviaciones nada notables del umbral de dolor en sí mismo, esto parece menos probable. Los estudios en los efectos de antagonistas de receptores NMDA específicos en sensibilización subjetiva y comportamental comparada con umbrales de dolor aclararía esta cuestión; y también mostrarían los parámetros de características de sensibilización diferenciando entre subgrupos de pacientes con dolor realmente asociados con el “wind-up” u otros procesos NMDA sensitivos a altos niveles. Esto ayudaría a especificar el significado de las observaciones clínicas y ensayos piloto demostrando efectos positivos de un número de antagonistas NMDA en medicación adyuvante de dolor (**Quack, 1994; Persson et al., 1995**).

Nuestros hallazgos mostraron que la desagradabilidad/ intensidad de dolor percibida no fue diferente para los dos tipos de temperaturas, como en el estudio de **Morin y Bushnell (1998)**. Basado en ello, la desagradabilidad puede ser mediada por la actividad neural similar en el área 24 cingulada anterior (ACC) para el dolor al calor y al frío, y mostró una correlación significativa con la sensación de intensidad de dolor con independencia de la temperatura usada (**Craig et al., 1996**).

3.5.9. *Papel relativo de la sensibilización central y periférica después de la LM*

Encontramos una más alta y rápida sensibilización al nivel en el grupo dorsal de NP, pero no en otra parte del cuerpo o con estímulo de frío. Es ampliamente aceptado que los procesos periféricos y centrales pueden jugar un papel en la fisiopatología de los síntomas del DN. La sensibilización de las unidades receptoras nociceptivas, a generación de impulsos ectópicos espontáneos o inducidos por estímulo, la “multiplicación” de impulsos, y la transmisión efática son mecanismos fisiopatológicos resueltos en el nivel periférico que pueden explicar la sintomatología de los pacientes (**Serra, 1999**).

En una comparación de la actividad de los nociceptores A β y C en rata y humano se vio que a pesar de la aparente disparidad entre la sumación temporal perceptiva y la adaptación nociceptora, mecanismos centrales y periféricos se proponen para reconciliar la relación entre la actividad nociceptora y la percepción de dolor (**Andrew et al., 1999**).

3.5.10. *Pacientes Crónicos con Siringomielia.*

La mayoría de los pacientes con Siringomyelia (64%) presentaron lesión atraumática y el resto de ellos traumática en la mayoría de los casos, por accidente de tráfico. Todos fueron pacientes crónicos, el 91% estaban medicados desde que sufrieron disestesias. Observando las imágenes de estos pacientes pudimos observar una

lesión más alta (cavidades Siringomiélicas más altas), por tanto con más daño medular en la sustancia blanca en 10 de nuestros 11 pacientes (**Ver ejemplo en Appendix Picture 3.7 y 3.8**). Estos hallazgos fueron consistentes con **Vierck et al. (1990)**, quien expuso que la sustancia blanca juega un rol en el DN después de la lesión, mientras que la gris puede ser la causa del comienzo del DN por debajo del nivel de lesión junto con la sustancia blanca. Algunos estudios han indicado la existencia de una posible lesión más alta en la sustancia gris en el extremo rostral de la lesión en pacientes NP con LM respecto a los sin dolor NoNP (**Finnerup y Jensen, 2004**). Sin embargo, no parece haber cambios en la sustancia gris en nuestras imágenes de resonancia magnética (debido a la baja resolución de éstas), con pacientes con Siringomielia, ni tampoco tuvimos imágenes de los otros tipos de pacientes.

3.5.11. Estimulación térmica en pacientes con Siringomielia.

La estimulación térmica con frío nos proporcionó respuestas más bajas al nivel de lesión en el grupo NoNP, pero más altas que los HV por encima del nivel en los pacientes NP y NoNP. Los del grupo SYR presentaron similar número de respondientes que HV, incluso cuando fueron reducidos para el resto de las temperaturas.

Más recientemente, **Ducreux et al. (2006)** no encontró diferencia significativa en la magnitud de déficit sensoriales entre pacientes con y sin DN, sugiriendo que las lesiones de las vías espinotalámicas no son suficientes para el desarrollo del dolor central. Sin embargo, un patrón diferente de déficit sensoriales fue observado entre pacientes con dolor espontáneo solamente ($n = 11$) y pacientes con dolor espontáneo y alodinia ($n = 20$), significando que los mecanismos del DN central causados por la Siringomielia no pueden ser considerados como simple amplificación del dolor normal. Datos de neuroimagen funcional y psicofísica demostraron diferentes síntomas de DN central mantenidos por distintos mecanismos. En pacientes sólo con dolor espontáneo, la pérdida sensorial fue significativamente más asimétrica y hubo una relación directa entre la extensión de déficit termosensoriales (p.e. desaferentación) y la intensidad del dolor de quemazón. En contraste, los pacientes con alodinia presentaron déficit térmicos reducidos, en términos de magnitud y extensión. Además, los déficit sensoriales fueron diferentes entre pacientes con alodinia al frío y táctil, sugiriendo distintos mecanismos fisiopatológicos relacionados con las sub-modalidades de alodinia.

Sus estudios de fMRI posteriormente lo confirmaron, mostrando que diferentes subtipos de alodinia se asociaron a distintos patrones de actividad cerebral, lo cual no necesariamente corresponde a la “matriz de dolor” involucrada en el dolor fisiológico agudo. La corteza prefrontal fue el único área consistentemente activado por dolores evocados patológicos, sugiriendo que la alteración de los mecanismos moduladores del dolor a alto nivel podrían jugar un importante papel en la alodinia debido a lesión central. Desde una perspectiva clínica, estos datos sugieren que estos síntomas deberían responder diferencialmente al tratamiento (**Attal et al., 2000, 2002**) y confirmar en la importancia de una clasificación de pacientes con DN basada en mecanismos, incluyendo el dolor central.

3.5.12. Problemas Metodológicos asociados a la medida de BST/QST del DN en LM.

3.5.12.1. Cuestionario de Diagnóstico de Dolor Neuropático (DN4)

Aunque no encontramos diferencias significativas entre los grupos para la mayoría de las preguntas, las medianas indican que el cuestionario DN4 es capaz de distinguir a los grupos de dolor en nuestra muestra (en medias) (NP y SYR = 4.00) de los grupos sin dolor (NoNP = 2.25 y HV=0.00), siendo el punto de corte para el diagnóstico de DN un total de 4/10. Por tanto podemos pensar que esta herramienta exploratoria considerada como puntuación total pudo ser usada en clínicas para un mejor diagnóstico del DN. Como **Bouhassira et al. (2005)**, también encontramos que la prevalencia general de las cuestiones relacionadas con el examen sensorial (p.e. 16.7-61.1 % en los grupos NP y SYR) fue más baja que la de las cuestiones relacionadas con el informe (p.e. 9.1-81.8 % en los grupos NP y SYR). Las preguntas de la entrevista “hormigueo” y “entumecimiento” tienen la máxima significación en nuestras muestras, aunque es < 0.05 ($p=0.083$). No es sorprendente que los déficit sensoriales fueran mucho menos frecuentes en pacientes NP que en NoNP (**Carli et al., 2002; Giesecke et al., 2004; Petzke et al., 2003; Staud et al., 2003; Nielsen et al., 2005**). Los dolores evocados fueron también más frecuentes en NP, y aunque encontramos que la prevalencia de la alodinia a la presión fue diferente entre NP y NoNP, **Bouhassira** no encontró esta diferencia en su muestra.

Incluso aunque pusimos el objetivo en lesiones centrales, no podemos descartar una posible lesión periférica también implicada. Es interesante que la frecuencia de estas cuestiones fue similar entre pacientes presentando lesiones periféricas o centrales en la muestra de **Bouhassira**, excepto la cuestión relacionada con el dolor

incrementado por presión lo cual fue más frecuente en pacientes con una lesión periférica (p.e. 54% vs 31%, $p < 0.01$). En consecuencia, podemos proponer que el cuestionario DN4 incluye en su evaluación tanto lesiones centrales como periféricas y por tanto es válido. En conclusión para el DN4 (Versión española del cuestionario) podemos decir que aquellas cuestiones relacionadas con el dolor evocado diferenciarán claramente entre los grupos de LM con y sin dolor con una incidencia pequeña, pero las cuestiones relacionadas con la entrevista no presentaron la significación deseada y fueron menos adecuadas para ser consideradas separadamente.

3.5.12.2. La Importancia del Sitio de Estimulación en Estudios Experimentales de Dolor.

Nosotros estimulamos la piel con vello ya que queríamos excitar los mecanorreceptores y nociceptores sensibles al calor, aunque algunos resultados de hace tiempo indicaron que los receptores en la piel con vello humana no diferían considerablemente en sus características de los receptores de la piel humana sin vello o de los receptores animales en la piel con vello (Järvilehto et al., 1976). Ahora sabemos que de hecho difieren. La piel de la mano de la palma tiene umbrales de dolor al calor mucho mayores que la piel con vello (Taylor et al., 1993). Específicamente y junto con las medidas de velocidad de conducción Granovsky et al. (2005) encontró que la piel con vello de la mano, los estímulos de 41°C evocaron un potencial ultra-latencia mediado por las fibras C mientras que 51°C evocó un potencial de latencia mediado por aferentes Ad. En contraste, las respuestas de la eminencia thenar de la mano a 41° y 51°C fueron mediadas por fibras C, lo cual resulta en sensaciones de “dolor secundario” cuando se estimula mediante calor (Campbell and LaMotte, 1983; Price et al., 1994). El estímulo más intenso de calor aplicado a la piel sin vello (51°C) no evocó una respuesta mediada Ad, porque la palma humana tiene pocos (si alguno) receptores AMH tipo 2 mientras que los de tipo 1 pueden ser excitados por estimulación de láser infrarrojo inocuo (Haimi-Cohen et al., 1983; Tillman et al., 1995). En la piel con vello y a intensidades moderadas del estímulo el incremento de la medida de sensibilización es probablemente mediada por fibras AMH tipo 2 (Treede et al., 1998; Kleinböhl et al., 2006). Como Kleinböhl et al. (2006), encontramos sumación temporal del primer dolor con los filamentos von Frey, lo que ahora es menos controvertido aunque sólo ha sido mostrado convincentemente en un estudio en humanos hasta ahora (Nielsen and Arendt-Nielsen, 1998).

3.5.12.3. Diferencias Individuales en Sensibilidad al Dolor: Respondedores y No-Respondedores

Como ha sido mencionada en la Introducción, una de las características más llamativas del dolor es el amplio rango de variación en la respuesta a estímulos idénticos (Nielsen et al., 2005). Con el sistema TSAR, más altos niveles de respuesta fueron obtenidos en HV y NoNP con calor al nivel de la lesión, pero NP y SYR lo hicieron con calor y frío por encima del nivel. Los métodos BST/QST mostraron un amplio rango de variación de respuestas, dependiendo del sitio de estimulación y de los instrumentos usados (Ver Tabla 3.8).

La sensibilidad incrementada al dolor puede también ser un factor de riesgo para el dolor crónico y el dolor relacionado con la incapacidad. Esto es apoyado por la investigación que demuestra que varias condiciones crónicas se hallan asociadas a un aumento de sensibilidad al dolor inducido experimentalmente (Carli et al., 2002; Giesecke et al., 2004; Petzke et al., 2003; Staud et al., 2003; Nielsen et al., 2005), como pudimos ver en nuestros grupos de LM, NP y SYR, en la estimulación psicofísica.

Recientes estudios indican que las diferencias individuales en las puntuaciones de la escala VAS en estímulos experimentales están correlacionados con diferencias individuales en dolor relacionada con la actividad cerebral (Coghill et al., 2003), y están parcialmente influenciados por factores genéticos (Diatchenko et al., 2005; Kim et al., 2004; Solovieva et al., 2004; Zubieta et al., 2003). Estos hallazgos proporcionan evidencia crucial de que las diferencias individuales en dolor *informado* reflejan diferencias reales en dolor *experimentado*. Utilizar un solo estímulo fijado es problemático para muchas modalidades estímulares porque el amplio rango de variación individual tiende a producir efectos de suelo y/o techo, p.e. no existe un nivel estimular que sea tolerable y doloroso a la vez para todos los sujetos. La alternativa es examinar cada sujeto con temperaturas dolorosas pero tolerables para los sujetos, y extrapolar las puntuaciones (Nielsen et al., 2005), lo cual es lo que nosotros resolvimos hacer para poder ver las respuestas a la estimulación térmica, aunque significa que no tener en cuenta todas las respuestas ya que muchas de ellas no se produjeron (las respuestas no dolorosas por debajo de 1.45 en la puntuación e-VAS no fueron analizadas). Los resultados de Nielsen et al. (2005) indican que la función de fuerza aceleradora es un modelo excelente de funciones estímulo-respuestas individuales evocadas por contacto doloroso con calor.

Uno de los principales problemas de este estudio fue la falta de pacientes que respondieron con tasa de dolor al estímulo aplicado. Ocurrió con el estímulo de frío principalmente, aunque también con el calor. Para resolverlo,

hicimos pruebas en voluntarios sanos e incrementamos las temperaturas aplicadas (49°-53°C). Desafortunadamente nuestro baño no nos permitió disminuir la temperatura dada por el Peltier por debajo de 3°C. En consecuencia, pudimos observar que el estímulo fue más doloroso pero también menos capaz de ser mantenido y tolerado durante 30 seg por el voluntario, mucho más desagradable para un paciente con LM. Como parece, la probabilidad de finalizar un ensayo es mayor con las temperaturas usadas (media=48°C para la estimulación con calor; y media=3°C para la estimulación con frío), sin olvidar que las diferencias individuales de algunos sujetos nos hicieron introducir alguna variación en las temperaturas usadas [47°C (en 1 sujeto), 49°C (en 1 sujeto) y 43°C (en 8 sujetos) y 13°C (en 1 sujeto)].

La presentación de los estímulos al azar eliminaría la predisposición a las expectativas (Petzke, et al. 2003), sin embargo decidimos seguir un protocolo fijado debido a limitaciones con las temperaturas del sistema TSAR que usamos (el frío tardó más que el calor), por ejemplo el tiempo entre ensayos no hubiera sido el mismo entre sujetos causado por una mayor/ menor espera. Los resultados de Nielsen et al. (2005) mostraron tasas de dolor aumentado, curvas más planas y reducción de los umbrales de dolor en las series randomizadas. Aunque la randomización elimina ciertas expectativas, también puede introducir otras. Si algunos de los estímulos dados son percibidos como bastante dolorosos, la randomización introduce la expectativa de que todos los estímulos pueden ser dolorosos (Nielsen et al., 2005) y estamos de acuerdo con ello.

Casi el 70 % de nuestros pacientes estaban medicados con Amitriptilina y/o Gabapentina, especialmente esta última reduce la alodinia. Se encontró una reducción de la alodinia táctil en ratas (Wallin et al., 2002) y la Gabapentina oral, administrada a voluntarios sanos en un régimen similar a los usados en el tratamiento crónico del DN, reducen las medidas de sensibilización central provocadas por capsaicina intradérmica (Gottrup et al., 2004). Estos efectos positivos pueden haber distorsionado y “adormecido” la sensibilidad a la nocicepción incrementando los umbrales (hiperalgesia). Esto puede ser una de las principales razones por la que no pudimos recoger más respuestas de dolor en nuestra muestra.

3.5.13. Respuestas Dolorosas y No Dolorosas al BST/QST

Analizamos cualquier sensación con el método QST percibido mayor que 0.5 en la escala VAS, así pudimos estudiar las sensaciones de desagradabilidad y dolor. Sin embargo, las sensaciones dolorosas fueron escasas e insuficientes en el grupo de pacientes, abriendo la controversia sobre cuánto dolor es necesario para considerar signos de dolor como la alodinia y la hiperalgesia. Las definiciones de la IASP de estos términos (ver introducción capítulo 2) no aluden a ninguna tasa de puntuación para distinguirlos entre ellos. Además afirman que “la actividad inducida en el nociceptor y las vías nociceptivas por el estímulo nocivo no es dolor, que siempre es un estado psicológico, incluso cuando podemos apreciar bien que el dolor muy a menudo tiene una causa física” (ver Mecanismos psicológicos en capítulo 4). Quizá lo que hemos categorizado en este estudio no puede ser llamado alodinia o hiperalgesia a la estimulación mecánica /térmica, pero pensamos que aquellas sensaciones experimentadas por los pacientes son cercanas en cualidad, solo que no en cantidad, y deben permitir el estudio del dolor en términos de fibras, vías y mecanismos implicados en el proceso de dolor.

Sin embargo, elegimos un VAS mayor o igual a 1.45 para la evaluación de las curvas de respuesta de dolor, ya que observamos que la mayoría de pacientes que respondieron a la estimulación térmica con el TSAR lo hicieron en ese punto de corte. Sin embargo, algunos sujetos produjeron moderadas curvas de sensación con VAS menores que 1, que no estaban teniendo en cuenta por el análisis de las curvas de dolor, aunque no las descartamos para futuras investigaciones, ya que la información provista por la respuesta de las curvas de sensación podría representar diferentes patrones de tal respuesta. En el estudio de Morin y Bushnell (1998), la evaluación de la desagradabilidad durante el calor y frío dolorosos tuvo paralelas puntuaciones de intensidad percibida, pero fueron menores que las de intensidad.

3.5.14. Condiciones de Estimulación Térmica Tónica

3.5.14.1. Problemas Temporales de la Estimulación Térmica

Utilizamos un estímulo de 30 seg ya que fue suficiente para provocar en nuestro estudio piloto un máximo de respuestas de dolor con el eVAS y suficiente para mostrar una curva de dolor con algunos parámetros interesantes como el VAS máximo, el modulus de los primeros 10 seg, el modulus de los primeros 30 seg, y la pendiente principalmente. Este tipo de estímulo ha sido ampliamente usado anteriormente (Yarnitsky et al.,

1992 usó 40 seg de estimulación o 30 seg en **Granot et al., 2003** por ejemplo). Sin embargo, no pudimos obtener siempre curvas completas para comparar, por la heterogeneidad entre las muestras y las diferentes tolerancias individuales de cada sujeto.

Algunos estudios ya informaron de que los estímulos repetitivos pueden incrementar o disminuir la sensación percibida (**Pertovaara and Kojo, 1985; Staud et al., 2001; Tillman et al., 1995; Yarnitsky and Ochoa, 1990**). Se esperó que los estímulos tónicos pudieran sensibilizar las vías sensoriales y causar un incremento en las puntuaciones de dolor de los siguientes estímulos. Sin embargo, las puntuaciones de dolor para los estímulos fásicos (47°C de 30 seg de duración) no fueron cambiados por un estímulo tónico previo (47°C de 70 seg de duración) a pesar de una media alta de intensidad de dolor de 5.4 ± 2.3 en el estudio de **Granot et al. (2003)** con voluntarios sanos. Además, las puntuaciones de dolor fásico y tónico fueron significativamente correlacionados en este estudio. Así, una previa aproximación de que los estímulos tónicos y fásicos son diferentes y deberían ser usados separadamente no es válida, al menos usando los específicos parámetros de ese estudio. Estos resultados apoyan los estudios que indican un fuerte efecto de sensibilización en los pacientes con dolor pero no en voluntarios sanos (**Eide and Rabben, 1998; Kleinböhl et al, 1999**).

Usamos temperaturas nocivas sin habituación previa y por tanto pueden ser consideradas como “más nocivas” y consecuentemente más dolorosas en voluntarios sanos y pacientes con dolor también. Además utilizamos temperaturas más bajas para el frío (usualmente 3°C) y ligeramente más altas para el calor (usualmente 48°C) que el estudio de **Granot et al. (2003)**, así que después de experimentos previos, decidimos usar aquellas temperaturas ya que parecieron representar los umbrales para los voluntarios sanos.

Morin y Bushnell (1998) usaron varios rangos de temperaturas entre -5° y 23° °C y temperaturas de calor desde 41° a 48° °C y encontró que 47° °C y 9° °C fueron los umbrales de calor y de frío respectivamente (VAS=5) en los sujetos sanos. Su método fue más gradual para tolerar estímulos dolorosos ya que la tasa de temperaturas es continua y el área del cuerpo puede habituarse mejor a la estimulación nociva, como en el estudio de **Staud et al. (2004)** con pacientes con fibromyalgia.

3.5.14.2. Análisis de los componentes de la Respuesta de Dolor: Respuesta e-VAS de la Pendiente, Máximo e Integral.

En la curva de respuesta al dolor al calor detectamos una pendiente mayor en los pacientes NP con lesiones dorsales al nivel de la lesión, y mayores Modulus para los primeros 10 y 30 s en los pacientes NP versus SYR por encima del nivel. Los pacientes SYR puntuaron más dolor que los NP por encima del nivel. La respuesta de la curva de dolor al frío mostró que los pacientes con SYR puntuaron más Modulus de 10 s que los HV al nivel, y los NP más Modulus de 10 s que los NoNP por encima del nivel.

Morin y Bushnell (1998) mostró una función de aceleración estímulo-respuesta positiva en el rango de calor y negativa en el frío en una pequeña muestra de voluntarios sanos, con un cambio en la pendiente cerca del umbral del dolor para ambos rangos. Las pendientes entre calor inocuo y nociceptivo fueron significativamente diferentes y tuvieron similar tendencia entre frío inocuo y nociceptivo. Por ejemplo, la pendiente para el dolor al calor fue 69.7 ± 36.4 , y para el frío fue de 2.1 ± 0.6 (valores absolutos). La pendiente más acusada se encontró en el rango de calor.

No se encontraron diferencias en picos de latencias entre los niveles de dolor al calor y los de frío, ambos continuaron incrementándose ligeramente hasta casi el final del periodo de 30 seg de estimulación. Los tiempos de percepción máxima del calor y frío tampoco difirieron, pero ambas de esas percepciones alcanzaron una meseta antes del final del periodo de estimulación. En este momento los sujetos continuaron sintiendo calor o frío por un periodo de tiempo. Para el calor nociceptivo y el calor y el frío inocuos, fue corto (2.8-5.5 seg) pero para la estimulación fría dolorosa el retraso fue significativamente más largo (13.7 seg). Estos resultados se explicaron por la hipótesis de que el dolor al calor, la sensación de frescor y al calor inocuo parecen depender de la temperatura de superficie, mientras que el dolor al frío fue relacionado con la temperatura subcutánea, sugiriendo diferentes receptores para el calor nociceptivo y para el frío nociceptivo.

Si observamos nuestros resultados (**Ver Tabla 3.10 y la sección 3.4.5**), vemos, consistentemente con el estudio de **Morin y Bushnell (1998)**, que la pendiente en la estimulación por calor al nivel fue más pronunciada que la del frío, los grupos de LM presentaron reducidas pendientes en contraste con el HV en los estímulos de calor y mayores en calor en contraste con el HV (excepto en el grupo NoNP). Algunas diferencias pudieron verse (no significativas) ya que el grupo NP presentó la misma pendiente (0.7) a ambas temperaturas. En el sitio de control, sólo el grupo de SYR obtuvo pendientes que diferían con las de otros grupos, o sea, mayores pendientes para el

frío y menores para el calor. La amplia extensión de la desaferentación en estos pacientes mostró el daño en las vías espinotalámicas, y pareció ser menos pronunciada en el grupo NP. Los grupos que presentaron más puntuaciones de dolor al nivel fueron HV y SYR por encima del nivel para estímulos de calor y frío a ambos niveles en el grupo SYR. Así, se dieron reducidas puntuaciones en los grupos de LM agudos.

La respuesta de dolor fue menos mantenida (mediante el Modulus de 10 seg) en el grupo HV y más en el SYR en la estimulación al calor al nivel, y significativamente más mantenida en los grupos NP y NoNP en el sitio control aunque NP tuvo los mismos valores al nivel. Esto podría significar que incluso en los sitios sin dolor, los tractos espinotalámicos están alterados en estos pacientes NP, como hemos mostrado antes en el examen QST térmico. Sólo con la estimulación al frío el grupo NP presentó similar afectación con más altas tasas junto con el grupo de SYR. Por tanto, para el grupo NP y principalmente para los pacientes SYR son los más afectados en cuanto a vías espinotalámicas anormales se refiere.

3.5.14.3. Descriptores Sensoriales de Dolor Cualitativos

Los descriptores verbales se escogieron para describir el dolor al calor difirieron de los escogidos para describir el dolor al frío, con un rango más amplio de palabras consistentemente elegidas para el dolor al frío (“punzante”, “aguijoneante”, “pinchazos” y “doloroso” principalmente) que para el dolor al calor (sólo “quemante”) se encontraron en el estudio de **Morin and Bushnell (1998)**. Diferentes cualidades se encontraron en nuestros resultados, al nivel de lesión con estimulación al calor “puntual” y “quemante” fueron los más presentes y “puntual”, “frío” y “difuso” con estimulación al frío; por encima de la lesión tanto con frío como con calor, “puntual” y “frío” fueron los más presentes.

3.5.14.4. Dolor irradiado

La prevalencia en dolor irradiado no depende del nivel de lesión que el paciente tuviera, ya que pudimos ver que estuvo presente tanto en lesiones cervicales como dorsales, incompletas y completas, y si respondía o no a la estimulación térmica, más aún es dependiente de la temperatura (más presente en 48°C) y del sitio de estimulación (más presente al nivel). Las vías propioespinales pueden estar probablemente implicadas en este fenómeno; sin embargo no existía un claro patrón de radiación ya que tanto en el grupo cervical como dorsal presentó radiación al nivel o por debajo del nivel de la lesión.

3.5.15. Ventaja relativa del BST/QST y el Sistema térmico de estimulación.

En general, la cepilladura suave no pudo provocar ninguna respuesta en absoluto; y la sensación de vibración, discriminación entre dos puntos e hiperalgesia por debajo del nivel no proporcionó diferencias significativas entre ninguno de los grupos. Podemos pensar que pudo ser posiblemente causado por la medicación en los pacientes con dolor y también debido a la falta de pacientes para el análisis que presentó el estudio. La sensación de vibración se detectó mejor en los sujetos HV que los NP al nivel de la lesión, lo cual indica que el instrumento Rydel-Seiffer es tan bueno como otras herramientas más caras y más costosas como el vibrómetro (**Pestronk et al., 2004**). **Bowsher (1999)** expuso que los déficit para las modalidades mecánicas de baja intensidad, como el tacto y la vibración, con comunes en pacientes con dolor central debido a LM. Pudimos observarlo sólo en nuestro grupo de pacientes NP, comparado con HV, pero no hubo déficit en otros grupos. Como antes, pudimos ver daño en las fibras A β y la columna dorsal lemniscal medial (**Boivie et al., 1994; Beric et al., 1988**).

Algunos autores (**Eide et al., 1996**) no encontraron diferencias significativas en los umbrales BST/QST entre áreas dolorosas y no dolorosas denervadas (al nivel, por debajo y por encima de la lesión), y también ocurrió con las reducciones de sensaciones de tacto, vibración, posición y discriminación entre dos puntos. Encontramos que sólo al nivel de la lesión nuestros sujetos tuvieron diferentes puntuaciones de dolor y también los umbrales fueron diferentes al nivel, pero no por debajo o por encima del nivel. La explicación más probable pudo residir en la hipótesis de que el CPG está actuando al nivel de la LM durante la fase aguda, involucrando las fibras AB principalmente en vista de las reducciones en umbral y vibración. Además, otro mecanismo relacionado con las sensaciones térmicas está implicado en el DN: las vías espinotalámicas, muy importantes en el mantenimiento de DN, involucrando fibras Ad y C, ya que la estimulación al calor y frío y sumación temporal por el QST y el sistema TSAR fueron significativamente diferentes en los niveles de lesión examinados entre los grupos. Como la estimulación térmica es también anormal por encima del nivel (estímulo de calor con el QST y TSAR), esto significa que todo el cuerpo del paciente está afectado, presumiblemente dependiendo de la extensión dermatómica de su dolor, y posiblemente debido a un mecanismo de mantenimiento descrito anteriormente: las vías espinotalámicas.

La técnica de QST de discriminación entre dos puntos se encontró reducida en los pacientes SYR vs NoNP sólo al nivel, lo cual pudo significar una representación cortical incrementada (**Song et al., 1993; Ducreux et al., 2006**) del nivel de lesión sólo en pacientes crónicos con dolor central y lesión extensa, ya que no se encontró con NP en pacientes agudos. Esta simple medición de precisión parece una buena herramienta para separar los pacientes NoNP y dolor crónico al nivel de la lesión, aunque no para una fase más aguda de la LM.

La cepilladura usada para evaluar la Alodinia Dinámica presentó mayores puntuaciones en HV que NP, indicando que no parece ser una buena herramienta por debajo del nivel de lesión para estimar daño en las fibras A β al menos para el DN medicado con Amitriptilina/Gabapentina.

La hiperalgesia y la alodinia dependen de cambios en el procesamiento del SNC (**Baumann et al., 1991**) y pudo no ser suficientemente provocado en nuestras muestras de sujetos diferencialmente tanto debido a las características de los instrumentos (von Frey y cepilladura) como por el tratamiento farmacológico.

El tubo de calor distinguió entre pacientes crónicos con dolor (SYR) que presentaron más dolor, y NoNP y HV al nivel de lesión, involucrando el rol de las fibras C y Ad, fácilmente excitadas por un simple tubo de agua caliente. Por debajo del nivel de lesión pudimos observar que los grupos NoNP y NP presentaron puntuaciones más altas de VAS que el HV, lo que podría indicar daño en los tractos espinotalámicos incluso cuando los pacientes LM no presentaron dolor. De estos grupos, SYR presentó más intensidad de dolor con el VAS.

Las fibras Ad y C (**Wasner et al., 2004**) fueron excitadas por una gota de acetona indicando otra vez más dolor en pacientes de dolor crónicos (SYR) que NoNP al nivel de la lesión. Por debajo del nivel, los sujetos HV y SYR encontraron más dolor que los NoNP. Parece que en los grupos NoNP y NP las fibras Ad fueron específicamente excitadas en este tipo de estimulación. Esto puede querer decir que el calor nocivo a 48°C (tubo) permitió a las fibras C proporcionar el correcto mensaje neural, pero no a las fibras Ad **Wasner et al. (2004)** sugirió que el mentol sensibiliza los nociceptores C vasoactivos periféricos sensibles al frío y activa fibras Ad específicas del frío. La estimulación con acetona- como con mentol- puede ser también una forma de conseguir sensibilización central basada en la actividad continua en los nociceptores C periféricos sensibles al frío.

Eide et al., (1996) obtuvo resultados más significativos en QST que nosotros, pero el método fue diferente, por ejemplo usó filamentos von Frey más gruesos (6.65 unidades) para medir la sumación temporal. Varios de los pacientes informaron de una sensación de picazón-pinchazo en las áreas denervadas que fue más prominente que la sensación térmica, que fue demostrada tres veces más frecuentemente en zonas denervadas dolorosas que no dolorosas. Su sensibilidad táctil fue más reducida en las áreas denervadas no dolorosas que dolorosas, pero la diferencia, como en nuestros resultados, tampoco fue significativa. Como tampoco se encontró para las sensaciones de tacto, vibración, posición o discriminación entre dos puntos. En el 22% de los pacientes el dolor tipo “wind-up” pudo ser evocado usando un von Frey de 1.65 unidades. La diferencia para la sumación temporal entre áreas denervadas dolorosas y no dolorosas en pacientes NP por debajo del nivel de lesión fue significativa con similar número de von Frey.

3.5.16. Limitaciones del Método de Examen de Dolor Térmico Tónico.

Las principales limitaciones del examen BST (QST pueden relacionarse con la falta de respuesta al dolor de los pacientes, el limitado VAS conseguido (sin la posibilidad de obtener medidas de la integral o de la pendiente como el sistema peltier), y el examen térmico tónico no fue factible debido a la fluctuación de la temperatura después del contacto con la piel. Los pacientes LM y los voluntarios sanos identificaron las respuestas sensitivas por debajo del nivel de lesión con BST/QST pero no con la estimulación térmica tónica aplicada con el sistema peltier. La *habituación* en forma de fatiga de las fibras nociceptivas cutáneas (**Kleinböhl et al. 2006**) no es probable ya que después de la estimulación QST los sujetos habían tenido un descanso de unos 7-10 minutos, así que las fibras cutáneas no estaban sensibilizadas desde la anterior estimulación al momento de la estimulación con el sistema TSAR. Otras explicaciones pueden ser posibles, como los efectos acumulativos de una repetitiva *anticipación al dolor inducida por estrés* informada por la mayoría de los pacientes específicamente a la máquina del TSAR, pero no por el grupo HV. De hecho, el nivel de examen se aplicó siempre por debajo, y el efecto de anticipación fue probablemente mucho mayor en el comienzo de la sesión del TSAR. La anticipación y el estrés pudieron producir analgesia, lo cual puede haber producido un umbral más alto, y así ni el calor ni el frío pudieron detectarse por debajo del nivel de lesión.

Otras limitaciones metodológicas fueron identificadas en el curso del estudio. El estímulo no se presentó en intervalos contrabalanceados de presentación de los estímulos, ya que teníamos que esperar 40 seg para pre-

calentar o pre-enfriar el estimulador térmico para proporcionar un estímulo verdadero de acuerdo a la temperatura requerida en cada caso. La observación a un periodo constante entre ensayos hubiera sido excesivo para el sujeto y en consecuencia más cansancio, lo que habría afectado a las valoraciones de dolor. Las razones por las cuales no pudimos recoger más pacientes en nuestra muestra son debidas a la falta de número suficiente de pacientes en cada grupo y a que la mayoría de pacientes estaban medicados. Finalmente, la desagradabilidad a la estimulación térmica no fue medida ya que fue difícil para el paciente dividir su atención a más de tres importantes tareas ordenadas (intensidad de dolor, escoger descriptores de una lista, localizar el sitio de dolor).

3.5.17. Avances realizados en este estudio.

Estos tres instrumentos estudiados (DN4, BST/QST y estimulación térmica tónica) han demostrado su utilidad en condiciones experimentales, y mientras BST/QST ya fueron utilizados durante los últimos 15-20 años en la clínica para el diagnóstico del DN, los otros dos pueden también complementar el diagnóstico.

La versión española del DN4 ha confirmado ser fiable, estable y válida para el diagnóstico diferencial de las condiciones de dolor neuropáticas, ya que es capaz de diferenciar los componentes neuropáticos y nociceptivos del dolor, con el mismo punto de corte que en la versión original. Es fácil de responder por el paciente y también de calcular la puntuación total, gracias a su escala de 10 preguntas. Las medidas psicofísicas introducidas aquí poseen potenciales aplicaciones en QST clínico y pueden proporcionar marcadores clínicos de síndromes de dolor agudos y clínicos. El BST ha demostrado su utilidad y fiabilidad a lo largo de varios estudios en las últimas décadas, y es factible y disponible para todos los investigadores clínicos, médicos y en general para cualquiera que trabaje con pacientes con DN, y no se necesita un complicado entrenamiento. El método térmico TSAR proporciona características estímulo-respuesta a lo largo de una configuración de frecuencia de estímulo e intensidad combinados, lo que el QST no puede conseguir. El sistema informatizado es fácil de usar y provee de una gran cantidad de datos computados que se necesitan para construir las curvas de dolor y medir sus fases. Esto significa más precisión en los datos dados para el paciente con los que trabajar. Este estudio no se restringe a la evaluación de la estimulación térmica sino también a la tasa subjetiva de dolor informada por el paciente y una evaluación neuropsicofísica de las vías implicadas.

3.5.18. Investigación Futura: Mejora de los Sistemas de Medida de Dolor.

Existe una gran necesidad de estudios psicofísicos de la sensación de dolor en población sin dolor, para la base de un mejor entendimiento de las respuestas patológicas, para mejorar las técnicas del actual diagnóstico y tratamiento del dolor (**Gracely, 1994; Granot et al., 2003**). Con las posibilidades que pueden proporcionar la electrofisiología y los estudios de imágenes cerebrales, láser y CHEPs, se podrán conseguir estudios más eficientes.

Usando imágenes de resonancia magnética (MRI) para evaluar la función cerebral, **Koyama et al. (2005)** y **Coghill (2003)** encontraron que las personas que decían que el mismo estímulo de calor era intensamente doloroso presentaban profunda activación de las regiones cerebrales importantes para el dolor; en contraste, quienes dijeron que el mismo estímulo fue sólo moderadamente doloroso tenían mínima activación de esas mismas áreas. Los voluntarios sanos que informaron de altos niveles de dolor mostraron activación aumentada en áreas del cerebro importantes en el dolor: la corteza somatosensorial primaria, que contribuye a la percepción de dónde se localiza un estímulo doloroso en el cuerpo y cómo es su intensidad, y la corteza anterior cingulada, que está involucrada en el procesamiento de sensaciones desagradables evocadas por el dolor. Sin embargo, existe poca diferencia entre los sujetos en activación del tálamo, que está involucrado en la transmisión de señales de dolor de la médula espinal a más altas regiones cerebrales. La información dolorosa entrante es procesada por la médula espinal en una manera generalmente similar entre individuos, pero una vez que el cerebro está involucrado, la experiencia se vuelve muy diferente de un individuo a otro. La mayoría de las diferencias individuales en sensibilidad al dolor se deben probablemente a la combinación de factores cognitivos, como la experiencia pasada con el dolor, el estado emocional en el momento en que se experimenta el dolor, y las expectativas sobre el dolor. Últimos resultados proporcionados por **Koyama et al. (2005)** y **Coghill (2003)** confirman que una representación mental de un evento sensorial futuro puede modular significativamente los procesos neurales que subyacen a la formulación de la experiencia sensorial real y proporciona introspección de como las expectativas positivas disminuyen la gravedad de los estados de enfermedad crónicos.

Una de sus varias utilidades es evaluar QST mediante pulsos sencillos de láser infrarrojo, para medir los umbrales de dolor individual y umbrales sensoriales. La estimulación de calor irradiado por láser de CO₂ activa selectivamente fibras Ad y C en la piel con vello para minimizar las influencias mecanoreceptivas y para mantener control preciso de la intensidad y frecuencia estimulares. Tras el estímulo, se les pregunta a los sujetos

si éste fue detectado como caliente, punzante, desagradable y si era doloroso. Utilizando el método de los límites, cada serie ascendente terminó en la primera tasa “dolorosa” y el umbral de dolor y de sensación fue calculado como la media de las siguientes tres series. Los pulsos láser fueron percibidos como “calor punzante” en la intensidad no dolorosa o como “pinchazos de alfiler” dolorosos para más alta intensidad, indicando así sensaciones nociceptivas al primer dolor (**Kleinbohl et al., 2006**). Sin embargo, el láser no está exento de problemas derivados del hecho de que la temperatura de línea basal sólo puede recuperada por termorregulación y flujo de superficie de calor pasivo en la piel mimetizando la “sensibilización perceptiva” durante la repetición del estímulo (**Brugmans et al., 1991; Kleinbohl et al., 2006**).

El CHEPs presenta grandes amplitudes y cortas latencias cuando se evoca desde la piel con o sin vello, un efecto que aumenta con la intensidad del estímulo (**Granovsky et al., 2005**). La latencia media de los potenciales mediados por fibras C que registraron fue más corta que la obtenida por una breve estimulación láser de áreas muy pequeñas de la piel (**Bragard et al., 1996; Kakigi et al., 2003; Opsommer et al., 1999**). Además, las latencias medias para los potenciales de contacto por calor mediados por Ad son ligeramente más largos que aquellos informados por los potenciales evocados mediados por Ad mediante una breve estimulación láser de áreas mayores de la piel (**Bromm and Lorenz, 1998; Kakigi and Shibasaki, 1991; Kakigi et al., 2000; Lorenz and Garcia-Larrea, 2003**). Comparada con la mayoría de técnicas de estimulación, las ventajas del método CHEP incluyen el control del pico de temperatura y la posibilidad de estimular más receptores con una duración más larga del pulso en una mayor área de superficie. Una de las aplicaciones podría incluir la capacidad para evaluar la función de la fibra C por láser y calor por contacto para la detección de polineuropatías de fibras pequeñas (**Krarpup, 2003; Granovsky et al., 2005**).

3.5.19. Conclusiones

Aunque el DN se identificó usando el cuestionario DN4 en los grupos NP y SYR reclutados en este estudio, un análisis detallado de las respuestas sensoriales al examen estándar BST y QST proporciona información adicional en la presencia de signos de dolor y mecanismos al, por debajo y por encima del nivel de la LM. El examen tónico térmico proporciona importante información asociada con las respuestas de dolor al y por encima del nivel de LM mientras que las técnicas estándar BST/QST evalúan adecuadamente la función sensorial no dolorosa a todos los niveles relativos a la LM. Al nivel de la lesión, BST/QST y las técnicas de estimulación tónica térmicas se diferenciaron entre los pacientes NP dorsales y cervicales, y entre pacientes SYR y HV. Es importante decir que las técnicas de estimulación tónica térmicas por encima del nivel de lesión también detectaron cambios en la función sensitiva entre SYR y HV. Sugerimos que el desarrollo posterior de técnicas combinadas con análisis detallado de los componentes del eVAS será instrumental en la valoración de la función sensorial y la fisiopatología del centro espinotalámico/supraespinal de dolor después de la LM, cuando se combine con procedimientos estándar BST/QST.

3.5.20. Agradecimientos

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CHAPTER 4

QUALITY OF LIFE AND SPONTANEOUS PAIN INTENSITY DURING ACUTE AND CHRONIC SPINAL CORD INJURY NEUROPATHIC PAIN

4.1. Introduction

Central Neuropathic Pain (pain initiated or caused by a primary lesion or dysfunction in the central nervous system, **IASP, 1994**) is a major persistent problem in acute and chronic spinal cord injury (SCI) patients, associated with changes in mood and function, independent of the evolution of the lesion. A successful diagnostic and treatment strategy for SCI-NP depends upon adequate assessment of both physical and psychosocial factors (**Yeziarski et al., 1996; Siddall et al., 1997; Bryce, 2000**).

Psychological factors are linked to the presence or severity of pain and other factors such as depressive symptoms and perceived stress (**Siddall et al., 2003**), and with personal characteristics related to adaptation and coping skills necessary for improving Quality of Life (QoL) (**Haythornthwaite et al., 2000**). QoL is a broadly-defined umbrella term that encompasses numerous themes, concepts, and factors such as self-perception of general physical health, similar perceptions of psychological health and emotional well-being, meaningful and worthwhile interpersonal relationships, active and satisfying sexual relationships, as well as spirituality to name a few (**Schumaker, 1990; Renwick et al., 1996**). To date no longitudinal studies have been attempted to describe the impact of NP development on standardized psychosocial factors, like catastrophizing and praying.

Some authors like **Turk (1992; 2001)** have mentioned that most of the instruments developed for chronic pain patients are not appropriate for use with SCI patients because of the additional impact of physical limitations as a consequence of the injury, that may influence pain perception and subsequent negative responses (**Widerström-Noga et al., 1999**). In addition, some physical factors such as the level of the SCI lesion (**Putzke et al., 2002**), found a significant effect on 14 out of 27 studies, and the specific pain mechanisms associated with these factors may have different impact on QoL. However, and although pain-related reduction in daily activities was not associated with injury level, severe pain is likely to affect activity levels significantly (**Widerström-Noga et al., 2002**).

4.1. Coping Strategy Questionnaire and Catastrophizing

The Coping Strategy Questionnaire-Revised version (CSQ-R) (**Riley et al., 1997**) consists of 27 items, measuring 6 dimensions of coping techniques in a self-report measure of cognitive and behavioural strategies: “Praying”, “Catastrophizing” (these two are the most studied), “Ignoring Pain Sensations”, “Distancing from pain”, “Coping Self Statements” and “Distraction”. Internal consistency coefficients range from 0.57 to 0.89 (**Gil et al., 1989; Keefe et al. 1987; Spinhoven et al., 1989**) and the test-retest reliability for subscales ranged from 0.68 to 0.91 (**Rosenstiel and Keefe, 1983; Main and Waddell, 1991**). Concurrent validity of the CSQ has been extensively studied and supported. The CSQ scales have explained significant variance in adjustment and well-being in numerous studies (**Rosenstiel and Keefe, 1983; Beckham et al., 1991; Main and Waddell, 1991**). The CSQ-R has shown robust psychometric properties, namely a sounder factor structure, but it has had limited exposure in patient populations because of its recent development (**Riley et al., 1997; Riley et al., 1999a; Robinson et al. 1997**).

It has become the most frequently used measure for the assessment of coping in chronic pain patients and the subject of considerable research (**Jensen et al., 1991**) and some of its factors, particularly “Catastrophizing” (expecting or worrying about major negative consequences from a situation, including one of minor importance), has been discussed extensively among studies. Although

preliminary, **Jensen et al. (1991)** found that patients who believe that they can control their pain, and who avoid catastrophizing about their pain condition, and who believe that they are not severely disabled, appear to feel better than those who do not. Such beliefs may mediate some of the relationships between pain severity and adjustment to it. Furthermore, a recent study has suggested that Catastrophizing should be described as an elaborate construct made up of both cognitive appraisal and affective components, as a complex combination of perceived lack of control, lack of positive affect, and presence of intense negative affect (**Jones et al., 2003**). CSQ Catastrophizing scale was the single most powerful predictor of depression (although scales like Coping Self Statements also contributed), disability and pain severity in chronic pain patients (**Tan et al., 2001**), all consistent with the cognitive-behavioural models of pain. In the same way, Catastrophizing was the most strongly factor associated with depressive mood at 3-12 weeks (sub-acute phase) and at the 6month follow-up (**Trunchon and Côté, 2005**) in low back pain patients.

Furthermore several studies have observed that Catastrophizing, but not other coping strategies, was consistently associated to psychological measures of anxiety and pain interference in daily activity. Indeed high levels of Catastrophizing were associated with higher pain severity and psychological stress, and higher levels of pain were related with low self-efficiency (**Turner et al., 2002**). The relationship between Catastrophizing and pain appears to emerge early in life and shows remarkable consistency, predicting severe pain in patients with arthritis 6 month later (**Sullivan et al., 1995**). It is necessary to consider that intense pain may also directly cause Catastrophizing thinking (**Sullivan et al., 2001**), though more research is needed to address this question. **Sullivan et al. (2001)** suggested that Catastrophizing might best be viewed from the perspective of a hierarchical level of analysis, where social factors and social goals may play a role in the development and maintenance of Catastrophizing, whereas appraisal-related processes may point to the mechanisms that link Catastrophizing to pain experience.

The Praying-Hoping factor, as assessed with the CSQ, has previously been considered a passive and maladaptive coping strategy; however might be an adaptive coping strategy for some individuals in certain circumstances. Coping has been defined generally as intrapsychic and action-oriented efforts to manage stressful environmental and internal demands that tax a person's resources (**Robinson et al., 1997**). Indeed, **Turner and Clancey (1986)** reported that increased use of praying and hoping was related to decreases in self-report of pain intensity. Additionally, other researchers found that Praying-Hoping was the coping strategy most reported in a sample of patients with chronic pain (**Ashby and Lenhart, 1994; Haythornthwaite et al., 2000**).

The Coping behaviour factor virtually always occurs in a social context and is both affected by the context and contributes to its change. In other words, coping is not individualistic but intricately entwined in the influences of one's ethnocultural environment and subcultural context, and that is where one learns the foundation for coping. And because of that "active" praying-hoping actually might be a culturally developed coping mechanism that might be adaptive for some communities as in the study by **Hastie et al., (2004)**. **Turner et al. (2000)** found that Coping scores significantly and independently predicted physical disability, but not depression, whereas Catastrophizing independently predicted depression but not disability.

The CSQ-R has shown robust psychometric properties, namely a sounder factor structure, but it has had limited exposure in patient populations because of its recent development (**Riley et al., 1997; Riley et al., 1999a; Robinson et al., 1997**).

Multidimensional Pain Inventory – Spinal Cord Injury version

The Multidimensional Pain Inventory – Spinal Cord Injury version (MPI-SCI, **Widerström-Noga et al., 2002**) assesses patients' appraisal of pain, the impact of pain on specific domains of their lives and specific behaviours that are performed or avoided because of the pain (**Hadjistavropoulos et al., 1999**). The MPI-SCI was derived from the The West Haven-Yale Multidimensional Pain Inventory (WHYMPI) which has been shown to have good psychometric properties (**Kerns et al., 1985**;

Bernstein, 1995), the factor structure has been confirmed in several studies (**Bergström et al, 1998; Lousberg, 1999; Riley, 1999b**), it has been demonstrated to have good reliability (**Kerns and Jacob, 1992**) and validity as an assessment tool for a number of chronic pain patients and conditions (**Turk, 1998**), and it is sensitive to change (**Turk, 1998**). The internal consistency of the MPI-SCI subscales ranged from fair (.60) for Affective Distress to substantial (.94) for Pain Interference with activities. The subscales of the MPI-SCI (ie, life interference [$r=.81$], affective distress [$r=.71$], solicitous responses [$r=.86$], distracting responses [$r=.85$], general activity [$r=.69$], pain interference with activities [$r=.78$], pain severity [$r=.69$], negative responses [$r=.69$]) showed adequate stability. In contrast, the stability of the support ($r=.59$) and the life control subscales ($r=.31$) was unacceptably low. All MPI-SCI subscales, with the exception of the perceived responses by significant others subscales, showed good convergent, discriminant, and concurrent validity. Therefore the MPI-SCI appears to be a reasonable measure for evaluating chronic pain impact after SCI (**Widerström-Noga et al., 2002**).

Although the MPI-SCI has been demonstrated to have good reliability (**Kerns and Jacob, 1992**) and validity as an assessment tool for a number of chronic pain patients and conditions (**Turk, 1998**), is sensitive to change (**Turk, 1998**), and appears to be a reasonable measure for evaluating chronic pain impact after SCI, supplementary instruments should be included as exposed **Widerström-Noga et al. (2006)**. Although the pain-related reduction in daily activities has not been associated with injury level, severe pain intensity is likely to affect these activity levels significantly (**Widerström-Noga et al., 2002**). In addition, physical factors such as the level of the spinal lesion (**Putzke et al., 2002**) and different pain mechanisms (presence of allodynia, hyperalgesia, etc) may also directly affect QoL in these patients.

To date no longitudinal descriptive studies have been attempted to examine *spontaneous* pain intensity and its relationship to QoL factors in acute SCI neuropathic pain patients (**Siddall et al., 1999**), although psychological factors have been linked to the presence and intensity of pain and depressive symptoms up to five years (**Siddall et al., 2003**). Although pain intensity using VAS scales have been used extensively in patients to obtain repeated measures of pain intensity over time (**Price, 1999**), they have not so far been combined with standard QoL scales to identify the relationship with psychosocial characteristics of patients with chronic pain. Such a longitudinal description and association of pain intensity and psychosocial factors may provide a better understanding of the impact of NP development on daily life in SCI patients and provide better measures to assess treatment effects.

4.2. Objectives

4.2.1. Objectives of the study

Identify significant change in the most important Quality of Life (QoL) factors over the time of injury, derived from both the CSQ-R and MPI-SCI, and relate these changes to *spontaneous* pain intensity and unpleasantness from 2 up to 12 months after SCI. The influence of physical SCI factors such as the level and nature of injury was also examined on the development of cognitive-behavioural factors.

4.2.2. Study Hypothesis

We hypothesized that several QoL factors would correlate highly with both *spontaneous* pain intensity and unpleasantness and with other factors, and would be influenced by physical factors associated with SCI, such as cervical/thoracic lesions and traumatic/non traumatic aetiology.

4.3. Methods

4.3.1. Criterion of Selection

4.3.1.1. Inclusion Criteria

The patients of the present study were recruited at the Paraplegic National Hospital of Toledo (Spain), and covered all the Spanish population territory. We revised a total of 258 clinical histories of in-patients and 30 of them participated as volunteers, from the 1st of July 2003 to the 1st of March 2005. Their aetiology of SCI was either traumatic or atraumatic. Ages were comprised between 18 and 75 years, understood and spoke Spanish and agreed and signed the consent form. Each patient received standard hospital treatment that included analgesics prescribed after the first assessment of pain in this study. BST was performed at 2, 3, 4, 6, and 12 months after spinal cord lesion onset.

The patients presented Neuropathic Pain type, usually suffering “burning” and/or “pressing” sensation mainly, at any dermatomal level of the body above the conus medullaris (T10) and motor-sensitive complete or incomplete spinal lesion (according to the SCI scale “ASIA” by the American Spinal Injury Association : categories A (complete sensitive and motor lesion), B and C (incomplete sensitive/motor lesion)); evaluated since two months after the trauma (acute phase depending on their neurological stability). Patients were required to have a pain intensity greater than 3 on the Visual Analogue Scale ratio scale (VAS), equivalent to “moderate” on the MPQ PPI scale (Mild, Moderate, Severe, Agonizing, Unbearable; **Lázaro et al., 2001**) two months after the SCI. Patients could also manifest any other type of pain distinct from neuropathic (nociceptive, osteomuscular, oncologic, etc) as long as that it was less severe. Patients with spasms related to NP were permitted, independently of their level localization.

4.3.1.2. Exclusion Criteria

Patients presenting psychogenic pain, multiple sclerosis, peripheral neuropathies, complex regional pain syndrome (CRPS), cognitive impairment, incapacity for verbal communication, severe hypoacusia or demency, were excluded, as well patients who were not able to be tested on the first assessment (before pharmacological treatment began). Patients with spasms unrelated to NP were also excluded from the study.

4.3.1.3. Experimental groups

Longitudinal QoL analysis was performed in the study population as a whole, followed by a temporal analysis of these factors according to the level of injury, cervical versus thoracic SCI, and patients with traumatic or atraumatic injury.

4.3.1.4. Patients Studies General Design

All procedures were approved by the Human Ethics Committee (Comité Ético de Investigación Clínica del “Complejo Hospitalario de Toledo-SESCAM”) in accordance with the Declaration of Human Rights, Helsinki, 1975. The patients were informed of the nature and purpose of the study and voluntarily signed the informed consent form by which they entered to participate in our research project, allowing them to abandon the study of their own free will.

4.3.2. Pain and QoL measures

4.3.2.1. Spontaneous pain intensity and unpleasantness

As has been previously described in section 3.1.5.2. (**Chapter 2**), global *spontaneous* pain intensity and unpleasantness were measured using VAS ratio scales. A score of “0” represented “no pain sensation” and “10” represented “the worst imaginable pain”. Specifically two different scores of pain

intensity were measured: 7 day pain intensity (average pain intensity reported by the patient during the last week) and pain unpleasantness (sensation of discomfort associated with the pain during the last week). When the patient reported that pain/unpleasantness both at and below the level of the lesion were present, measures at the level of maximum pain were measured.

4.3.2.2. Coping Strategy Questionnaire-Revised Version (CSQ-R)

The Coping Strategy Questionnaire-Revised (CSQ-R) (Riley et al., 1997) consists of 27 items of the original CSQ (48 item), measuring 6 dimensions of coping techniques in a self-report measure of cognitive and behavioral coping strategies. Items are rated on a six-point Likert scale. Participants are asked to rate how often they use these coping styles (0=never; 6=always). Recent factor analysis (Riley and Robinson, 1997; Robinson et al., 1997) suggests that the scale is best represented by a six-factor solution including Praying, Ignoring Pain Sensations, Distancing from pain, Catastrophizing, Coping Self Statements and Distraction. It has the original domains of the CSQ, except for the Increasing Behavioral Activities scale, which is deleted from the CSQ-R (it only consists in one item, question 45 that typically loads on the Diverting Attention scale). (See the CSQ-R Spanish version in Protocol in Appendix 4.2.1)

4.3.2.3. Multidimensional Pain Inventory – Spinal Cord Injury Version (MPI-SCI)

The MPI-SCI was derived from the The West Haven-Yale Multidimensional Pain Inventory (WHYMPI) which has good psychometric properties (Kerns et al., 1985; Bernstein, 1995), the factor structure has been confirmed in several studies (Bergström et al, 1998; Lousberg, 1999; Riley, 1999b), it has been demonstrated to have good reliability (Kerns and Jacob, 1992) and validity as an assessment tool for a number of chronic pain patients and conditions (Turk et al., 1998), and it is sensitive to change (Turk et al., 1998).

The Multidimensional Pain Inventory – Spinal Cord Injury Version (MPI-SCI) (Widerström-Noga et al., 2002) is a self-report questionnaire which assesses the patients' appraisal of pain, the impact of pain on specific domains of their lives and specific behaviours that are performed or avoided because of the pain (Hadjistavropoulos et al., 1999). It comprises of 3 sections: section 1 (pain impact), section 2 (responses by significant others) and section 3 (common activities) and has been factor analyzed to include 12 scales. Eight of these 12 scales include cognitive, affective, social and behavioural responses such as: Pain Severity, Life Interference, Life Control, Affective Distress, Support, Negative Responses from Others, Solicitous Responses from Others, and Distracting Responses from Others. The remaining 4 scales assess the degree of participation in various types of daily activities: Household Activities, Activities Away from Home, Social Activities and Outdoor Activities (Widerström-Noga et al., 2002). The responses were measured on a range of "0" (not at all present) to "6" (extremely present). The MPI-SCI comprises of 2 additional items after each item in section 3 to define the degree to which pain and other consequences of SCI reduced patient participation in these specified activities (Widerström-Noga et al., 2002). (See the MPI-SCI Spanish version in Appendix 4.2.2-4.2.9).

4.3.2.4. Statistical Data Analysis

The statistical comparison of the patients' data was analyzed by using the software SPSS version 12.0.1, with parametric tests like Greenhouse-Geisser which was chosen to perform repeated measures ANOVA for *spontaneous* pain, unpleasantness and the different factors in thirty patients. Correlations between the variables were also achieved.

4.4. Results

4.4.1. Diagnostic and Demographic Data

Also described in **2.4.1. section**, this sample of 30 patients were recruited from the Paraplegic National Hospital of Toledo (Spain), and cover all the territory of Spanish population. Age average in our sample (N=30 patients) was 39 years (SD +/- 13) with a range between 21 and 71 years. One third of them were women (33.3 %). The most frequent cause for SCI in our hospital was Traffic Accident: 40% very close to Atraumatic Injury (36.7 %); other causes were: Fall (13.3 %), Diving Accident (6.7 %), Gun Shot Wound (3.3 %). The diagnostic was cervical lesion in half of the patients :26.7 % =high cervical lesion (C2-C4), el 23.3 % low cervical lesion (C5-C8), el 16.7 % high thoracic lesion (D1-D4) and the 33.3 % low thoracic lesion (D5-D10) , the most prevalent between them. We included either complete lesions ASIA A: 63.3 % (2/3) as incompletes (ASIA B y C: 10 % and 36.7 %, respectively). The time of onset in Neuropathic Pain (NP) in the majority of patients was between the second (40% of total) and third (46.7%) month after the spinal lesion. The descriptive statistics reported previously in **Table 1.1** shows a progressive increase in NP (Neuropathic Pain) intensity along the repeated measures (VAS mean goes to 2.73 at 2 months of injury to 5.36 at 12 months), some more pronounced and clear with the Unpleasant measure of VAS (mean goes to 3.24 at 2 months of injury to 6.00 at 12 months).

The descriptive statistics reported in **Table 4.1** shows a progressive increase in NP (Neuropathic Pain) intensity along the repeated measures with the 7day VAS (described in **Chapter 2**) in a combined at level and below the level of injury pain intensity (the range of the scale was 0-10; mean is 2.73 at 2 months of injury and 5.36 at 12 months), some more pronounced and clear with the Unpleasant measure of VAS (mean is 3.24 at 2 months of injury and 6.00 at 12 months).The descriptive statistics of the CSQ-R, MPI-SCI and VAS are shown in **Tables 4.2-4.7**.

The net score of the CSQ-R scales was compared with the possible scores, which vary within each factor and is the following: Ignoring pain (min= 0, mean= 9.82, max= 19.64); Distancing (min= 0, mean= 8.27, max= 16.53); Coping Self Statements (min= 0, mean= 7.74, max= 15.48); Praying (min= 0, mean= 6.28, max= 12.56); Catastrophizing (min= 0, mean= 11.85, max= 23.70); Distraction (min= 0, mean= 10.37, max= 20.74). The patients did not seem to use any of the CSQ-R strategies at 2 months time of injury (**Table 4.2**), since the scores are lesser than the mean values of the possible range. However, at 12 months time we can observe an increase in their use, though they keep on showing low scores: Coping Self Statements looks to be the most used, and so are during the following assessments; Coping Self Statements mean is 3.93 (2m) and 9.27 (12m). Therefore is Ignoring pain ,which mean goes from 2.26 at 2m to 4.45 at 12 m. From 3 months Praying is also used, with an increasing mean of 2.53 (2m) and 5.69 (12m). Some CSQ-R factors show small scores, like Distancing which mean is 1.18 (2m) and 2.09 (12m) and Distraction with a mean of 4.03 (2m) and 8.09 (12m). Catastrophizing shows a mean of 1.92(2m) and 7.37 (12m).

The possible scores of the MPI-SCI factors are: Interference (min= 0, mean= 30, max= 60); Support (min= 0, mean= 12, max= 24); Pain Severity (min= 0, mean= 12, max= 24); Life Control (min= 0, mean= 18, max= 36); Affective Distress (min= 0, mean= 9, max= 18); Negative Responses (min= 0, mean= 12, max= 24); Solicitous Responses (min= 0, mean= 15, max= 30); Distracting Responses (min= 0, mean= 12, max= 24); Household Chores (min= 0, mean= 15, max= 30); Outdoor work (min= 0, mean= 15, max= 30); Activities away from home (min= 0, mean= 12, max= 24); Social Activities (min= 0, mean= 12, max= 24). MPI-SCI factors also increment progressively in time (**Table 4.3**), showing more than double of the value at 12 months after the injury in all of them. Patients start giving

scores in Household Chores, Activities Away from Home and Social Activities at 4 months time and Outdoor Work at 12 months.

	2m 7dVAS	2m UnpVAS	3m 7dVAS	3m UnpVAS	4m 7dVAS	4m UnpVAS	6m 7dVAS	6m UnpVAS	12m 7dVAS	12m UnpVAS
N	30	29	30	27	27	26	24	22	18	18
Mean	2.73	3.24	2.97	4.20	4.13	5.08	4.21	5.98	5.36	6.00
St Dev	3.96	4.33	3.55	4.11	3.68	3.73	3.78	3.50	3.08	3.29

Table 4.1. Table of means and Standard Deviations of 7 day VAS and Unpleasantness VAS at 2,3,4,6 and 12 months time.

CSQ-R factors	2m (N=30)		3m (N=29)		4m(N=26)		6m(N=24)		12m(N=17)	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
ignoring pain	2.26	4.25	4.65	4.26	4.16	4.10	4.65	4.10	4.43	3.93
distancing	1.18	3.31	1.79	3.29	1.65	3.50	1.57	3.26	2.09	3.62
coping self statements	3.93	5.85	7.94	5.89	8.50	6.36	10.28	6.05	9.27	4.71
praying	2.53	4.51	3.95	4.57	4.01	4.74	5.13	4.83	5.69	5.23
catastrophizing	1.92	3.69	3.70	4.69	4.50	5.77	4.59	4.36	7.37	6.65
distraction	4.03	7.46	6.72	7.79	6.25	7.40	8.17	8.43	8.09	7.93

Table 4.2. Table of means and Standard Deviations of CSQ-R at 2,3,4,6 and 12 months time.

MPI-SCI factors	2m			3m			4m			6m			12m		
	Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	N
factor 1 interference	7.82	13.55	30	12.62	15.17	30	13.95	15.10	29	14.78	16.43	27	24.23	15.91	17
factor 2 support	3.93	5.94	30	6.18	6.27	30	9.00	6.81	29	8.69	6.67	27	8.75	3.96	17
factor 3 pain severity	4.01	5.80	30	5.95	6.62	30	7.59	6.19	29	7.04	5.26	27	9.69	5.09	17
factor 4 life control	5.11	8.31	30	6.87	8.66	30	9.86	7.79	29	9.83	7.40	27	11.16	5.58	17
factor 5 affective distress	.93	1.43	30	1.36	1.52	30	1.66	1.61	29	1.61	1.50	27	2.82	1.43	17
factor 6 negative responses	1.33	3.95	30	2.42	4.94	30	2.67	4.08	29	2.04	3.42	27	3.00	3.53	17
factor 7 solicitous responses	5.46	9.49	30	10.91	11.77	30	11.64	10.00	29	10.76	10.24	27	16.58	10.58	17

factor 8 distracting responses	3.14	6.05	30	5.25	6.20	30	5.93	5.61	29	5.93	5.90	27	7.40	5.29	17
factor 9 household chores	.00	.00	26	.00	.00	30	.50	2.69	29	1.21	4.44	27	4.31	5.58	17
factor 10 outdoor work	.00	.00	30	.00	.00	30	.00	.00	29	.00	.00	27	.82	1.70	17
factor 11 activities away from home	.00	.00	30	.00	.00	30	.02	.093	29	.20	.96	27	5.82	4.78	17
factor 12 social activities	.00	.00	30	.00	.00	30	.20	1.05	29	.47	1.70	27	4.86	4.94	17

Table 4.3. Table of means and Standard Deviations of MPI-SCI at 2,3,4,6, and 12 months time.

	N	Minimum	Maximum	Mean	SD
2m Max pain 7day VAS either at/below	15	.0	10,0	3,100	3,9288
2m Max Unpleasantness VAS either at/below	15	.0	10,0	4,567	4,5586
3m Max pain 7day VAS either at/below	15	.0	10,0	3,500	4,0796
3m Max Unpleasantness VAS either at/below	14	.0	10,0	5,107	3,9768
4m Max pain 7day VAS either at/below	13	.0	9,5	3,308	3,5797
4m Max Unpleasantness VAS either at/below	13	.0	10,0	5,192	3,8054
6m Max pain 7day VAS either at/below	13	.0	10,0	3,692	3,8651
6m Unpleasantness VAS either at/below	12	.0	10,0	5,750	3,3405
12m Max pain 7day VAS either at/below	7	.0	7,0	3,714	2,5797
12m Max Unpleasantness VAS either at/below	7	.0	7,5	4,571	2,7451

Table 4.4. Table of means and Standard Deviations of 7day VAS and Unpleasantness VAS at 2,3,4,6, and 12 months time (cervical group).

	N	Minimum	Maximum	Mean	SD
2m Max pain 7day VAS either at/below	15	.0	10,0	2,367	4,0947
2m Max Unpleasantness VAS either at/below	14	.0	10,0	1,821	3,7190
3m Max pain 7day VAS either at/below	15	.0	10,0	2,433	2,9633

3m Max Unpleasantness VAS either at/below	13	,0	10,0	3,231	4,1814
4m Max pain 7day VAS either at/below	14	,0	9,0	4,893	3,7323
4m Max Unplesantness VAS either at/below	13	,0	10,0	4,962	3,7995
6m Max pain 7day VAS either at/below	11	,0	10,0	4,818	3,7635
6m Unpleasantness VAS either at/below	10	,0	10,0	6,250	3,8460
12m Max pain 7day VAS either at/below	11	,0	10,0	6,409	2,9985
12m Max Unpleasantness VAS either at/below	11	,0	10,0	6,909	3,3972

Table 4.5. Table of means and Standard Deviations of 7day VAS and Unpleasantness VAS at 2,3,4,6, and 12 months time (thoracic group).

	N	Minimum	Maximum	Mean	SD
ignoring pain CSQ factor 2m	15	,00	7,66	2,4393	2,97344
distancing CSQ factor 2m	15	,00	10,53	,8340	2,73036
Coping Self Statements CSQ factor 2m	15	,00	15,48	5,4080	6,30637
Praying CSQ factor 2m	15	,00	12,56	3,7700	5,36181
catastrophizing CSQ factor 2m	15	,00	16,18	2,9433	4,46774
distraction CSQ factor 2m	15	,00	18,55	5,6559	8,33549
ignoring pain CSQ factor 3m	14	,00	9,89	4,1671	3,48404
distancing CSQ factor 3m	14	,00	10,53	1,6418	3,00299
Coping Self Statements CSQ factor 3m	14	,00	15,48	8,9379	5,54936
Praying CSQ factor 3m	14	,00	12,56	5,6155	4,97587
catastrophizing CSQ factor 3m	14	,00	13,84	3,9514	5,22226
distraction CSQ factor 3m	14	,00	19,19	7,0101	8,11260
ignoring pain CSQ factor 4m	13	,00	11,46	4,5962	3,91754
distancing CSQ factor 4m	13	,00	9,23	1,7958	3,48532
Coping Self Statements CSQ factor 4m	13	,00	15,48	9,1300	5,86176
Praying CSQ factor 4m	13	,00	12,56	4,1269	4,82259
catastrophizing CSQ factor 4m	13	,00	21,30	4,3446	6,80063
distraction CSQ factor 4m	13	,00	18,55	6,0537	7,08446
ignoring pain CSQ factor 6m	13	,00	13,68	5,1960	4,69822
distancing CSQ factor 6m	13	,00	12,24	1,8719	4,05793
Coping Self Statements CSQ factor 6m	13	,00	15,48	10,2131	6,49961

Praying CSQ factor 6m	13	,00	12,56	4,5590	4,74552
catastrophizing CSQ factor 6m	13	,00	11,33	3,7315	3,68510
distraction CSQ factor 6m	13	,00	20,74	7,3354	8,25768
ignoring pain CSQ factor 12m	6	,00	7,76	3,9730	3,34706
distancing CSQ factor 12m	6	,00	9,85	2,5017	4,14852
Coping Self Statements CSQ factor 12m	6	,00	15,48	9,8300	5,40994
Praying CSQ factor 12m	6	,00	11,68	3,8767	5,38480
catastrophizing CSQ factor 12m	6	,00	13,35	6,1717	5,63360
distraction CSQ factor 12m	6	,00	20,74	5,5537	8,31120
factor 1 Interference MPI 2m	15	,00	38,63	10,4006	13,51364
factor 2 support MPI 2m	15	,00	17,50	4,8500	5,64564
factor 3 pain severity MPI 2m	15	,00	17,50	5,8500	6,48336
factor 4 life control MPI 2m	15	,00	26,83	6,3889	8,70747
factor 5 affective distress MPI 2m	15	,00	4,67	1,1111	1,52058
factor 6 negative responses MPI 2m	15	,00	19,50	1,8333	5,27770
factor 7 solicitous responses MPI 2m	15	,00	28,00	7,3911	10,97581
factor 8 distracting responses MPI 2m	15	,00	18,50	3,8833	6,62036
factor 9 household chores MPI 2m	12	,00	,00	,0000	,00000
factor 10 outdoor work MPI a los 2 meses	15	,00	,00	,0000	,00000
factor 11 activities away from home MPI 2m	15	,00	,00	,0000	,00000
factor 12 social activities MPI a los 2 meses	15	,00	,00	,0000	,00000
factor 1 Interference MPI 3m	15	,00	50,00	12,8970	15,74615
factor 2 support MPI 3m	15	,00	16,50	6,2167	5,65043
factor 3 pain severity MPI 3m	15	,00	17,25	6,7500	6,50000
factor 4 life control MPI 3m	15	,00	26,00	7,6289	9,59562
factor 5 affective distress MPI 3m	15	,00	5,00	1,7111	1,71763
factor 6 negative responses MPI 3m	15	,00	18,50	2,5167	5,14822
factor 7 solicitous responses MPI 3m	15	,00	30,00	10,7600	10,68308
factor 8 distracting responses MPI 3m	15	,00	16,50	5,3000	5,95084
factor 9 household chores MPI 3m	15	,00	,00	,0000	,00000

factor 10 outdoor work MPI a los 3m	15	,00	,00	,0000	,00000
factor 11 activities away from home MPI 3m	15	,00	,00	,0000	,00000
factor 12 social activities MPI a los 3m	15	,00	,00	,0000	,00000
factor 1 Interference MPI 4m	14	,00	44,00	13,8889	15,40791
factor 2 support MPI 4m	14	,00	17,00	9,0893	6,86729
factor 3 pain severity MPI 4m	14	,00	19,50	7,3750	6,29847
factor 4 life control MPI 4m	14	,00	24,00	10,6667	7,94384
factor 5 affective distress MPI 4m	14	,00	3,67	1,5476	1,62042
factor 6 negative responses MPI 4m	14	,00	9,75	2,5000	3,47795
factor 7 solicitous responses MPI 4m	14	,00	25,00	12,9357	9,36052
factor 8 distracting responses MPI 4m	14	,00	16,50	5,9286	4,84314
factor 9 household chores MPI 4m	14	,00	,00	,0000	,00000
factor 10 outdoor work MPI a los 4m	14	,00	,00	,0000	,00000
factor 11 activities away from home MPI 4m	14	,00	,00	,0000	,00000
factor 12 social activities MPI a los 4m	14	,00	,00	,0000	,00000
factor 1 Interference MPI 6m	14	,00	48,60	14,4667	17,66958
factor 2 support MPI 6m	14	,00	18,50	9,6786	6,91947
factor 3 pain severity MPI 6m	14	,00	14,50	6,8393	5,06649
factor 4 life control MPI 6m	14	,00	25,00	10,2429	7,72374
factor 5 affective distress MPI 6m	14	,00	4,67	1,4524	1,63617
factor 6 negative responses MPI 6m	14	,00	8,00	1,5536	2,66238
factor 7 solicitous responses MPI 6m	14	,00	25,00	11,6714	11,31224
factor 8 distracting responses MPI 6m	14	,00	16,50	6,1429	6,52268
factor 9 household chores MPI 6m	14	,00	,00	,0000	,00000
factor 10 outdoor work MPI a los 6m	14	,00	,00	,0000	,00000
factor 11 activities away from home MPI 6m	14	,00	,00	,0000	,00000
factor 12 social activities MPI a los 6m	14	,00	,00	,0000	,00000
factor 1 Interference MPI 12m	6	,00	37,00	20,5000	14,56560
factor 2 support MPI 12m	6	3,00	11,50	8,3056	3,24580

factor 3 pain severity MPI 12m	6	,00	12,75	8,0000	4,68775
factor 4 life control MPI 12m	6	,33	14,00	8,0833	5,09111
factor 5 affective distress MPI 12m	6	1,00	5,33	3,0556	1,75647
factor 6 negative responses MPI 12m	6	,00	2,75	,6250	1,11524
factor 7 solicitous responses MPI 12m	6	,00	30,00	14,0333	12,27056
factor 8 distracting responses MPI 12m	6	,00	10,00	5,4583	4,45089
factor 9 household chores MPI 12m	6	,00	5,00	2,0000	1,89737
factor 10 outdoor work MPI a los 12m	6	,00	,00	,0000	,00000
factor 11 activities away from home MPI 12m	6	,00	6,00	3,4167	2,74165
factor 12 social activities MPI a los 12m	6	,00	8,75	2,3333	3,41931

Table 4.6. Table of means and Standard Deviations of CSQ-R and MPI-SCI at 2,3,4,6, and 12 months time (cervical group).

	N	Minimum	Maximum	Mean	SD
ignoring pain CSQ factor 2m	15	,00	18,97	2,0864	5,34411
distancing CSQ factor 2m	15	,00	14,52	1,5190	3,87699
Coping Self Statements CSQ factor 2m	15	,00	14,77	2,4580	5,15289
Praying CSQ factor 2m	15	,00	11,68	1,2971	3,17834
catastrophizing CSQ factor 2m	15	,00	6,80	,9040	2,38566
distraction CSQ factor 2m	15	,00	19,19	2,3977	6,34392
ignoring pain CSQ factor 3m	15	,00	15,24	5,0953	4,94907
distancing CSQ factor 3m	15	,00	10,26	1,9197	3,63600
Coping Self Statements CSQ factor 3m	15	,00	15,48	7,0000	6,22901
Praying CSQ factor 3m	15	,00	12,56	2,3907	3,66892
catastrophizing CSQ factor 3m	15	,00	12,39	3,4587	4,30054
distraction CSQ factor 3m	15	,00	20,01	6,4393	7,74493
ignoring pain CSQ factor 4m	13	,00	14,89	3,7158	4,38614
distancing CSQ factor 4m	13	,00	10,26	1,4935	3,65247
Coping Self Statements CSQ factor 4m	13	,00	15,48	7,8638	6,99632
Praying CSQ factor 4m	13	,00	12,56	3,8877	4,84741
catastrophizing CSQ factor 4m	13	,00	14,41	4,6608	4,80671

distraction CSQ factor 4m	13	,00	20,74	6,4474	7,98688
ignoring pain CSQ factor 6m	11	,00	9,08	4,0024	3,37717
distancing CSQ factor 6m	11	,00	6,63	1,2118	2,08652
Coping Self Statements CSQ factor 6m	11	,00	15,48	10,3600	5,79635
Praying CSQ factor 6m	11	,00	12,56	5,8103	5,07508
catastrophizing CSQ factor 6m	11	,00	15,75	5,6073	5,03627
distraction CSQ factor 6m	11	,00	20,74	9,1482	8,91805
ignoring pain CSQ factor 12m	11	,00	13,27	4,7078	4,34718
distancing CSQ factor 12m	11	,00	10,50	1,8709	3,49278
Coping Self Statements CSQ factor 12m	11	,00	15,48	8,9664	4,53420
Praying CSQ factor 12m	11	,00	12,28	6,6818	5,11890
catastrophizing CSQ factor 12m	11	,00	17,13	8,0236	7,31088
distraction CSQ factor 12m	11	,00	20,74	9,4740	7,75473
factor 1 Interference MPI 2m	15	,00	45,25	5,2433	13,54446
factor 2 support MPI 2m	15	,00	16,50	3,0167	6,27101
factor 3 pain severity MPI 2m	15	,00	12,50	2,1667	4,51947
factor 4 life control MPI 2m	15	,00	21,50	3,8333	7,97466
factor 5 affective distress MPI 2m	15	,00	4,00	,7556	1,35966
factor 6 negative responses MPI 2m	15	,00	6,25	,8167	1,98311
factor 7 solicitous responses MPI 2m	15	,00	24,00	3,5333	7,62390
factor 8 distracting responses MPI 2m	15	,00	19,50	2,4000	5,54913
factor 9 household chores MPI 2m	14	,00	,00	,0000	,00000
factor 10 outdoor work MPI a los 2 meses	15	,00	,00	,0000	,00000
factor 11 activities away from home MPI 2m	15	,00	,00	,0000	,00000
factor 12 social activities MPI a los 2 meses	15	,00	,00	,0000	,00000
factor 1 Interference MPI 3m	15	,00	35,00	12,3521	15,11715
factor 2 support MPI 3m	15	,00	17,50	6,1500	7,03994
factor 3 pain severity MPI 3m	15	,00	18,25	5,1500	6,86008
factor 4 life control MPI 3m	15	,00	22,50	6,1111	7,88676
factor 5 affective distress MPI 3m	15	,00	4,33	1,0000	1,24722

factor 6 negative responses MPI 3m	15	,00	15,50	2,3167	4,89211
factor 7 solicitous responses MPI 3m	15	,00	31,00	11,0578	13,15295
factor 8 distracting responses MPI 3m	15	,00	19,50	5,2000	6,65153
factor 9 household chores MPI 3m	15	,00	,00	,0000	,00000
factor 10 outdoor work MPI a los 3m	15	,00	,00	,0000	,00000
factor 11 activities away from home MPI 3m	15	,00	,00	,0000	,00000
factor 12 social activities MPI a los 3m	15	,00	,00	,0000	,00000
factor 1 Interference MPI 4m	15	,00	36,27	14,0048	15,34762
factor 2 support MPI 4m	15	,00	17,25	8,9167	6,98830
factor 3 pain severity MPI 4m	15	,00	16,50	7,7833	6,29474
factor 4 life control MPI 4m	15	,00	24,83	9,1111	7,84818
factor 5 affective distress MPI 4m	15	,00	4,33	1,7553	1,64500
factor 6 negative responses MPI 4m	15	,00	13,50	2,8333	4,68248
factor 7 solicitous responses MPI 4m	15	,00	26,50	10,4333	10,74539
factor 8 distracting responses MPI 4m	15	,00	19,50	5,9333	6,42155
factor 9 household chores MPI 4m	15	,00	14,50	,9667	3,74388
factor 10 outdoor work MPI a los 4m	15	,00	,00	,0000	,00000
factor 11 activities away from home MPI 4m	15	,00	,50	,0333	,12910
factor 12 social activities MPI a los 4m	15	,00	5,67	,3778	1,46313
factor 1 Interference MPI 6m	13	,00	44,50	15,1119	15,75881
factor 2 support MPI 6m	13	,00	17,25	7,6346	6,48927
factor 3 pain severity MPI 6m	13	,00	16,50	7,2500	5,66881
factor 4 life control MPI 6m	13	,00	20,17	9,3849	7,31712
factor 5 affective distress MPI 6m	13	,00	4,00	1,7690	1,38355
factor 6 negative responses MPI 6m	13	,00	13,50	2,5705	4,12715
factor 7 solicitous responses MPI 6m	13	,00	24,00	9,7692	9,31311
factor 8 distracting responses MPI 6m	13	,00	13,50	5,6923	5,41425
factor 9 household chores MPI 6m	13	,00	19,20	2,5154	6,24925

factor 10 outdoor work MPI a los 6m	13	,00	,00	,0000	,00000
factor 11 activities away from home MPI 6m	13	,00	5,00	,4231	1,38212
factor 12 social activities MPI a los 6m	13	,00	7,00	,9744	2,39390
factor 1 Interference MPI 12m	11	,00	58,55	26,2675	16,91295
factor 2 support MPI 12m	11	2,00	15,50	9,0000	4,42578
factor 3 pain severity MPI 12m	11	,00	16,25	10,6136	5,27774
factor 4 life control MPI 12m	11	7,00	25,83	12,8336	5,29855
factor 5 affective distress MPI 12m	11	,67	4,33	2,6967	1,29525
factor 6 negative responses MPI 12m	11	,00	12,50	4,2955	3,75968
factor 7 solicitous responses MPI 12m	11	,00	31,00	17,9727	9,88300
factor 8 distracting responses MPI 12m	11	,00	15,50	8,4545	5,60337
factor 9 household chores MPI 12m	11	,00	16,50	5,5727	6,56721
factor 10 outdoor work MPI a los 12m	11	,00	6,00	1,2727	2,00454
factor 11 activities away from home MPI 12m	11	,00	16,25	7,1364	5,24090
factor 12 social activities MPI a los 12m	11	,00	14,00	6,2424	5,21502

Table 4.7. Table of means and Standard Deviations of CSQ-R and MPI-SCI at 2,3,4,6, and 12 months time (thoracic group).

Appendix Tables 4.8-4.45 contain the descriptive statistics for 7day VAS, CSQ-R and MPI-SCI, including cervical and thoracic groups of patients.

4.4.2. Intensity of Pain

Repeated Measures ANOVA was performed (Greenhouse-Geisser test used). We have observed no significant differences in pain measured with the 7day VAS (n=14) for any of the evaluated months (F (3.059, 39.765) =1.891; p=0.146) and neither with the Unpleasantness VAS (F (2.162, 17.296) = 0.876; p=0.565) (n=9). However, we can observe a trend for an increase in the intensity of pain along the repeated measures, with an acute ramp in 7 day VAS and two peaks at 3 and 6 months with the Unpleasantness VAS, being this one slightly higher in intensity (**Fig 4.1. and 4.2**). (The observed power is placed in the **Appendix** of this chapter)

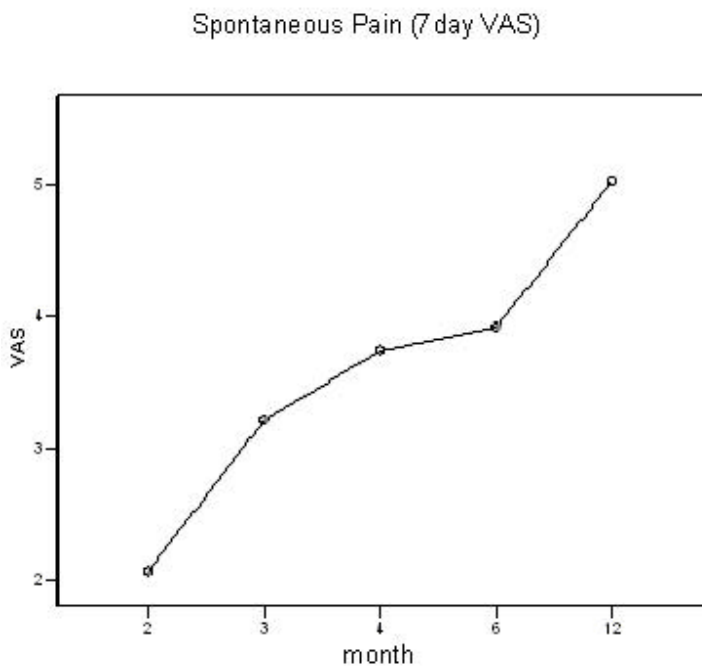


Fig 4.1. Intensity of pain presented in SCI patients, either at or below the level of the injury

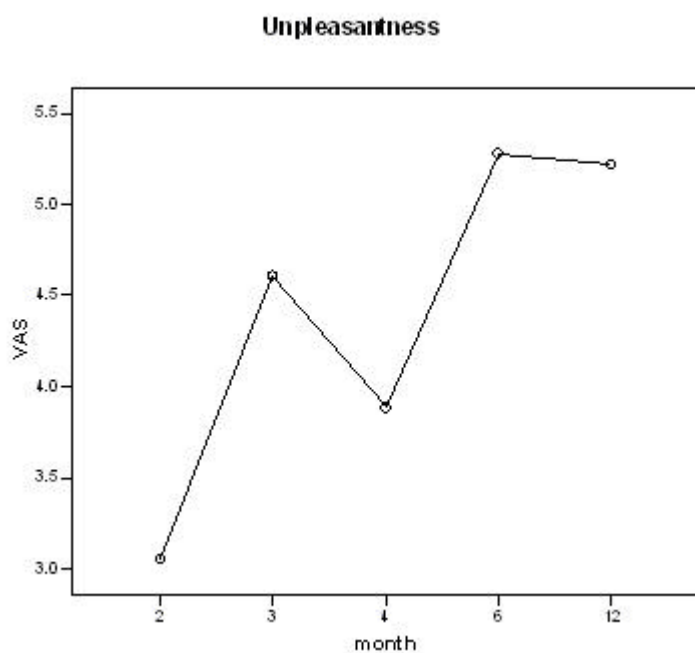


Fig 4.2. Unpleasantness of pain presented in SCI patients, either at or below the level of the injury

4.4.3. Correlations between Intensity of Pain, CSQ-R and MPI-SCI Factors.

In order to examine the relationship between the Intensity of Pain, CSQ-R and MPI-SCI factors we achieved Spearman’s Correlations (Tables 4.8-4.12). Also are included (as an illustrative way) the correlations of cervical and thoracic groups in Appendix Tables 4.4.-4.7 in this chapter.

	VAS		CSQ-R										MPI-SCI						
	7VAS	Unpl	Ign	Dsta	Cop	Pra	Cat	Dstr	Int	Sup	Sev	LCo	Aff	NeR	SoR	DiR	HCh	OWo	AAw
Unpl	.868																		
Ign	.707	.660																	
Dsta	.603	<i>.424</i>	.827																
Cop	.812	.924	.767	.641															
Para	.762	.773	.679	.601	.916														
Cat	.696	.756	<i>.366</i>	<i>.218</i>	.676	.732													
Dstr	.740	.748	.751	<i>.592</i>	.891	.932	.674												
Int	.749	.737	.866	.723	.817	.840	.697	.865											
Sup	.784	.903	.772	.689	.909	.691	<i>.551</i>	.694	.719										
Sev	.845	.958	.723	<i>.535</i>	.914	.798	.755	.774	.788	.907									
Lco	.729	.824	.746	.760	.893	.779	<i>.582</i>	.705	.787	.911	.811								
Aff	.800	.799	.695	<i>.569</i>	.840	.835	.807	.858	.816	.749	.819	.740							
NeR	.613	<i>.462</i>	<i>.378</i>	<i>.361</i>	<i>.461</i>	.629	.827	<i>.531</i>	.649	<i>.333</i>	<i>.570</i>	<i>.387</i>	.697						
SoR	<i>.520</i>	.745	.693	.635	.813	.656	<i>.351</i>	.648	.632	.817	.704	.799	.635	.216					
DiR	<i>.555</i>	.676	.777	.756	.808	.667	<i>.271</i>	.687	.655	.815	.694	.768	.629	<i>.230</i>	.963				
HCh	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Owo	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Aaw	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Sac	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

Table 4.8. Correlations between VAS, CSQ-R and MPI-SCI at 2 months time. *Note.* 7VAS= Intensity of pain 7days VAS; Unpl= Unpleasant VAS; CSQ-R Factors: Ign=Ignoring pain; Dsta=Distancing; Cop=Coping Self Statements; Pra=Praying; Cat=Catastrophizing; Dstr=Distraction MPI-SCI Factors: Int=Interference; Sup= Support; Sev=Pain Severity; LCo=Life Control; Aff=Affective Distress; NeR=Negative Responses; SoR=Solicitous Responses; DiR=Distracting Responses; HCh=Household Chores; OWo=Outdoor work; AAw=Activities away from home; Sac=Social Activities Bolded correlations are significant at $\alpha = .0001$; Not bolded correlations are significant at $\alpha = .005$ Italic correlations are not significant $\alpha = .005$

	VAS				CSQ-R								MPI-SCI						
	7VAS	Unpl	Ign	Dsta	Cop	Pra	Cat	Dstr	Int	Sup	Sev	LCo	Aff	NeR	SoR	DiR	HCh	OWo	AAw
Unpl	.625																		
Ign	.123	.243																	
Dsta	.336	.039	.589																
Cop	.527	.756	.674	.514															
Para	.690	.522	<i>.169</i>	<i>.397</i>	.618														
Cat	.497	.492	.298	<i>.338</i>	.406	.466													
Dstr	.498	<i>.334</i>	<i>.389</i>	.667	.617	.662	<i>.316</i>												
Int	.575	.626	<i>.283</i>	<i>.365</i>	.616	<i>.537</i>	<i>.242</i>	.500											
Sup	.572	.705	.434	<i>.372</i>	.727	.443	<i>.358</i>	<i>.333</i>	.808										
Sev	.653	.837	<i>.194</i>	<i>.221</i>	.696	.625	<i>.439</i>	<i>.356</i>	.759	.785									
LCo	.209	.451	.596	.453	.588	<i>.094</i>	<i>.192</i>	.166	.433	.695	<i>.479</i>								
Aff	.515	.628	<i>.282</i>	<i>.316</i>	.616	.423	.484	<i>.259</i>	<i>.587</i>	.644	.675	.431							
NeR	.541	.454	<i>-.107</i>	<i>-.030</i>	<i>.317</i>	<i>.552</i>	<i>.352</i>	<i>.267</i>	<i>.520</i>	.401	<i>.509</i>	<i>.163</i>	<i>.208</i>						
SoR	.487	.625	<i>.306</i>	<i>.273</i>	.620	<i>.397</i>	<i>.253</i>	<i>.251</i>	<i>.659</i>	.901	.714	.659	<i>.556</i>	<i>.419</i>					
DiR	.422	<i>.574</i>	<i>.426</i>	<i>.454</i>	.613	<i>.270</i>	<i>.256</i>	.665	.846	.621	.721	.760	.258	<i>.246</i>	.898				
HCh	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Owo	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Aaw	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Sac	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

Table 4.9. Correlations between VAS, CSQ-R and MPI-SCI at 3 months time. *Note.* 7VAS= Intensity of pain 7daysVAS; Unpl= Unpleasant VAS; CSQ-R Factors: Ign=Ignoring pain; Dsta=Distancing; Cop=Coping Self Statements; Pra=Praying; Cat=Catastrophizing; Dstr=Distraction MPI-SCI Factors: Int=Interference; Sup= Support; Sev=Pain Severity; LCo=Life Control; Aff=Affective Distress; NeR=Negative Responses; SoR=Solicitous Responses; DiR=Distracting Responses; HCh=Household Chores; Owo=Outdoor work; AAw=Activities away from home; Sac=Social Activities Bolded correlations are significant at $\alpha = .0001$; Not bolded correlations are significant at $\alpha = .005$ Italic correlations are not significant $\alpha = .005$

	VAS			CSQ-R							MPI-SCI								
	7VAS	Unpl	Ign	Dsta	Cop	Pra	Cat	Dstr	Int	Sup	Sev	LCo	Aff	NeR	SoR	DiR	HCh	OWo	AAw
Unpl	.725																		
Ign	.484	.467																	
Dsta	.209	.156	.585																
Cop	.510	.577	.621	.349															
Para	.539	.485	.428	.019	.610														
Cat	.634	.573	.606	.186	.375	.632													
Dstr	.512	.239	.642	.630	.567	.319	.218												
Int	.426	.397	.603	.340	.401	.295	.356	.547											
Sup	.415	.365	.519	.288	.659	.286	.286	.563	.616										
Sev	.704	.768	.530	.365	.524	.489	.618	.496	.578	.673									
Lco	.234	.615	.566	.482	.547	.264	.235	.518	.493	.589	.641								
Aff	.449	.331	.694	.268	.510	.445	.656	.344	.549	.591	.569	.437							
NeR	.338	.366	.227	.042	.480	.576	.372	.252	.330	.316	.493	.208	.138						
SoR	.581	.585	.632	.301	.757	.441	.422	.700	.651	.774	.724	.610	.550	.536					
DiR	.407	.506	.633	.523	.684	.266	.385	.622	.540	.685	.647	.732	.588	.364	.820				
HCh	.237	.078	<i>-.107</i>	<i>-.096</i>	.224	.368	<i>-.130</i>	.379	.263	.092	.238	<i>-.034</i>	<i>-.158</i>	.511	.286	<i>-.015</i>			
Owo	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Aaw	.237	.078	<i>-.107</i>	<i>-.096</i>	.224	.368	<i>-.130</i>	.379	.263	.092	.238	<i>-.034</i>	<i>-.158</i>	.511	.286	<i>-.015</i>	1.00	-	
Sac	.237	.078	<i>-.107</i>	<i>-.096</i>	.224	.368	<i>-.130</i>	.379	.263	.092	.238	<i>-.034</i>	<i>-.158</i>	.511	.286	<i>-.015</i>	1.00	-	1.00

Table 4.10 . Correlations between VAS, CSQ-R and MPI-SCI at 4 months time. *Note.* 7VAS= Intensity of pain 7daysVAS; Unpl= Unpleasant VAS; CSQ-R Factors: Ign=Ignoring pain; Dsta=Distancing; Cop=Coping Self Statements; Pra=Praying; Cat=Catastrophizing; Dstr=Distraction MPI-SCI Factors: Int=Interference; Sup= Support; Sev=Pain Severity; LCo=Life Control; Aff=Affective Distress; NeR=Negative Responses; SoR=Solicitous Responses; DiR=Distracting Responses; HCh=Household Chores; OWo=Outdoor work; AAw=Activities away from home; Sac=Social Activities Bolded correlations are significant at $\alpha = .0001$; Not bolded correlations are significant at $\alpha = .005$ Italic correlations are not significant $\alpha = .005$

	VAS		CSQ-R									MPI-SCI							
	7VAS	Unpl	Ign	Dsta	Cop	Pra	Cat	Dstr	Int	Sup	Sev	LCo	Aff	NeR	SoR	DiR	HCh	OWo	AAw
Unpl	.784																		
Ign	<i>.181</i>	<i>.422</i>																	
Dsta	<i>.357</i>	<i>.102</i>	<i>-.004</i>																
Cop	<i>.482</i>	.746	<i>.579</i>	<i>.174</i>															
Pra	<i>.462</i>	.700	<i>.313</i>	<i>-.046</i>	<i>.648</i>														
Cat	<i>.537</i>	<i>.584</i>	<i>-.084</i>	<i>.135</i>	<i>.387</i>	<i>.489</i>													
Dstr	<i>.125</i>	<i>.279</i>	<i>.372</i>	<i>.335</i>	.694	<i>.312</i>	<i>.230</i>												
Int	.658	<i>.560</i>	<i>.157</i>	<i>.161</i>	<i>.546</i>	<i>.377</i>	<i>.466</i>	<i>.163</i>											
Sup	<i>.432</i>	<i>.437</i>	<i>.412</i>	<i>.305</i>	<i>.602</i>	<i>.253</i>	<i>.326</i>	<i>.296</i>	<i>.557</i>										
Sev	.706	.774	<i>.348</i>	<i>.288</i>	.659	<i>.493</i>	<i>.367</i>	<i>.274</i>	.655	.789									
LCo	<i>.088</i>	<i>.397</i>	<i>.062</i>	<i>.099</i>	<i>.285</i>	<i>.138</i>	<i>.291</i>	<i>.235</i>	<i>.286</i>	<i>.594</i>	<i>.606</i>								
Aff	<i>.427</i>	<i>.415</i>	<i>.107</i>	<i>.378</i>	<i>.391</i>	<i>.325</i>	<i>.457</i>	<i>.392</i>	<i>.467</i>	<i>.484</i>	<i>.579</i>	<i>.371</i>							
NeR	<i>.251</i>	<i>.407</i>	<i>.142</i>	<i>.090</i>	<i>.284</i>	<i>.389</i>	<i>.552</i>	<i>.179</i>	<i>.102</i>	<i>.330</i>	<i>.315</i>	<i>.431</i>	<i>.519</i>						
SoR	<i>.289</i>	<i>.381</i>	<i>.504</i>	<i>.378</i>	<i>.653</i>	<i>.325</i>	<i>.093</i>	<i>.494</i>	<i>.301</i>	.846	.696	<i>.489</i>	<i>.520</i>	<i>.408</i>					
DiR	<i>.392</i>	<i>.401</i>	<i>.420</i>	<i>.579</i>	<i>.536</i>	<i>.419</i>	<i>.246</i>	<i>.385</i>	<i>.278</i>	.784	.712	<i>.456</i>	<i>.538</i>	<i>.530</i>	.899				
HCh	<i>.189</i>	<i>.366</i>	<i>-.140</i>	<i>-.033</i>	<i>.126</i>	<i>.363</i>	<i>.246</i>	<i>-.016</i>	<i>-.038</i>	<i>-.002</i>	<i>.241</i>	<i>.220</i>	<i>.268</i>	<i>.488</i>	<i>.178</i>	<i>.275</i>			
OWo	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
AAw	<i>.046</i>	<i>.282</i>	<i>-.022</i>	<i>-.094</i>	<i>.041</i>	<i>.237</i>	<i>.296</i>	<i>-.125</i>	<i>-.160</i>	<i>.033</i>	<i>.072</i>	<i>.227</i>	<i>.128</i>	.657	<i>.151</i>	<i>.266</i>	.865	-	
SAc	<i>.205</i>	<i>.370</i>	<i>-.154</i>	<i>-.024</i>	<i>.136</i>	<i>.373</i>	<i>.234</i>	<i>.000</i>	<i>-.020</i>	<i>-.006</i>	<i>.259</i>	<i>.207</i>	<i>.281</i>	<i>.454</i>	<i>.178</i>	<i>.270</i>	.998	-	.828

Table 4.11 . Correlations between VAS, CSQ-R and MPI-SCI at 6 months time. *Note.* 7VAS= Intensity of pain 7daysVAS; Unpl= Unpleasant VAS; CSQ-R Factors: Ign=Ignoring pain; Dsta=Distancing; Cop=Coping Self Statements; Pra=Praying; Cat=Catastrophizing; Dstr=Distraction MPI-SCI Factors: Int=Interference; Sup= Support; Sev=Pain Severity; LCo=Life Control; Aff=Affective Distress; NeR=Negative Responses; SoR=Solicitous Responses; DiR=Distracting Responses; HCh=Household Chores; OWo=Outdoor work; AAw=Activities away from home; Sac=Social Activities Bolded correlations are significant at $\alpha = .0001$; Not bolded correlations are significant at $\alpha = .005$ Italic correlations are not significant $\alpha = .005$

	VAS		CSQ										MPI-SCI						
	7VAS	Unpl	Ign	Dsta	Cop	Pra	Cat	Dstr	Int	Sup	Sev	LCo	Aff	NeR	SoR	DiR	HCh	OWo	AAw
Unpl	.863																		
Ign	.203	.476																	
Dsta	.200	.353	.773																
Cop	.463	.667	.617	.363															
Para	.665	.468	.020	.260	.289														
Cat	.636	.707	.447	.444	.508	.573													
Dstr	.477	.507	.601	.536	.641	.504	.613												
Int	.743	.665	.206	.331	.357	.641	.659	.558											
Sup	.512	.634	.462	.277	.528	.465	.562	.522	.551										
Sev	.854	.899	.313	.241	.624	.647	.718	.470	.741	.641									
Lco	.123	.299	.253	<i>-.044</i>	.341	<i>-.140</i>	.184	.113	<i>-.059</i>	<i>-.076</i>	.190								
Aff	.556	.596	.126	.428	.253	.599	.516	.171	.580	.550	.655	<i>-.292</i>							
NeR	.645	.473	.109	.170	.005	.370	.265	.137	.378	.278	.500	.186	.358						
SoR	.346	.503	.458	.255	.494	.237	.225	.406	.288	.544	.285	.055	.282	.068					
DiR	.541	.578	.505	.270	.588	.355	.549	.731	.451	.580	.427	.131	.146	.189	.793				
HCh	.071	<i>-.015</i>	.098	<i>-.089</i>	<i>-.020</i>	<i>-.012</i>	<i>-.338</i>	.058	.066	.355	.042	.079	<i>-.071</i>	.332	.066	<i>-.073</i>			
Owo	<i>-.088</i>	<i>-.032</i>	.385	.271	.195	.010	<i>-.022</i>	.288	<i>-.041</i>	<i>-.177</i>	<i>-.143</i>	.571	<i>-.373</i>	<i>-.049</i>	.381	.339	.044		
Aaw	.172	.268	.587	.319	.351	.101	.129	.385	.100	.412	.072	.398	<i>-.132</i>	.169	.718	.633	.337	.721	
Sac	.158	.035	.434	.190	.225	.042	<i>-.102</i>	.245	<i>-.092</i>	.106	<i>-.024</i>	.369	<i>-.331</i>	.317	.344	.389	.443	.676	.799

Table 4.12 . Correlations between VAS, CSQ-R and MPI-SCI at 12 months time. *Note*. 7VAS= Intensity of pain 7daysVAS; Unpl= Unpleasant VAS; CSQ-R Factors: Ign=Ignoring pain; Dsta=Distancing; Cop=Coping Self Statements; Pra=Praying; Cat=Catastrophizing; Dstr=Distraction MPI-SCI Factors: Int=Interference; Sup= Support; Sev=Pain Severity; LCo=Life Control; Aff=Affective Distress; NeR=Negative Responses; SoR=Solicitous Responses; DiR=Distracting Responses; HCh=Household Chores; OWo=Outdoor work; AAw=Activities away from home; Sac=Social Activities Bolded correlations are significant at $\alpha = .0001$; Not bolded correlations are significant at $\alpha = .005$ Italic correlations are not significant $\alpha = .005$

4.4.4. 7 day VAS and Unpleasant VAS Correlations

High significant positive correlations were obtained (Spearman Rho) between 7 day VAS and Unpleasantness VAS and all the other CSQ-R and MPI-SCI factors, (these ranged from $0.625 < r < 0.868$; $p=0.0001$) and both questionnaires at 2 months after injury ($0.603 < r < 0.924$; $p=0.0001$). Solicitous Responses and Distracting Responses seem more correlated with the Unpleasant measure of VAS ($r = 0.745$ and $r = 0.676$ respectively; $p=0.0001$) but Negative Responses are better correlated with 7 day VAS ($r = 0.613$; $p=0.0001$).

Pain Severity is the MPI factor that is highly correlated throughout all the measures (2, 3, 4, 6 and 12 months after SCI) either with 7 day VAS and Unpleasantness VAS, meaning that it can be considered as the same variable. But in month 3 after the spinal lesion, just Praying and Coping CSQ-R factors are highly correlated with intensity of pain ($r= 0.690$ in 7 day VAS and $r = 0.756$ in Unpleasantness VAS; $p=0.0001$). In the following months tested, all the high correlations between Pain Intensity and the questionnaires disappear except MPI-SCI Pain Severity ($r = 0.704$ and 0.768). Similar in month 6 after SCI, there are now high correlations with Unpleasantness VAS and Coping Self Statements and Praying ($r = 0.746$ and 0.700 ; $p=0.0001$) and MPI-SCI Interference ($r = 0.658$; $p=0.0001$). In the last assessment at 12 months the correlations are same as those at 4 months time.

4.4.5. CSQ-R Factors Correlations

At 2 months after SCI, most of the CSQ-R factors are highly correlated between them and also with MPI-SCI factors, for example Ignoring Pain with Distancing ($r = 0.827$), and Coping ($r = 0.767$), Praying ($r = 0.679$) and Distracting ($r = 0.751$). At 3 months Coping Self Statements is positively correlated with Ignoring pain, Praying and Distraction ($r = 0.674$, 0.618 and 0.617), Distraction with Distancing ($r = 0.667$) and Severity with Praying ($r = 0.625$). Coping Self Statements is also correlated with all of the MPI-SCI factors (but Negative Responses). At 4 months Distraction is positively correlated with Ignoring pain ($r = 0.642$) whilst Coping Self Statements correlates with Solicitous Responses ($r = 0.757$) and Distracting Responses ($r = 0.684$). At 6 months the only CSQ-R strategies highly correlated are Coping Self Statements and Distraction ($r = 0.694$). Coping Self Statements is also correlated with MPI-SCI factor Severity ($r = 0.659$). At 12 months the only CSQ-R strategies highly correlated are Ignoring pain and Distancing ($r = 0.773$).

4.4.6. MPI-SCI Factors Correlations

The MPI-SCI factors are also very highly correlated during the 2 month measure, disappearing along the months.

From 2 to 6 months time Solicitous Responses and Support ($r = 0.846$ at month 6) are good correlated; as well as Distracting Responses and Support ($r = 0.784$ at month 6); Severity and Support ($r = 0.789$ at month 6); Solicitous Responses and Severity ($r = 0.696$ at month 6); Distracting Responses and Severity ($r = 0.712$ at month 6) and Solicitous Responses and Distraction ($r = 0.899$ at month 6). At 4 and 6 months time patients begin to do some Household Chores and is perfectly correlated with Activities away from home ($r = 1.00$) and Social Activities ($r = 1.00$) at 4 months rather than at 6 months ($r = 0.865$ and 0.998 respectively). Negative Responses is positive correlated with Activities away from home only at 6 months time ($r = 0.828$), coinciding with the return of the patient to home.

4.4.7. Differences in the use of Cognitive Strategies

4.4.7.1. CSQ-R

Repeated Measures ANOVA (Greenhouse-Geisser test) was used for each factor of the questionnaire. There were no differences between the temporal moments in 5 of the factors (n=6): Ignoring pain (F(2.655, 29.207) = 1.152; p=0.341) (Fig 4.3); Distancing (F(1.606, 25.317)= 1.435; ; p=0.261) (Fig 4.4); Praying (F(2.367, 26.042) = 2.135; p=0.131) (Fig 4.5); Catastrophizing (F(2.471, 27.177) = 1.487; p=0.243) (Fig 4.6) ; Distraction (F(2.621, 28.830) = 1.056; p=0.376) (Fig 4.7).

Only Coping Self Statements factor was statistically significant (within-subjects) (F (2.302, 25.317) = 4.027; p=0.026) (Fig 4.8) and applying the post-hoc Tukey's honestly significant difference test, the difference between 2 month measure and the rest was significant (F(4,8) = 9.110; p=0.004). The descriptive data shows a general trend with an increase in all the factors in successive temporal measures, either they are positive (Ignoring pain, Distancing, Praying, Distraction, Coping Self Statements) or negative (Catastrophizing).

So that we can observe that patients do not use cognitive strategies at 2 months time, (values close to 0). However, at 12 months time we can observe an increase in their use (generally is the highest point score), though they keep on showing low scores in Ignoring pain (here the maximum is 4 compared with the maximum possible score =19.64), Distancing (here the maximum is 1.3 compared with the maximum possible score =16.53), Praying (here the maximum is 1.5 compared with the maximum possible score =12.56)and Distraction (here the maximum is 8 compared with the maximum possible score =20.74).One strategy very used to cope with pain is coping self statements (here the maximum is 9.5 with the maximum possible score =15.48). Catastrophizing is shown with a low presence (here the maximum is 5.8 with the maximum possible score =23.70).

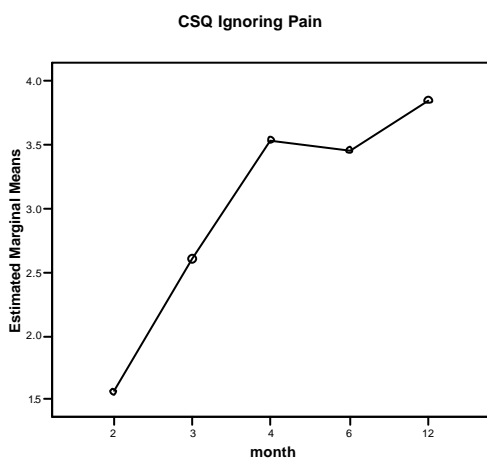


Fig 4.3. Scores for the factor Ignoring Pain

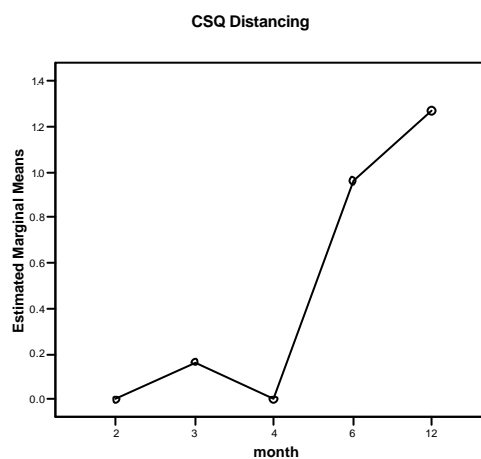


Fig 4.4. Scores for the factor Distancing

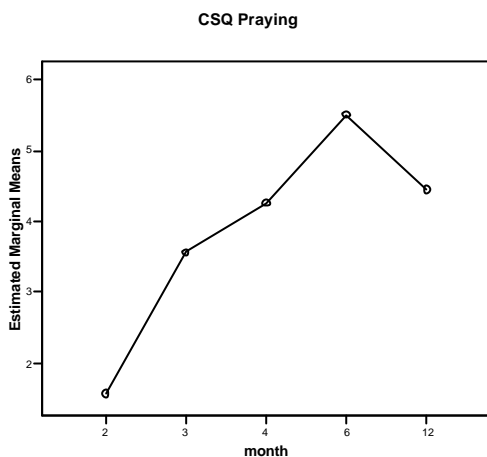


Fig 4.5. Scores for the factor Praying

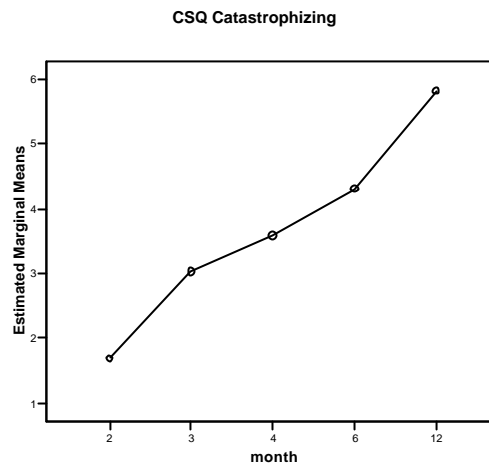


Fig 4.6. Scores for the factor Catastrophizing

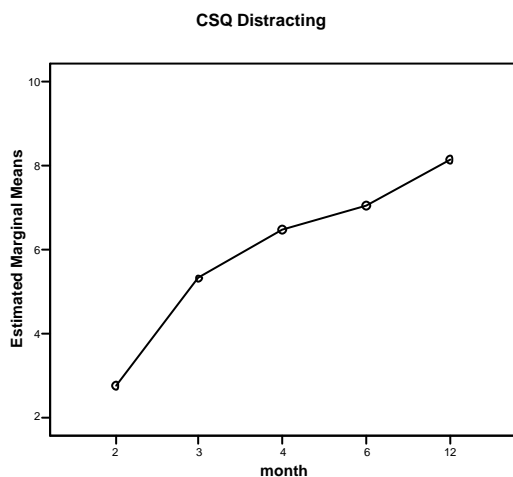


Fig 4.7. Scores for the factor Distracting

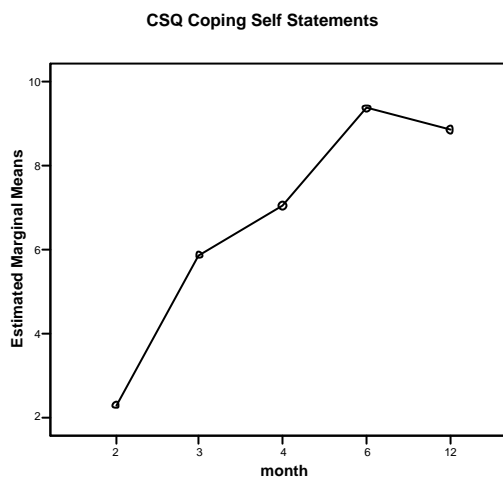


Fig 4.8. Scores for the factor Coping Self Statements

4.4.7.2. MPI-SCI

We used a Repeated Measures ANOVA (Greenhouse-Geisser or Sphericity assumed test if appropriate) for each factor of the questionnaire and we found differences between the temporal moments in 9 of the factors (n= 15): Interference (F (4, 34.496) = 3.578; p=0.031) (**Fig 4.9**); Support (F (3.017, 42.232) = 5.573; p=0.003) (**Fig 4.10**); Pain Severity (F (4, 46.223) = 3.144; p=0.030) (**Fig 4.11**); Life Control (F (4, 38.311) = 4.258; p=0.013) (**Fig 4.12**); Affective Distress (F (4, 40.121) = 5.033; p=0.005) (**Fig 4.13**); Solicitous Responses (F (4, 45.016) = 4.241; p=0.009) (**Fig 4.15**); Household Chores (F (4, 25.784) = 4.641; p=0.019) (**Fig 4.17**); Activities away from home (F (4, 16.477) = 19.726; p=0.000) (**Fig 4.19**); Social Activities (F (4, 21.844) = 9.162; p=0.002) (**Fig 4.20**). But there was no significant difference between the factors: Negative Responses (F (4, 38.690) = 0.742; p=0.524) (**Fig 4.14**); Distracting Responses (F (4, 38.198) = 1.915; p=0.148) (**Fig 4.16**) and Outdoor work (F (4, 14.000) = 2.059; p=0.173) (**Fig 4.18**).

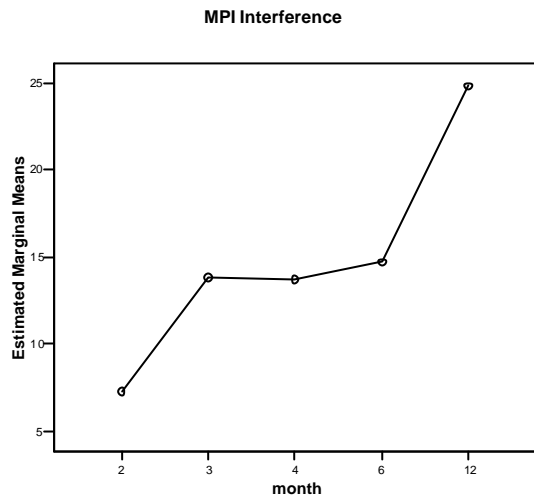


Fig 4.9. Scores for the factor Interference

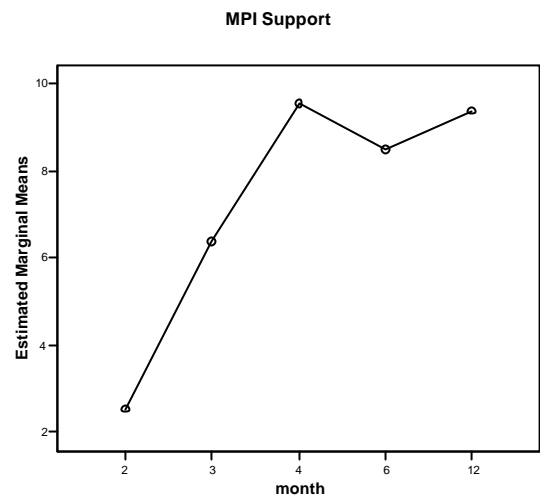


Fig 4.10. Scores for the factor Support

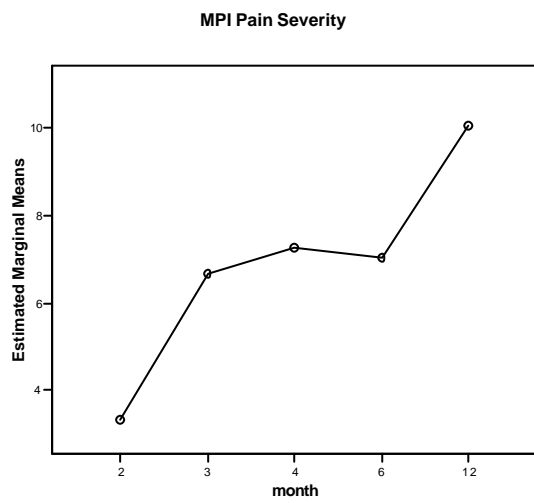


Fig 4.11. Scores for the factor Pain Severity

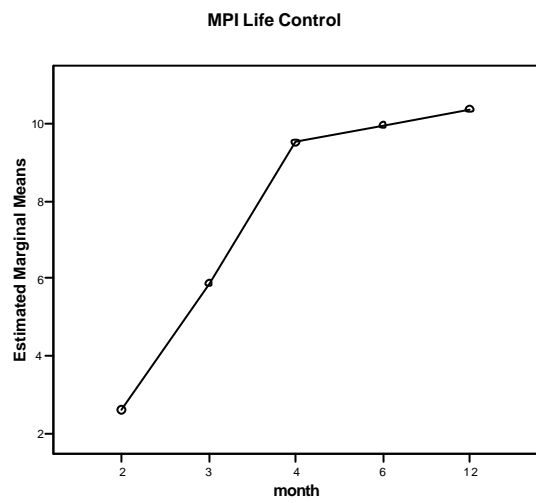


Fig 4.12. Scores for the factor Life Control

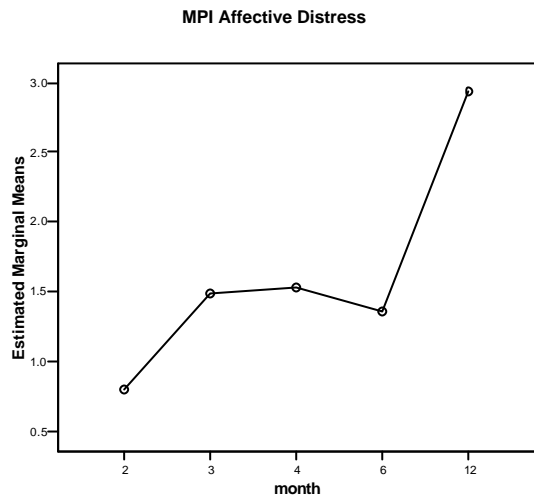


Fig 4.13. Scores for the factor Affective Distress

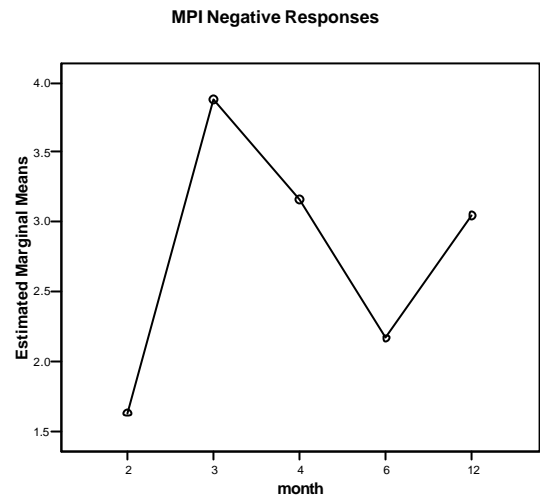


Fig 4.14. Scores for the factor Negative Responses

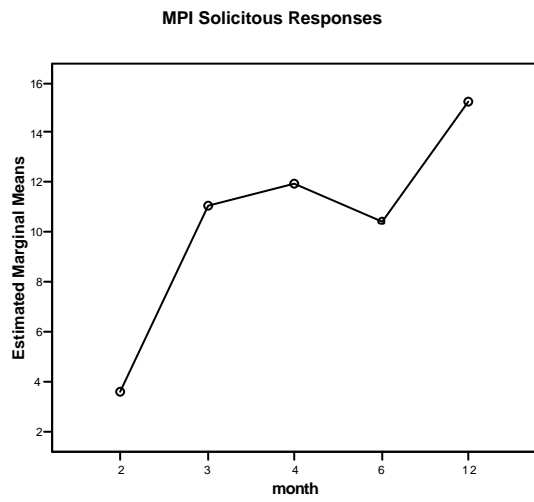


Fig 4.15. Scores for the factor Solicitous Responses

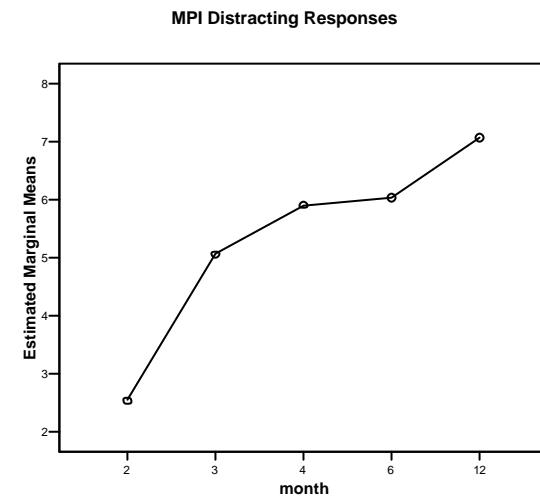


Fig 4.16. Scores for the factor Distracting Responses

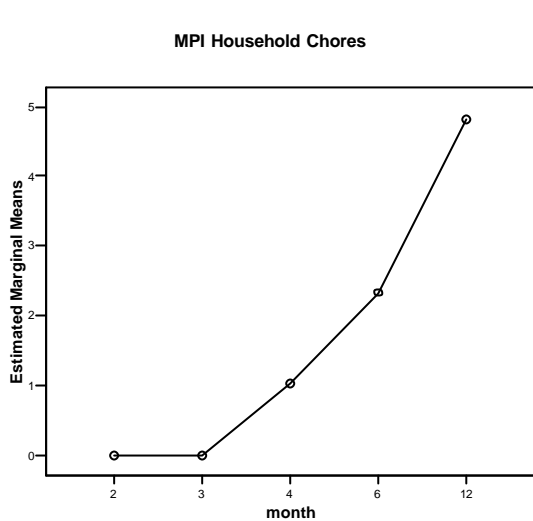


Fig 4.17. Scores for the factor Household Chores

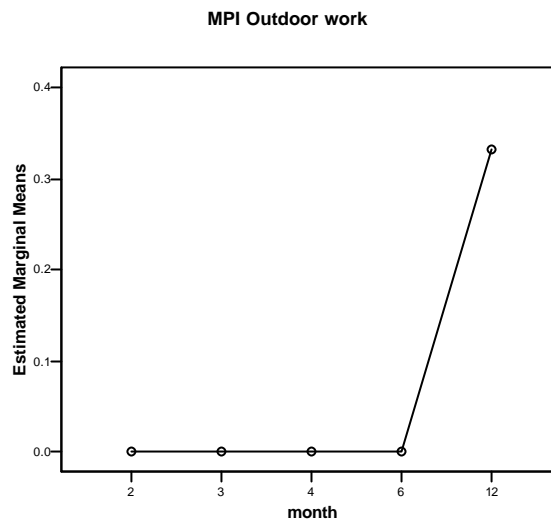


Fig 4.18. Scores for the factor Outdoor work

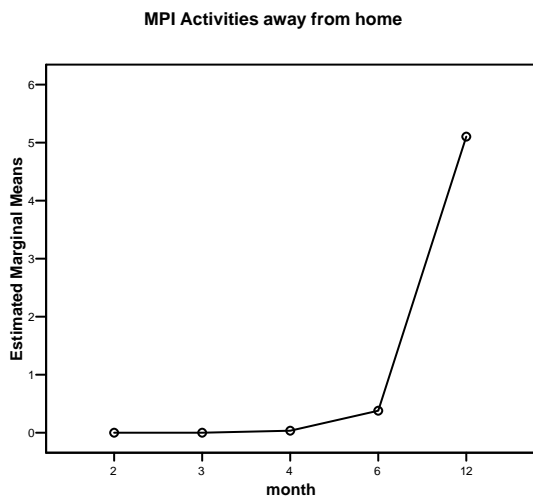


Fig 4.19. Scores for the factor Activities away from home

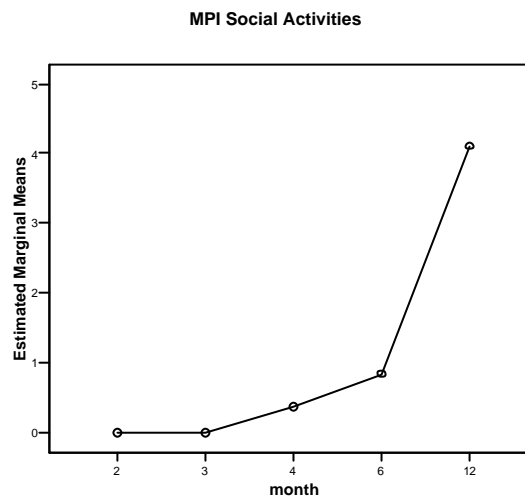


Fig 4.20. Scores for the factor Social Activities

4.4.7.3. Differences between groups.

The whole group of N=30 subjects was divided in two groups according to the aetiology, resulting in traumatic (n=6); atraumatic group (n=6) for the CSQ-R; and traumatic (n=8) and atraumatic group (n=7) for the MPI-SCI analysis.

It also was done according to the level of the spinal cord lesion, resulting in cervical (n=6) and thoracic group (n=9) for the analysis of the CSQ-R; and cervical (n=6) and thoracic group (n=9) for the MPI-SCI except for Household Chores factor (cervical group n=5, thoracic group n=9).

4.4.7.3.1. Cervical and Thoracic

4.4.7.3.1.1. CSQ-R

Repeated Measures ANOVA (Greenhouse-Geisser test) was performed for each factor of the questionnaire and found no differences between the temporal moments in 5 of the factors: Ignoring pain ($F(2.490, 24.901) = 0.987; p=0.403$) (**Fig 4.21**) ; Distancing ($F(1.751, 17.508) = 2.063; p=0.161$) (**Fig 4.22**) ; Coping Self Statements (statistically significant within-subjects) ($F(2.015, 20.153) = 3.685; p=0.043$) (**Fig 4.23**), shows a trend of being more used by patients with cervical injuries; meanwhile Praying ($F(2.649, 26.488) = 1.796; p=0.177$) (**Fig 4.24**) ; Catastrophizing ($F(2.388, 23.881) = 1.225; p=0.317$) (**Fig 4.25**) and Distraction ($F(2.526, 25.265) = 0.751; p=0.511$) (**Fig 4.26**) are more observed in the thoracic group.

The observed power that should be achieved by using different numbers of participants is not very high in general (see **Tables Appendix 4.2**) due to the lack of patients overall the measures in time. (Note: EMM= Estimated Marginal Means).

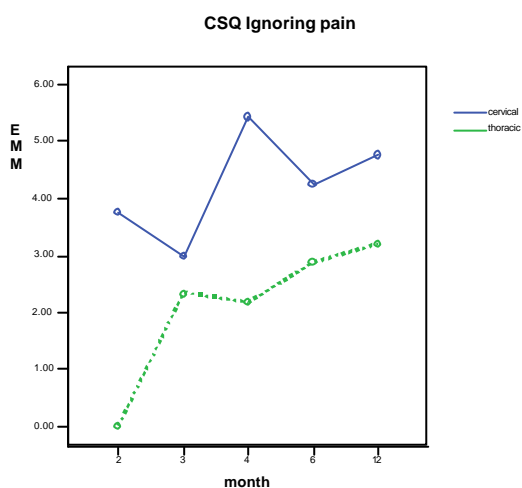


Fig 4.21. Scores for the factor Ignoring pain

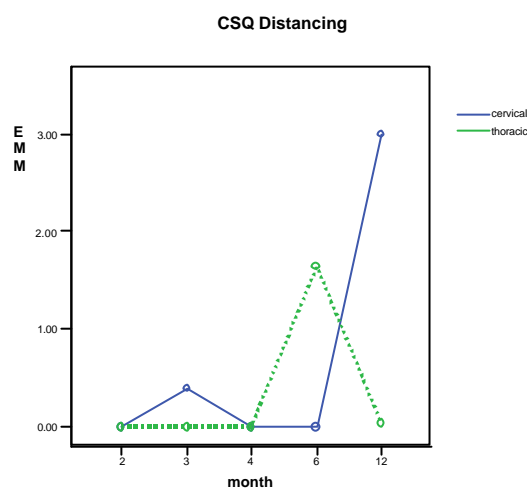


Fig 4.22. Scores for the factor Distancing

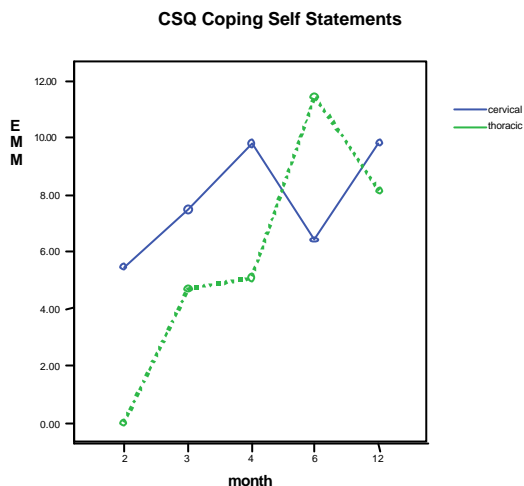


Fig 4.23. Scores for the factor Coping Self Statements

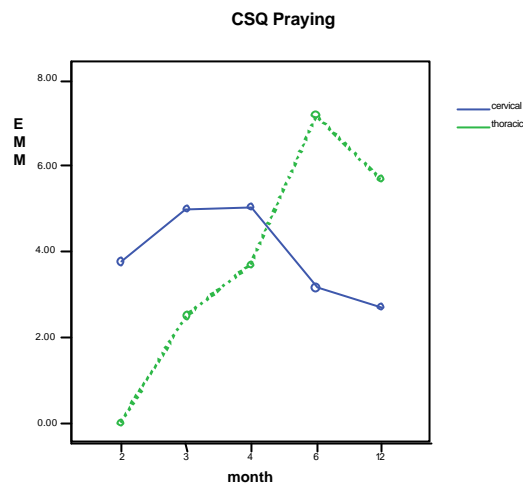


Fig 4.24. Scores for the factor Praying

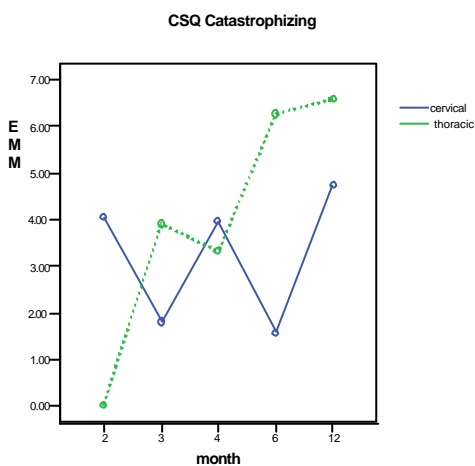


Fig 4.25. Scores for the factor Catastrophizing

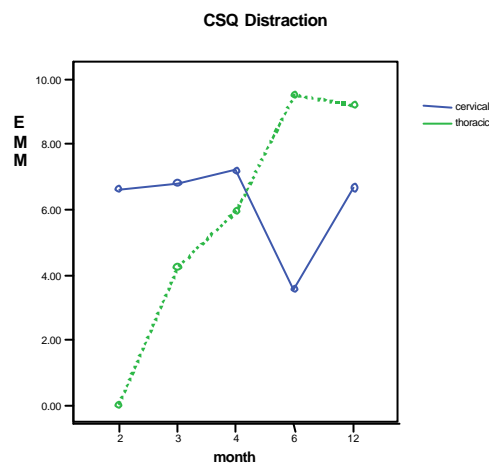


Fig 4.26. Scores for the factor Distraction

4.4.7.3.1.2. MPI-SCI

Repeated Measures ANOVA (Greenhouse-Geisser or Sphericity assumed test as appropriate) was used for each factor of the questionnaire and differences were found between the temporal moments in 7 of the factors.

Interference ($F(2.606, 33.876) = 3.066; p=0.047$) (**Fig 4.27**); and Support ($F(3.004, 39.046) = 4.625; p=0.007$) (**Fig 4.28**); are statistically significant and more present in patients with thoracic injuries and from month 4 in Support.

Life Control ($F(2.794, 36.320) = 3.551; p=0.026$) (**Fig 4.30**) shows significant levels of control from month 4 in the thoracic group of patients.

Affective Distress ($F(3.157, 41.042) = 5.372; p=0.003$) (**Fig 4.31**) shows a more constant distress in thoracic patients but at 12 month time looks the same increased distress.

Solicitous Responses ($F(3.189, 41.459) = 3.589; p=0.020$) (**Fig 4.33**) shows a significant and progressive increase in the responses given to the thoracic group.

Activities away from home ($F(1.188, 15.442) = 17.465; p=0.0001$) (**Fig 4.37**) and Social Activities ($F(1.574, 20.468) = 7.706; p=0.005$) (**Fig 4.38**) shows a significant and progressive increase in these kind of activities from month 4 and 3 respectively for the thoracic group whereas the cervical group starts at month 6.

But there was no significant difference between the factors: Pain Severity ($F(3.189, 41.462) = 2.446; p=0.074$) (**Fig 4.29**) with a trend to have more in Thoracic group ; Negative Responses ($F(4, 52) = 0.698; p=0.597$) (**Fig 4.32**) ; Distracting Responses ($F(2.698, 35.070) = 1.493; p=0.235$) (**Fig 4.34**) shows a trend to be higher in the thoracic group; Household Chores ($F(2.101, 25.213) = 3.177; p=0.057$) (**Fig 4.35**) shows an earlier significant start at month 3 for the thoracic group whereas the cervical one does at month 6 ; and Outdoor work ($F(1.000, 13.000) = 1.413; p=0.256$) (**Fig 4.36**) shows a trend for starting at month 6 by the thoracic group (when they come back home from hospital) but the cervical group does not seem to develop any work at all.

The observed power that should be achieved by using different numbers of participants is acceptable in general and is high for some of the factors (see **Tables Appendix 4.3**).

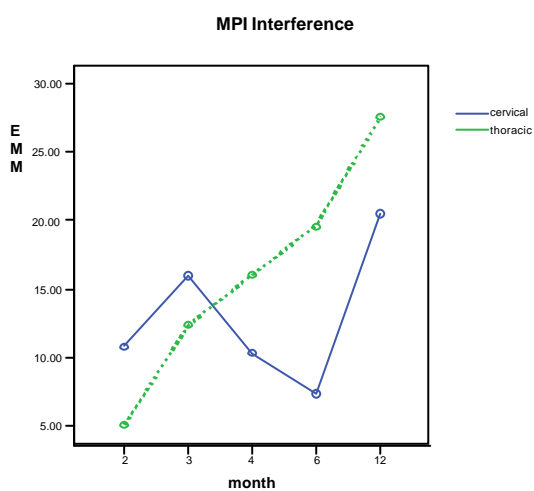


Fig 4.27. Scores for the factor Interference

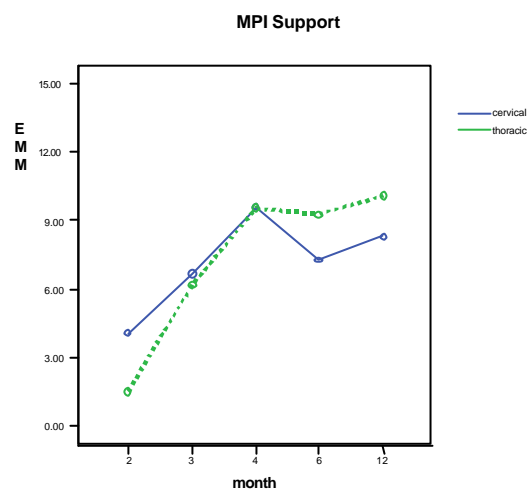


Fig 4.28. Scores for the factor Support

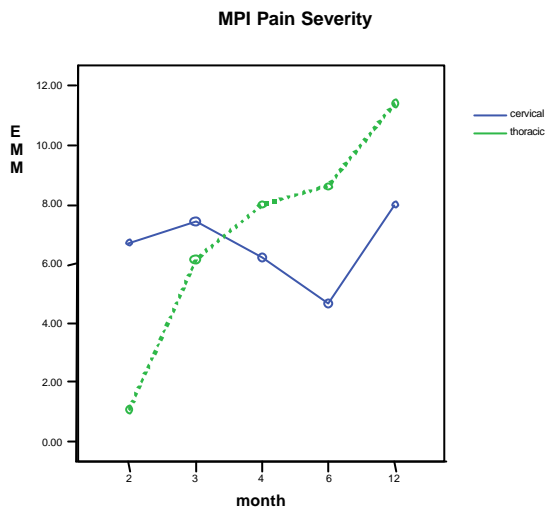


Fig 4.29. Scores for the factor Pain Severity

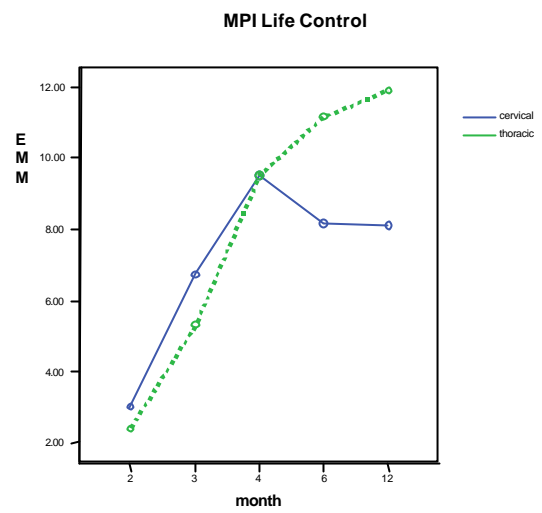


Fig 4.30. Scores for the factor Life Control

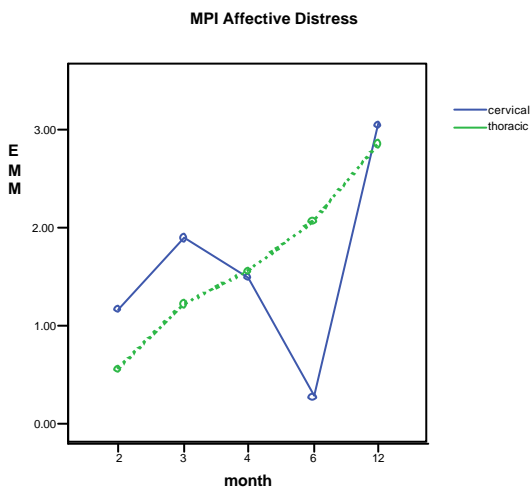


Fig 4.31. Scores for the factor Affective Distress

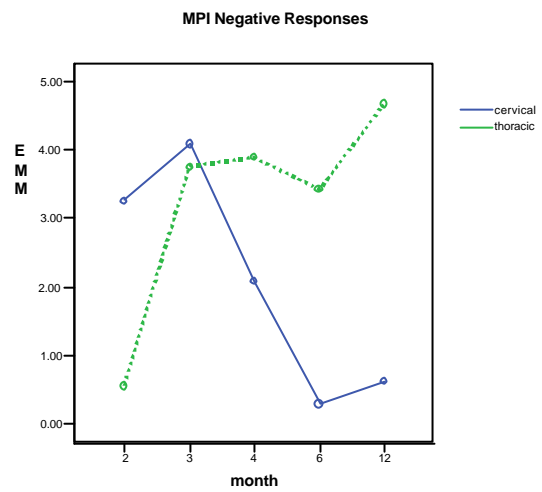


Fig 4.32. Scores for the factor Negative Responses

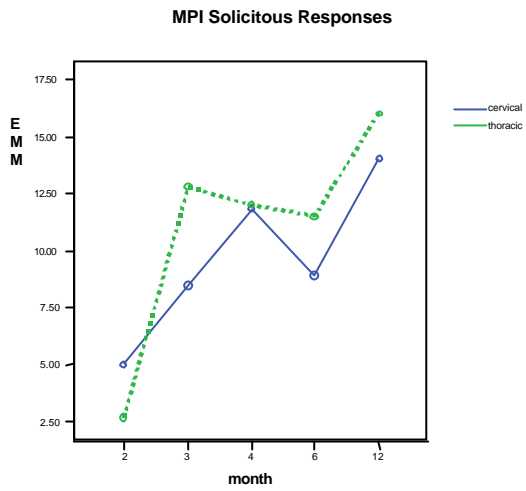


Fig 4.33. Scores for the factor Solicitous Responses

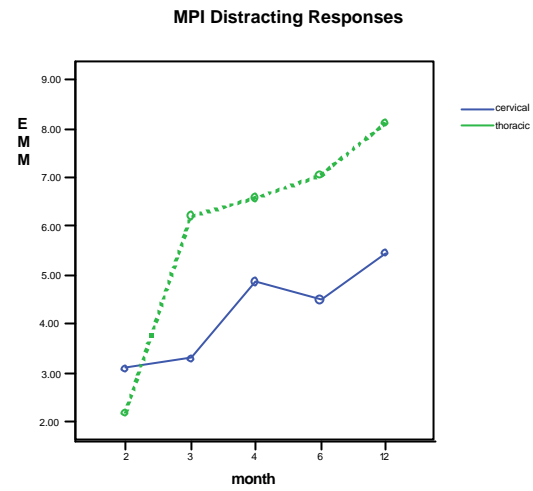


Fig 4.34. Scores for the factor Distracting Responses

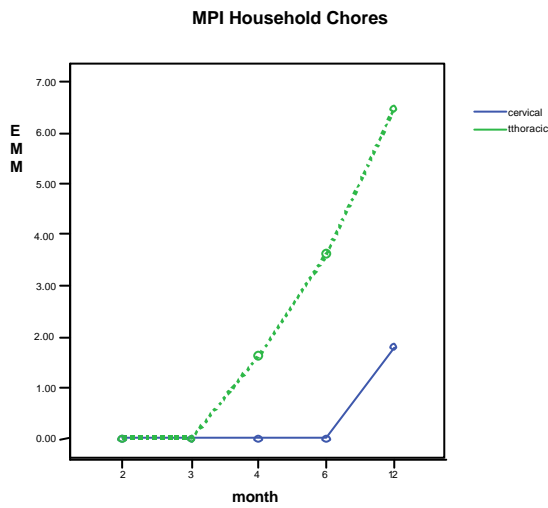


Fig 4.35. Scores for the factor Household Chores

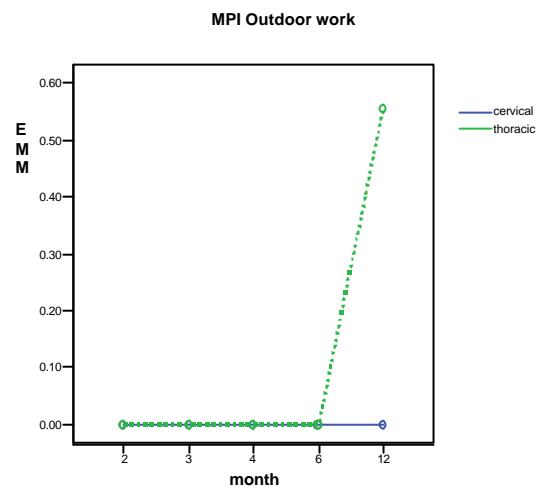


Fig 4.36. Scores for the factor Outdoor work

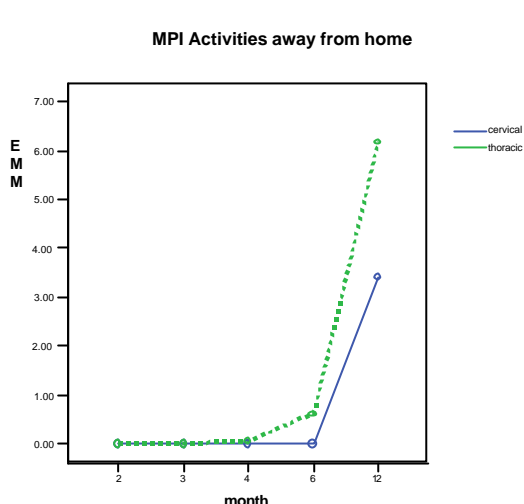


Fig 4.37. Scores for the factor Activities away from home

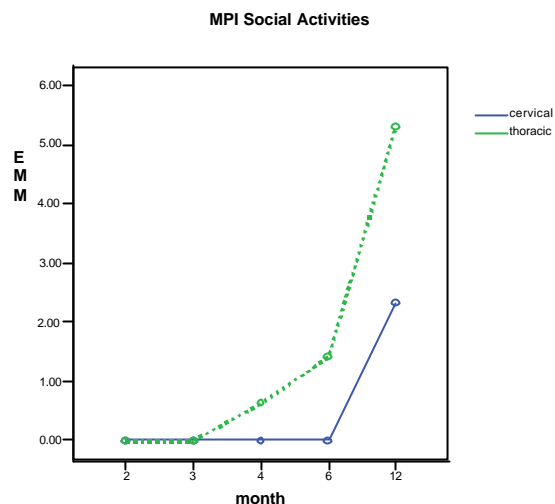


Fig 4.38. Scores for the factor Social Activities

4.4.7.3.2. Traumatic and Atraumatic Injury

4.4.7.3.2.1. CSQ-R

We used a Repeated Measures ANOVA with the Greenhouse-Geisser test for each factor of the questionnaire and we did not find differences between the temporal moments in 5 of the factors.

Ignoring pain ($F(2.617, 26.167) = 1.085; p = 0.367$) (Fig 4.39) and Distancing ($F(1.519, 15.192) = 1.481; p = 0.254$) (Fig 4.40) show a trend of being more used by patients with traumatic injuries; Praying ($F(2.274, 22.741) = 2.171; p = 0.132$) (Fig 4.41) shows a changing trend of being more used by patients with atraumatic injuries in the first months but not in month 12; Catastrophizing ($F(2.461, 24.610) = 1.423; p = 0.261$) (Fig 4.42) shows a trend of being more present in patients with traumatic injuries; Distraction ($F(2.706, 27.056) = 1.115; p = 0.356$) (Fig 4.43) shows a trend of being more used by patients with traumatic injuries from month 6.

Only Coping Self Statements factor was statistically significant (within-subjects) ($F(2.236, 22.363) = 4.122; p = 0.026$) (Fig 4.44) and shows a change in being more used by patients with atraumatic injuries in the first months but not in month 12.

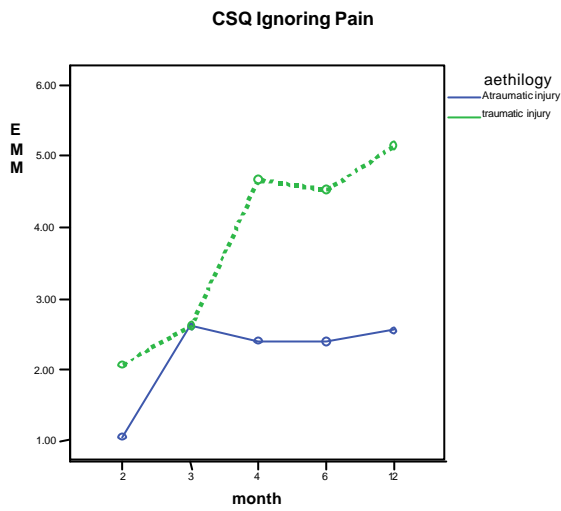


Fig 4.39. Scores for the factor Ignoring pain

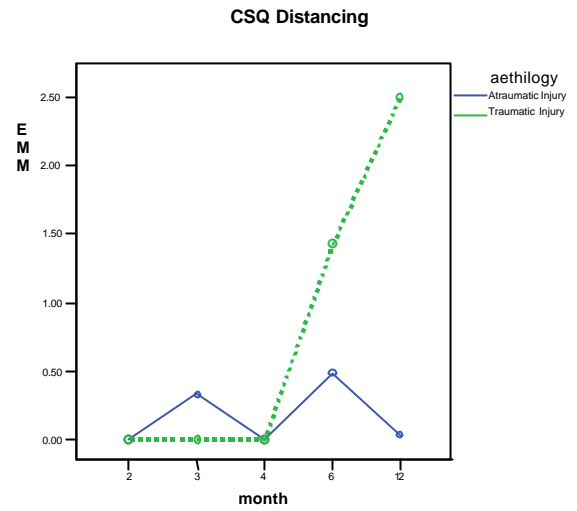


Fig 4.40. Scores for the factor Distancing

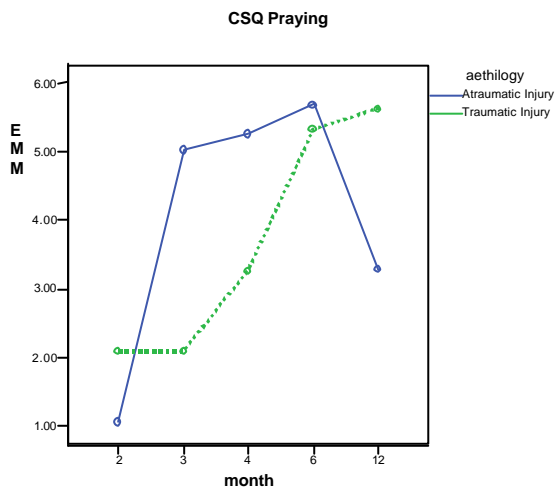


Fig 4.41. Scores for the factor Praying

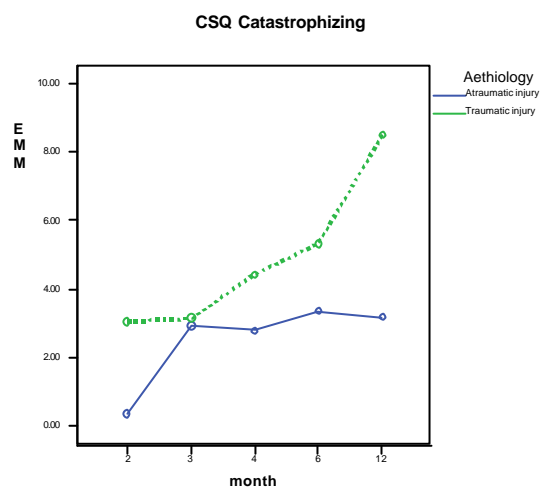


Fig 4.42. Scores for the factor Catastrophizing

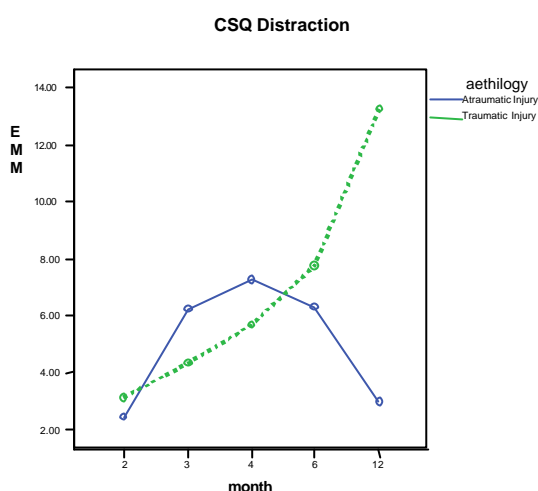


Fig 4.43. Scores for the factor Distraction

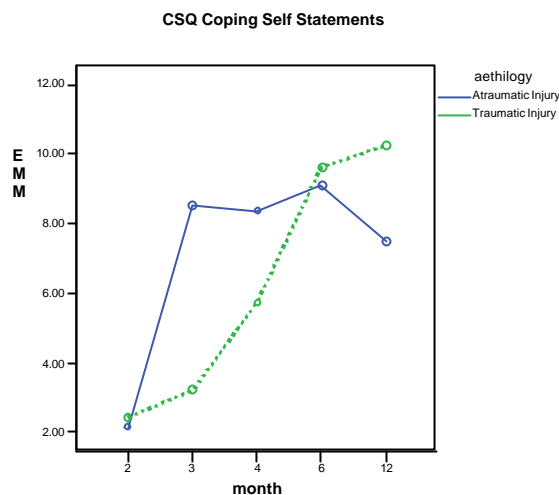


Fig 4.44. Scores for the factor Coping Self Statements

4.4.7.3.2.2. MPI-SCI

Repeated Measures ANOVA (Greenhouse-Geisser or Sphericity assumed test as appropriate) was used for each factor of the questionnaire and differences were found between the temporal moments in 9 of the factors.

Interference (F (4, 52) = 3.661; p=0.011) (**Fig 4.45**); Support (F (2.673, 34.749) = 6.278; p=0.002) (**Fig 4.46**); and Pain Severity (F (3.124, 40.610) = 3.366; p=0.026) (**Fig 4.47**) are statistically significant and more present in patients with traumatic injuries from month 4.

Life Control (F (4, 38.311) = 4.258; p=0.013) (**Fig 4.48**) shows significant levels at month 4 and 6 in traumatic patients, but there is no difference with the atraumatic group at 12 months time

Affective Distress (F (4, 52) = 5.059; p=0.002) (**Fig 4.49**) shows a fluctuation between the groups but at 12 month time looks the same increased distress.

Solicitous Responses (F (4, 52) = 4.622; p=0.007) (**Fig 4.51**) show a significant and progressive increase in the responses given to the traumatic group whereas the atraumatic presents more responses at month 3 and decreases after that.

Household Chores (F (2.019, 24.222) = 5.210; p=0.013) (**Fig 4.53**) show an earlier significant start at month 3 for the atraumatic group whereas the traumatic one does at month 6.

Activities away from home (F (1.161, 1.161) = 18.383; p=0.0001) (**Fig 4.55**) and Social Activities (F (1.491, 19.386) = 8.876; p=0.004) (**Fig 4.56**) show a significant and progressive increase in these kind of activities since earlier months for the atraumatic group, but then the traumatic gets more scores at 12 months.

But there was no significant difference between the factors: Negative Responses (F (4, 52) = 0.797; p=0.553) (**Fig 4.50**) ; Distracting Responses (F(4, 52) = 0.130; p=0.148) (**Fig 4.52**) and Outdoor work (F (1.000, 13.000) = 1.920; p=0.189) (**Fig 4.54**) show a trend for starting at month 6 by the traumatic but the atraumatic group does not seem to develop any work.

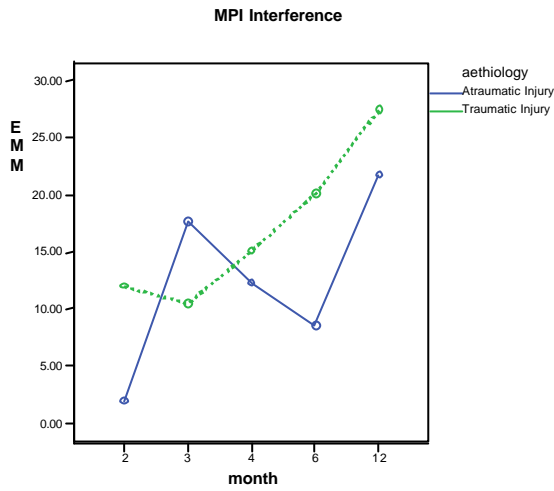


Fig 4.45. Scores for the factor Interference

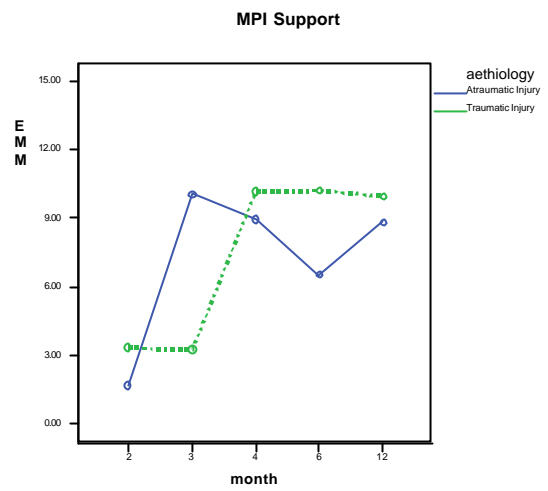


Fig 4.46. Scores for the factor Support

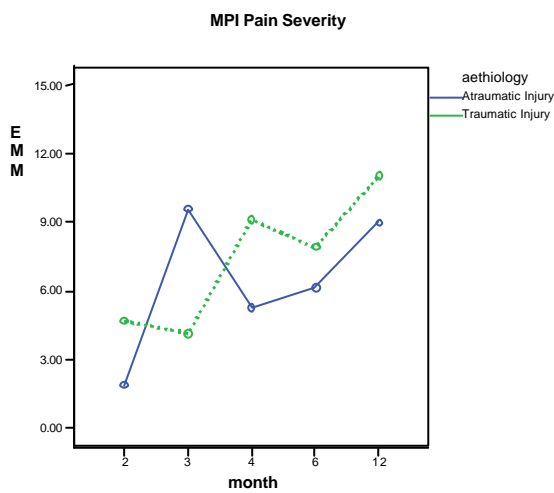


Fig 4.47. Scores for the factor Pain Severity

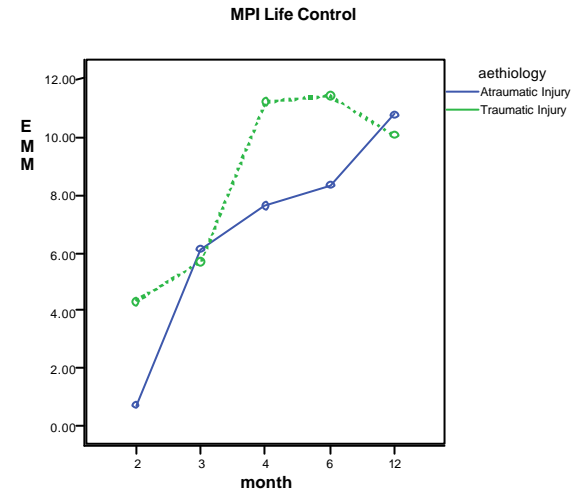


Fig 4.48. Scores for the factor Life Control

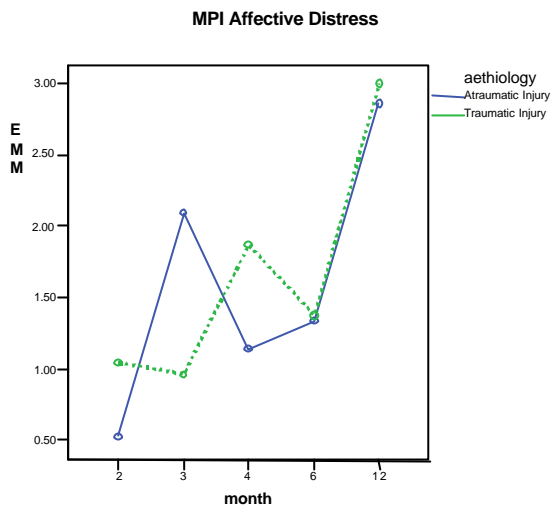


Fig 4.49. Scores for the factor Affective Distress

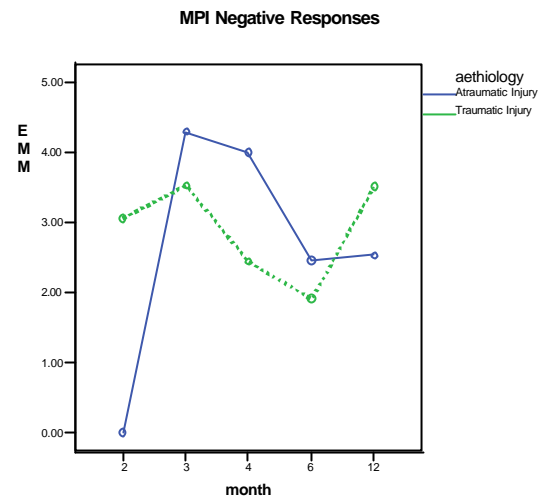


Fig 4.50. Scores for the factor Negative Responses

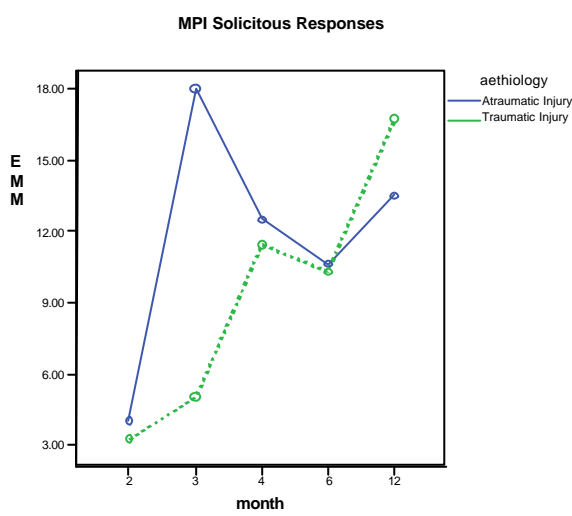


Fig 4.51. Scores for the factor Solicitous Responses

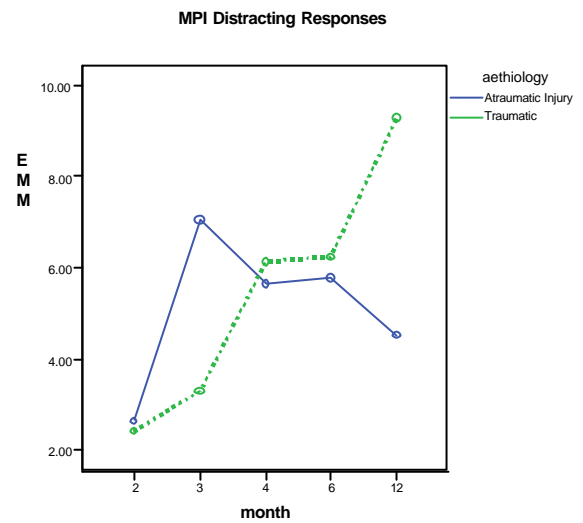


Fig 4.52. Scores for the factor Distracting Responses

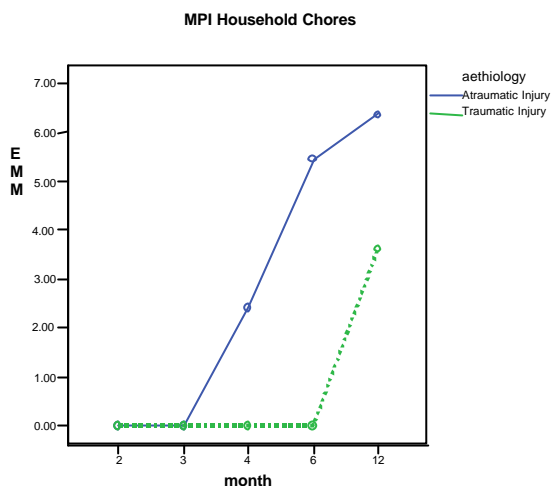


Fig 4.53. Scores for the factor Household Chores

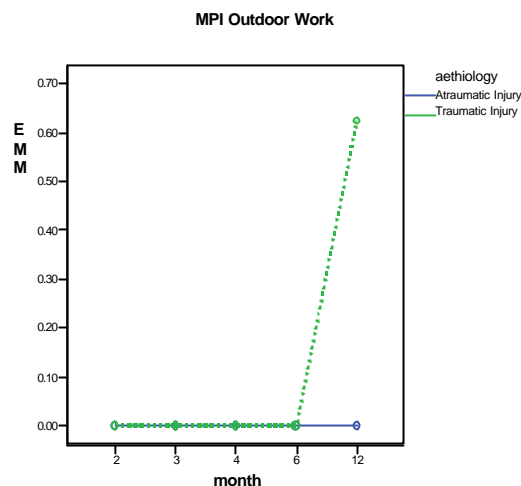


Fig 4.54. Scores for the factor Outdoor Work

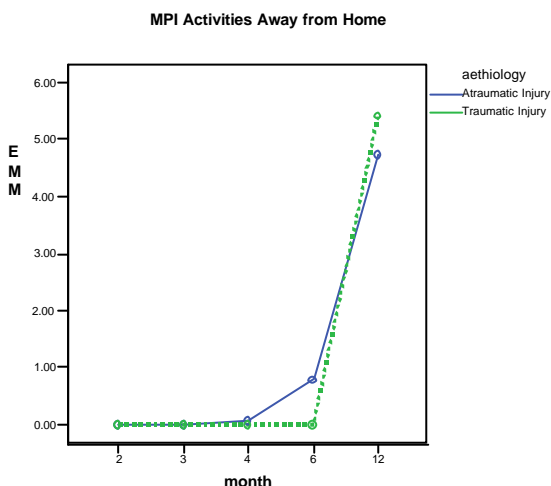


Fig 4.55. Scores for the factor Activities away from home

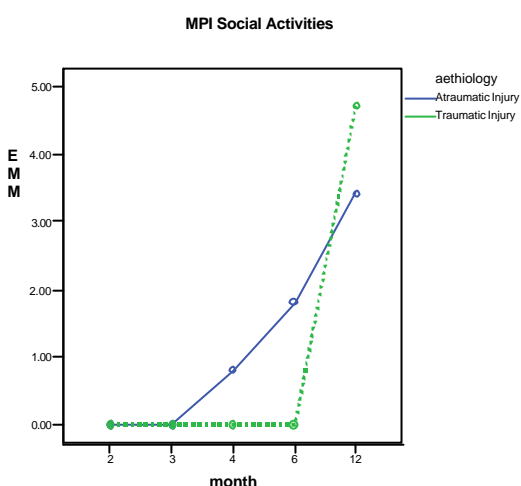


Fig 4.56. Scores for the factor Social Activities

4.5. Discussion

This is the first study to describe changes in *spontaneous ongoing* pain intensity and unpleasantness using a 7 day reported VAS scale, combined with cognitive-behavioural scales of quality of life (CSQ-R and MPI-SCI) during the acute and chronic phase of SCI in a selected neuropathic pain patient group. The results indicated that both pain intensity and unpleasantness increase, but with the latter developing at a later stage and at a higher intensity between 3 and 6 months after SCI. Although CSQ-R is a standard QoL scale previously used in SCI population scale, showed that alone is inadequate for the assessing of a physical functioning measure of adjustment such as disability, which may be complemented by the MPI-SCI. Importantly, the MPI-SCI scale includes important correlations with both pain intensity and unpleasantness after SCI; as such its use may be very useful as an instrument to evaluate the impact of pain in people and their significant others with SCI.

4.5.1. Utilization of Cognitive Strategies Against Pain

This study indicates that SCI patients use cognitive strategies like active pain Coping self statements (CSQ-R) and request Support and Solicitous Responses (MPI-SCI) during the first 12 months after injury; at 2 months the factors are close to zero with a slight increase in Ignoring Pain, Distancing, Praying and Distraction over the year. Interestingly, the analysis of negative factors such as Pain Catastrophizing (CSQ-R) revealed only a moderate level, even though patients experienced significant Pain Interference (MPI-SCI) at 12 months suggesting that the patient rarely magnifies or feels impotent against pain during its development over the first year.

Generally patients tend to utilize cognitive strategies (Solicitous Responses, Distracting Responses and Negative Responses) when the ongoing pain intensity is about 3 on the VAS scale, but these fail to correlate when the *spontaneous* pain intensity reaches 5 or 6, which may be interpreted that the use of these strategies is directly dependent on low but not high pain intensity. At higher pain intensity other psychological factors such as personality, depression, etc may mediate pain responses (Sullivan et al., 1990). Correlational analysis also revealed that support for these patients from months 3-4 with ongoing pain intensity was largely obtained with the use of Coping Self Statements and not from their relatives even though they had access to family members during the acute SCI phase.

In contrast Interference, Support, Affective Distress and Solicitous Responses significantly correlated with unpleasant pain intensity, indicating that the family attends and provides support when the patient experiences discomfort as an “affective” component of SCI pain.

During the acute 23 month period after SCI, most of the CSQ-R factors (Coping Self Statements, Praying, Distancing, Ignoring pain) are present and coexist. At 4 months post-SCI Coping Self Statements correlate with Solicitous and Distracting Responses, which may reflect the motivation of coping strategy utilization provided by the family relatives. Importantly Coping Self Statements and Distraction is also correlated with Severity at 6 months, indicating that patients use coping strategies to directly face the intense pain and unpleasantness. This relationship is not maintained at 12 months post-SCI whereby the only CSQ-R strategies to be highly correlated are Ignoring pain and Distancing. It is clear that the interrelationship between the coping strategies during the first 12 months measured by the CSQ-R questionnaire is not static, but constantly evolves from month to month.

The QoL factors measured using the MPI-SCI were highly correlated during the 2 month post-SCI period, although these were quickly lost afterwards: during the first 6 months after spinal injury, attempts in the use of some strategies like Distraction and Coping Self Statements though an increasing intensity of pain can be suggested. The relationship between Support and other factors like Solicitous Responses, Distracting Responses, Severity and Severity with Solicitous and Distracting Responses showed that at moderate pain intensities the relatives progressively displayed more responses towards the patient as the pain intensity developed.

From 4-6 months the patients began to perform some Household Chores which is correlated with Activities away from home and Social Activities, but is not maintained at 12 months after SCI, which we interpret as an initial motivation for the patient in daily activities as soon as possible, followed by a period of frustration caused by the disability in impeding the development of such activities. In contrast, Negative Responses is positively correlated with Activities away from home only at 6 months time, coinciding with the return of the patient to the home environment, probably due to family encouragement, support and an increase in patient confidence.

In general our study revealed an association between Catastrophizing and Pain Interference at 2, 6 and 12, but not at 3 and 4 months after SCI (probably due to the high expectation of functional recovery related to physical rehabilitation). Importantly high levels of Catastrophizing were associated with higher Pain Severity at 2, 3, 4 and 12 months and highly correlated with Affective Distress at every time point. In contrast, Catastrophizing correlated with Coping Self Statements only during the 2nd and 3rd months.

Our results are supported by a differential correlation of Catastrophizing and either cognitive or affective factors during pain identified by others (**Turner et al., 2002; Jones et al., 2003**).

Catastrophizing may contribute to increased pain intensity, but it is also possible that increased pain also contributes to an increased Catastrophizing (**Tan et al., 2001**). Indeed our observation that Catastrophizing relates to pain intensity as early as 2 months after SCI support in some way this inter-relationship, but it is not possible to establish a cause and effect of that (**Sullivan et al., 2001**). Furthermore **Sullivan et al. (2001)** suggested that Catastrophizing may contribute to heightened pain experience by increasing attentional focus on pain and/or by increasing emotional reactivity to pain. In the same way, our study showed a non correlation between Ignoring pain, Distancing and Life Control and a positive correlation between Affective Distress and Negative Responses in the majority of months evaluated.

Praying as a factor was not one of the most frequently used coping strategies in our SCI patients' population. Although Praying was progressively adopted up to 4 months, this strategy is not chosen after a year. Indeed at 2 months Praying is highly correlated with all factors; Coping Self Statements, Pain Severity and Distracting at 3 months, and only with Distraction at 4 months, similar to the reduction in correlations between factors observed over time for other QoL factors such as Coping Self Statements and Catastrophizing. However, as **Hastie et al. (2004)** proposed, people learns from the cultural context the foundation for coping, and factors like Coping Self Statements, which is related to Solicitous Responses and Distracting Responses (responses by significant others) are indeed affected by the environment.

4.5.2. Patterns in the use of Cognitive Strategies

Several attempts have been made to categorize and identify patient subgroups or patterns with regard to the coping strategy used. **Riley et al. (1999a)** found a two-factor structure for the coping subscales of the CSQ-R questionnaire across two samples of chronic pain patients: "cognitive" and "distraction". Three homogeneous subgroups were identified that consisted of a group with a high score for cognitive coping, a group with a low general overall rating for CSQ-R items, and finally a group with frequent endorsement of Catastrophizing and Distraction-related items. Analysis of these patients' subgroups may provide valuable information regarding differential response to pain treatment.

We therefore can observe different patterns in the use of strategies comparing the type of graphs simply by observation of their trends, regardless of the maximum score, (see the graphs in **4.4 Results** section):

Type 1) CSQ-R Ignoring pain, MPI-SCI Support and Solicitous Responses, showed a rapid increase in the use of the strategy up to 4 months followed by a minor decrease at 6 months and increase again at 12 months, which indicates that the support from the relatives is increasing;

Type 2) CSQ-R Distancing with a rapid increase from month 4 with a score of 0 meaning that patients start using this strategy by that time;

Type 3) MPI-SCI Interference, Pain Severity, Affective Distress, an increase up to month 3 then a plateau and up again in month 12, showing a stability in the perception of pain intensity and distress and interference with daily life, even when it is known that from month 3 to 6 VAS is progressively increasing ;

Type 4) CSQ-R Praying, Coping Self Statements, with an increase up to month 6 and then a decrease at month 12 showing that patients use the strategies mainly in the acute phase; and also MPI-SCI Life Control though this one slightly increased again at month 12;

Type 5) CSQ-R Catastrophizing and Distraction and MPI-SCI Distracting Responses showed a progressive increase in all the measures, indicating that the strategies are used regardless of the period tested.;

Type 6) MPI-SCI Negative Responses increased up to month 3 then went down till 6 and went up at month 12, interestingly we can see two dramatic increases in this response, not related with the pain intensity ;

Type 7) MPI-SCI Household Chores, Outdoor work and activities away from home, started from a score of 0, went up in months 3,6 and 4 respectively, according with the first departures from hospital as in-patients.

Studies of coping with pain present contradictions in focussing on behaviours. Typically they include rest, excessive passivity (**Brown and Nicassio, 1987; Jensen et al., 1991**) and Catastrophizing about pain (**Turner et al., 2000; Tan et al., 2001**). **Geisser et al. (1999)** have recently argued that the reduction of unhelpful coping strategies should be the main focus on treatment, rather than the increase of potentially helpful coping strategies. Particularly occluded by the dominance of coping are those classes of behaviour that are *automatic* and those that are not aimed at the direct control of the experience of sensations and emotions (**McCracken and Eccleston, 2003**).

There are just a small number of empirical studies that demonstrate a positive association between acceptance and successful adaptation to chronic pain, and these patients report less pain (**Jacob et al., 1993; Schmitz et al., 1996; McCracken, 2003**). Psychological acceptance of chronic pain has been defined as living with pain without reaction, disapproval or attempts to reduce or avoid it (**McCracken 1998; McCracken et al., 1999**).

McCracken and Eccleston (2003) showed in their study with chronic pain patients that coping variables were relatively weakly related to acceptance of pain and relatively unreliably related to pain adjustment variables. However, greater acceptance of chronic pain was associated with less pain, disability, depression, and pain-related anxiety, higher daily uptime, and better work status. Diverting attention and praying and hoping were consistently associated with greater pain and less healthy functioning, which we have observed in our population up to month 4 after injury. Acceptance of pain is not related to diverting attention or reinterpreting pain, is only minimally related to ignoring pain, and is negatively related to praying and hoping.

It has been demonstrated that when healthy subjects try not to experience experimentally induced pain, they have delayed recovery after pain exposure. (**Cioffi and Holloway, 1993**) and the failure has been shown to adversely affect report and pain tolerance (**Levine et al., 1993; Van den Hout et al., 2000**). Some other studies defend that the target for control attempts may be essential. Some studies have shown that perceived control over effects of pain or life in general are more important correlates of functioning than perceptions of control over pain itself. (**Tan et al., 2002; Jacob et al., 1993; Geisser, 1992**).

4.5.3. Physical factors: Cervical versus Thoracic SCI

Analysis of QoL factors obtained from cervical and thoracic SCI patients indicates a distinct pain coping pattern apparently unrelated to the level of physical disability associated with para- or tetraplegia, since less measurement fluctuation has been seen in the cervical group along most of the factors. We cannot affirm, as suggested by **Turner et al. (2000)**, that Coping scores predict physical disability in our population and agree with **Widerström-Noga, et al. (2002)** who proposed that the reduction in activity levels because of pain was independent of injury level.

Patients with cervical injuries tend to adopt different CSQ-R cognitive strategies to pain than the thoracic group, such as Ignoring pain, Distancing and Coping Self Statements; whilst Praying, Catastrophizing and Distraction are more frequently utilized in the thoracic SCI group. Interference, Support, Life Control, and Solicitous Responses from the MPI-SCI questionnaire indicated the presence of these factors after thoracic SCI in patients. A significant and progressive increase in the factors Social Activities and Activities away from home was observed from 3-4 months, respectively, following thoracic SCI, and a delay up to 6 months after cervical SCI. Interestingly Affective Distress was generally greater after thoracic SCI as well, but at 12 month time presented the same increased distress. A non-significant trend was also observed with higher ratings observed for Pain Severity, Distracting Responses, Household Chores and Outdoor work in the thoracic SCI group.

Interestingly the neurological level of the SCI, cervical versus thoracic (American Spinal Injury Association, ASIA), was identified in one study as the only variable explaining health-related QoL, and that spinal cord lesion caused more depression and distress in patients with motor incomplete lesion than those with complete lesion. (Dahlberg et al., 2005).

In a chronic pain population (average 9.8 yrs of injury) **Widerström-Noga et al. (2004)** identified clusters of patients based on coping strategies; the “Dysfunctional” and the “Adaptive Copers”, where cervical SCI was associated with first subtype. In contrast we did not identify such a trend between our cervical and thoracic SCI groups with Coping Self Statements analysis rather that the cervical SCI population employed this strategy earlier in time than thoracic group.

Interference, Support, Life Control, Solicitous Responses (statistically significant) and Negative Responses from the MPI-SCI showed more presence in patients with thoracic injuries.

Activities away from home and Social Activities showed a significant and progressive increase in these sorts of activities from month 4 and 3 respectively for the thoracic group whereas the cervical group started at month 6. Affective Distress was more constant in thoracic patients as well but at 12 month time showed the same increased distress.

Although there was no significant difference between Pain Severity, Distracting Responses, Household Chores and Outdoor work still was highly more presented in the thoracic group.

4.5.4. Physical factors: Traumatic versus Atraumatic SCI

In general the atraumatic patient group tended to neglect the use of some CSQ-R strategies after a trial period, perhaps because they did not perceive them as useful against pain; as was the case with Coping Self Strategies ($p=.026$), Praying and Distraction; whilst the traumatic population tended to use most of the coping strategies up to one year after SCI, even though they also showed the highest level of Catastrophizing ($p=.261$).

Interference, Support, Pain Severity, Solicitous Responses factors from the MPI-SCI are significantly more prevalent in patients with traumatic injuries up to 4 months after SCI. Life Control showed a significant level at 4 and 6 months after SCI in traumatic patients, but there was no difference when compared to the atraumatic group at 12 months. Patients with traumatic SCI presented some particularities such as emotional trauma and denial of the reality, sometimes combined with post-traumatic stress, and social support is provided to a greater extent of patients with chronic illness like cancer or lesions caused by surgery. The intensity of pain, due to the implication of such psychological and social factors, is experienced as more excruciating than in our current atraumatic group sample.

Presence of activities such as Household Chores is significant at 3 months for patients with atraumatic SCI, whereas this activity did not begin until 6 months in the traumatic lesion population.. Similarly, Activities away from home and Social Activities showed a significant and progressive increase during the earlier months for atraumatic SCI patients, compared to the traumatic SCI group with equivalent scores observed at 12 months after SCI. These results can be interpreted in the traumatic patient population as more time required after the post-traumatic experience to return to daily activities and to cope with the reality of their situation; whilst atraumatic patients have settled to the SCI situation in a more gradual way.

4.5.5. Benefits of the Study

Our study is the first one that assembles psychophysical scales (7 day VAS and Unpleasantness VAS) and cognitive-behavioural scales for the psychological assessment (CSQ-R and MPI-SCI) with repeated measures along the acute and chronic phase of the SCI in NP patients.

We could identify significant changes in the most important factors involved in the Quality of Life (QoL), derived from the two questionnaires, and related these changes to both pain intensity and the level of SCI in a selected sample of patients with neuropathic pain from 2 up to 12 months after SCI. Several QoL factors correlated highly with VAS intensity and physical factors associated with SCI mainly in early stages of the injury. The trends showed several and different coping strategies are used by patients with cervical and thoracic lesions. This is very interesting for the future treatments, since pain management programs could approach the psychotherapy in a more accurate and personalized way depending on the level of the lesion of each patient.

On the other hand, both CSQ-R and MPI-SCI questionnaires have demonstrated different utility in the assessment of strategies used in NP and SCI, and they would rather be used in a complementary way. Every patient from the 1st of July 2003 to the 1st of March 2005 was included in the study always in case they fulfilled the inclusion-exclusion criteria required. Thus, in terms of age, type of injury, gender and the rest of the demographic (the patients came from any region of Spain) and clinical data, we may generalise the results obtained to the Spanish SCI population. These data are comparable with previous studies in SCI population in ethnic group, marital status and cause of SCI, except the level of injury, which in our case was above the T10 medullaris and the majority of studies also include some patients with low paraplegia (Turner et al., 2002; Widerström-Noga, 2002).

4.5.6. Limitations of the study

As in Chapter 2 study, the major limitation was the amount of missing data mainly in month 12 after the injury, since it was lesser possible for the patients to complete the VAS and questionnaires assessment. For this reason, the diminished total N made the analysis difficult and in some occasions just made possible to draw a trend of what could happened evolutionarily in our NP patients.

A potential limitation is also the ratio of men/women recruited, where twice the number of men were included (consistent with the distribution of the SCI patients in Spain) and the small number of patients who reached the inclusion criteria (N=30), which may compromise the generalisability of our results to the SCI population. However, the homogeneity of the specific SCI neuropathic pain sample population and the inclusion of a wide variety of lesions and aetiologies strengthen this study as a true representation of the situation in the acute setting.

4.5.7. Conclusions and Future Lines in Research

In summary, high levels of Catastrophizing are associated with higher levels of pain intensity and high psychological stress, as well as a general trend for an increase in QoL factors measured by the CSQ-R and MPI-SCI from 2 months to 12 months after SCI. Cervical group patients utilize different cognitive strategies such as Ignoring pain, Distancing and Coping Self Statements, whilst Praying, Catastrophizing and Distraction are more frequently utilized in the thoracic SCI group.

Importantly, the increase in Catastrophizing is accompanied by a paradoxical increase in several positive cognitive strategies for pain, such as Ignoring pain, Distancing, Praying, Distraction and Coping Self Statements. Whether or not these coping strategies are effective in modulating pain severity, it is likely that training provided to the patients by the Psychological and Psychiatric Unit of this rehabilitation hospital facilitates the adoption of learned strategies during chronic SCI. These results have implications for designing assessment protocols and treatment interventions adequate for spinal cord injury patients with the overall objective of coping with pain symptoms during their psychosocial rehabilitation. Furthermore, the identification of those QoL factors that reliably correlate with pain severity after SCI would be able to offer an effective measure of efficacy in treatments.

The application of psychophysical scales (VAS) combined with cognitive-behavioural scales for the psychological assessment (CSQ-R and MPI-SCI) provides a real comparison of the data obtained from the patient. The VAS scale has been widely used in patients with repeated measures (Price, 1999), but

the QoL scales need more research to trace the characteristics and features of the patients with chronic pain.

The CSQ-R (Coping Strategies Questionnaire–Revised) alone seems to be inadequate for the prediction of a physical functioning measure of adjustment such as disability, which is why we chose the MPI-SCI as well which complements such factors.

The MPI-SCI (Multidimensional Pain Inventory – Spinal Cord Injury version) modified appears to be a reasonable instrument with which to evaluate the impact of pain in people with SCI and the response of their significant others to pain. However, because activity levels are different, depending on whether a person presents tetraplegia or paraplegia, and because other consequences of SCI decrease activity levels more than pain, the frequency with which a person participates in a particular activity may not necessarily reflect impairment from pain itself. (**Widerström-Noga et al., 2002**).

Do changes in coping responses merely reflect, or actually influence, adjustment to chronic pain? In our study we could observe that it does not seem the case, since increments in the different positive strategies against pain do not mean a positive change in pain severity, rather the opposite. However, it could be a matter of quantitativity, in terms of how much change is needed to infer a significant change in pain intensity.

Future research should be focused on individual treatments which attend to the own necessities of each patient. Therefore, more appropriate questionnaires would focus on the level of the injury and practical and real possibilities of practising activities would mean a big improvement in these questionnaires. Also a scale of pain rating like the VAS is necessary as we have seen previously (MPI-SCI), something that CSQ and CSQ-R lack of it.

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CHAPTER 4 APPENDIX

Name: _____ Date: _____

Los sujetos que experimentan dolor han desarrollado varias formas de afrontamiento, o relación con su dolor. Estas incluyen decirse cosas a sí mismos cuando experimentan dolor, o dedicarse a diferentes actividades. Debajo se muestra una lista de cosas que los pacientes han informado que hacen cuando sienten dolor. Para cada actividad, quiero que indiques, usando la escala de abajo, cuánto te dedicas a esa actividad cuando sientes dolor, donde un 0 indica que nunca haces eso cuando experimentas dolor, un 3 indica que algunas veces haces eso cuando experimentas dolor, y un 6 indica que siempre lo haces cuando experimentas dolor. Recuerda, puedes utilizar cualquier punto a lo largo de la escala.

0 1 2 3 4 5 6

Nunca hago eso Algunas veces hago eso Siempre hago eso

Cuando siento dolor.....

- 1. Trato de mantener la distancia del dolor, casi como si el dolor estuviera en el cuerpo de otra persona.
- 2. Trato de pensar en algo agradable.
- 3. Es terrible y siento que nunca va a conseguir mejorar algo.
- 4. Me digo a mí mismo que debo ser valiente y continuar a pesar del dolor.
- 5. Me digo a mí mismo que puedo superar el dolor.
- 6. Es horrible y siento que me vence.
- 7. Siento que mi vida no merece la pena ser vivida.
- 8. Ruego a Dios que no dure mucho.
- 9. Trato de no pensar en ello como mi cuerpo, sino más bien como algo separado de mí.
- 10. No pienso a cerca del dolor.
- 11. Me digo a mí mismo que no puedo dejar que el dolor se ponga en el camino de lo que tengo que hacer.
- 12. No le presto ninguna atención.
- 13. Finjo que no está ahí.
- 14. Me preocupo todo el tiempo de si se acabará.
- 15. Repito en mi mente experiencias agradables del pasado.
- 16. Pienso en gente con la que disfruto haciendo cosas.
- 17. Rezo para que el dolor se pare.
- 18. Imagino que el dolor está fuera de mi cuerpo.
- 19. Sigo adelante como si nada hubiera pasado.
- 20. Aunque duele, sigo adelante.
- 21. Siento que no puedo soportarlo más.
- 22. Lo ignoro.
- 23. Confío en mi fe en Dios.
- 24. Siento como que no puedo seguir.
- 25. Pienso en las cosas que disfruto haciendo.
- 26. Hago algo con lo que disfruto, como ver al televisión o escuchar música.
- 27. Finjo que no es una parte de mí.

Protocol 4.1. CSQ questionnaire (Spanish version)

Appendix D
INVENTARIO MULTIDIMENSIONAL DE DOLOR
(Para individuos con lesión medular)

Fecha: _____
 ¿Cuándo le comenzó el dolor? Mes: _____ Año: _____

Instrucciones

Uno de los factores más importantes de nuestra evaluación incluye la examinación de su dolor desde su punto de vista por el hecho que usted obviamente es la persona que mejor puede identificar su dolor. Las siguientes preguntas están diseñadas para detallar aspectos de su dolor y en la manera que le afecta su vida. El cuestionario tiene tres secciones: las primeras dos están relacionadas a los aspectos de su dolor crónico; la última sección, además, toma en consideración otras consecuencias de su lesión medular (parálisis, pérdida de control sobre la evacuación del vientre o la vejiga, disminución de función sexual, sensaciones raras que no le causan dolor, y etcétera). Debajo de cada pregunta hay una escala donde usted llena su respuesta. Lea cada pregunta con cuidado y en la escala haga un círculo alrededor del número que correctamente aplique a su condición. Si encuentra que la pregunta no le aplica a usted, por favor haga un círculo alrededor del número que está delante de la pregunta. Cuando usted complete el cuestionario, revise sus respuestas para verificar que usted ha respondido a todas las preguntas. Use la última página para añadir información o comentarios adicionales que nos puedan asistir a entender mejor su situación con el dolor.

Antes de comenzar, conteste las dos siguientes preguntas de pre-evaluación.

1. Algunas preguntas en el cuestionario se refieren a la persona a quien usted se siente más apegada. Esta persona puede ser su esposo o esposa, pero puede estar relacionada con usted de otra manera. Es muy importante que usted identifique a alguien en esta capacidad. Indique con cual de las siguientes personas usted considera que tiene dicha relación (por favor, escoja solamente una):

- | | | |
|--|--|---|
| <input type="checkbox"/> Esposo / Esposa | <input type="checkbox"/> Compañero / Compañera | <input type="checkbox"/> Compañero de casa o de cuarto |
| <input type="checkbox"/> Amigo / Amiga | <input type="checkbox"/> Vecino | <input type="checkbox"/> Padre, Madre, Hijo, Hija u otro familiar |
| <input type="checkbox"/> Otra persona: _____ | | |

2. ¿Usted actualmente vive con esta persona?

- Sí
 No

Cuando conteste las preguntas que refieren a un esposo o una esposa, siempre responda en referencia a esta persona que usted acaba de indicar.

- | | | | | | | | |
|--|------------------------------|---|---|---|---|---|---------------------------------------|
| | 0 | 1 | 2 | 3 | 4 | 5 | 6 |
| | <i>nunca puedo anticipar</i> | | | | | | <i>frecuentemente puedo anticipar</i> |
| 10. ¿Cuánto ha cambiado su dolor su habilidad para participar en actividades sociales o de recreo? | | | | | | | |
| | 0 | 1 | 2 | 3 | 4 | 5 | 6 |
| | <i>ningún cambio</i> | | | | | | <i>ha cambiado extremadamente</i> |
| 11. ¿Cuánto se limita usted en sus actividades para prevenir un aumento en su dolor? | | | | | | | |
| | 0 | 1 | 2 | 3 | 4 | 5 | 6 |
| | <i>nada</i> | | | | | | <i>mucho</i> |
| 12. ¿Cuánto le ha cambiado su dolor la satisfacción o el placer que usted recibe de sus actividades familiares? | | | | | | | |
| | 0 | 1 | 2 | 3 | 4 | 5 | 6 |
| | <i>ningún cambio</i> | | | | | | <i>ha cambiado extremadamente</i> |
| 13. ¿Qué tan preocupado está su esposo(a) por usted a causa de su dolor? | | | | | | | |
| | 0 | 1 | 2 | 3 | 4 | 5 | 6 |
| | <i>no está preocupado</i> | | | | | | <i>está extremadamente preocupado</i> |
| 14. Durante <i>la última semana</i> , ¿cuánto control siente que usted ha tenido sobre su vida? | | | | | | | |
| | 0 | 1 | 2 | 3 | 4 | 5 | 6 |
| | <i>ningún control</i> | | | | | | <i>mucho control</i> |
| 15. En un día típico, ¿cuánto cambia su dolor (aumenta o mejora)? | | | | | | | |
| | 0 | 1 | 2 | 3 | 4 | 5 | 6 |
| | <i>no cambia</i> | | | | | | <i>cambia bastante</i> |
| 16. ¿Cuánto sufre usted a causa de su dolor? | | | | | | | |
| | 0 | 1 | 2 | 3 | 4 | 5 | 6 |
| | <i>no sufro</i> | | | | | | <i>sufro extremadamente</i> |
| 17. ¿Qué tan frecuentemente puede usted hacer algo que reduce su dolor? | | | | | | | |
| | 0 | 1 | 2 | 3 | 4 | 5 | 6 |
| | <i>nunca</i> | | | | | | <i>muy frecuentemente</i> |
| 18. ¿Cuánto ha cambiado su dolor sus relaciones con su esposo(a), familia u otras gentes? | | | | | | | |
| | 0 | 1 | 2 | 3 | 4 | 5 | 6 |
| | <i>no ha cambiado</i> | | | | | | <i>ha cambiado extremadamente</i> |
| 19. ¿Cuánto ha cambiado su dolor la satisfacción que usted recibe de su trabajo (____ marque aquí si usted no trabaja actualmente) | | | | | | | |
| | 0 | 1 | 2 | 3 | 4 | 5 | 6 |
| | <i>no ha cambiado</i> | | | | | | <i>ha cambiado extremadamente</i> |
| 20. ¿Cuánta atención le presta su esposo(a) a causa de su dolor? | | | | | | | |
| | 0 | 1 | 2 | 3 | 4 | 5 | 6 |
| | <i>no me presta atención</i> | | | | | | <i>me presta mucha atención</i> |
| 21. Durante <i>la última semana</i> , ¿cuánto siente usted que se ha podido enfrentar a sus problemas? | | | | | | | |
| | 0 | 1 | 2 | 3 | 4 | 5 | 6 |
| | <i>no he podido</i> | | | | | | <i>he podido muy bien</i> |

Protocol 4.2.3. Section 1 of MPI-SCI questionnaire (Questions 10 to 21, Spanish version).

Sección II

En esta sección estamos interesados en saber como su esposo(a) (u otra persona con la que usted vive o pasa la mayoría de su tiempo) responde cuando sabe que usted tiene mucho dolor. En la escala debajo de cada pregunta, haga un círculo alrededor del número que indique que tan frecuente su esposo(a), u otra persona, le responde en este modo cuando su dolor es muy fuerte.

- | | | | | | | | |
|---|---|---|---|---|---|---|---------------------------|
| 1. Me ignora. | 0 | 1 | 2 | 3 | 4 | 5 | 6 |
| <i>nunca</i> | | | | | | | <i>muy frecuentemente</i> |
| 2. Me pregunta si me puede ayudar y como. | 0 | 1 | 2 | 3 | 4 | 5 | 6 |
| <i>nunca</i> | | | | | | | <i>muy frecuentemente</i> |
| 3. Me lee. | 0 | 1 | 2 | 3 | 4 | 5 | 6 |
| <i>nunca</i> | | | | | | | <i>muy frecuentemente</i> |
| 4. Se irrita conmigo. | 0 | 1 | 2 | 3 | 4 | 5 | 6 |
| <i>nunca</i> | | | | | | | <i>muy frecuentemente</i> |
| 5. Hace el trabajo o los quehaceres que yo debería hacer. | 0 | 1 | 2 | 3 | 4 | 5 | 6 |
| <i>nunca</i> | | | | | | | <i>muy frecuentemente</i> |
| 6. Me habla de otras cosas para distraerme del dolor. | 0 | 1 | 2 | 3 | 4 | 5 | 6 |
| <i>nunca</i> | | | | | | | <i>muy frecuentemente</i> |
| 7. Se frustra conmigo. | 0 | 1 | 2 | 3 | 4 | 5 | 6 |
| <i>nunca</i> | | | | | | | <i>muy frecuentemente</i> |
| 8. Trata de que yo descanse. | 0 | 1 | 2 | 3 | 4 | 5 | 6 |
| <i>nunca</i> | | | | | | | <i>muy frecuentemente</i> |
| 9. Trata de que yo participe en una actividad. | 0 | 1 | 2 | 3 | 4 | 5 | 6 |
| <i>nunca</i> | | | | | | | <i>muy frecuentemente</i> |
| 10. Se enoja conmigo. | 0 | 1 | 2 | 3 | 4 | 5 | 6 |
| <i>nunca</i> | | | | | | | <i>muy frecuentemente</i> |
| 11. Me da medicina para el dolor. | 0 | 1 | 2 | 3 | 4 | 5 | 6 |
| <i>nunca</i> | | | | | | | <i>muy frecuentemente</i> |

Protocol 4.2.4. Section 2 of MPI-SCI questionnaire (Questions 1 to 11, Spanish version).

- | | | | | | | | |
|---|---|---|---|---|---|---|---------------------------|
| 12. Me anima para que yo trabaje en un pasatiempo. | 0 | 1 | 2 | 3 | 4 | 5 | 6 |
| <i>nunca</i> | | | | | | | <i>muy frecuentemente</i> |
| 13. Me consigue algo de comer o beber. | 0 | 1 | 2 | 3 | 4 | 5 | 6 |
| <i>nunca</i> | | | | | | | <i>muy frecuentemente</i> |
| 14. Prende la televisión para distraerme del dolor. | 0 | 1 | 2 | 3 | 4 | 5 | 6 |
| <i>nunca</i> | | | | | | | <i>muy frecuentemente</i> |

Protocol 4.2.5. Section 2 of MPI-SCI questionnaire (Questions 12 to 14, Spanish version).

	b. El dolor reduce mi participación en esta actividad:					
	0	1	2	3	4	5
	<i>nunca</i>					6
						<i>muy frecuentemente</i>
7.	Ir al cine:					
	a. ¿Con qué frecuencia usted participa en esta actividad?					
	0	1	2	3	4	5
	<i>nunca</i>					6
						<i>muy frecuentemente</i>
	b. El dolor reduce mi participación en esta actividad:					
	0	1	2	3	4	5
	<i>nunca</i>					6
						<i>muy frecuentemente</i>
8.	Visitar amigos:					
	a. ¿Con qué frecuencia usted participa en esta actividad?					
	0	1	2	3	4	5
	<i>nunca</i>					6
						<i>muy frecuentemente</i>
	b. El dolor reduce mi participación en esta actividad:					
	0	1	2	3	4	5
	<i>nunca</i>					6
						<i>muy frecuentemente</i>
9.	Ayudar con la limpieza de la casa:					
	a. ¿Con qué frecuencia usted participa en esta actividad?					
	0	1	2	3	4	5
	<i>nunca</i>					6
						<i>muy frecuentemente</i>
	b. El dolor reduce mi participación en esta actividad:					
	0	1	2	3	4	5
	<i>nunca</i>					6
						<i>muy frecuentemente</i>
10.	Reparar el automóvil (____ marque aquí si usted no tiene un automóvil):					
	a. ¿Con qué frecuencia usted participa en esta actividad?					
	0	1	2	3	4	5
	<i>nunca</i>					6
						<i>muy frecuentemente</i>
	b. El dolor reduce mi participación en esta actividad:					
	0	1	2	3	4	5
	<i>nunca</i>					6
						<i>muy frecuentemente</i>
11.	Viajar en automóvil o en autobús:					
	a. ¿Con qué frecuencia usted participa en esta actividad?					
	0	1	2	3	4	5
	<i>nunca</i>					6
						<i>muy frecuentemente</i>
	b. El dolor reduce mi participación en esta actividad:					
	0	1	2	3	4	5
	<i>nunca</i>					6
						<i>muy frecuentemente</i>
12.	Visitar familia (____ marque aquí si usted no tiene familia más cerca que 100 millas):					
	a. ¿Con qué frecuencia usted participa en esta actividad?					
	0	1	2	3	4	5
	<i>nunca</i>					6
						<i>muy frecuentemente</i>
	b. El dolor reduce mi participación en esta actividad:					

Protocol 4.2.7. Section 3 of MPI-SCI questionnaire (Questions 7 to 12, Spanish version).

- | | | | | | | | |
|--|--------------|---|---|---|---|---|---------------------------|
| | 0 | 1 | 2 | 3 | 4 | 5 | 6 |
| | <i>nunca</i> | | | | | | <i>muy frecuentemente</i> |
| 13. Hacer la comida: | | | | | | | |
| a. ¿Con qué frecuencia usted participa en esta actividad? | 0 | 1 | 2 | 3 | 4 | 5 | 6 |
| | <i>nunca</i> | | | | | | <i>muy frecuentemente</i> |
| b. El dolor reduce mi participación en esta actividad: | | | | | | | |
| | 0 | 1 | 2 | 3 | 4 | 5 | 6 |
| | <i>nunca</i> | | | | | | <i>muy frecuentemente</i> |
| 14. Lavar el automóvil (____ marque aquí si usted no tiene automóvil): | | | | | | | |
| a. ¿Con qué frecuencia usted participa en esta actividad? | 0 | 1 | 2 | 3 | 4 | 5 | 6 |
| | <i>nunca</i> | | | | | | <i>muy frecuentemente</i> |
| b. El dolor reduce mi participación en esta actividad: | | | | | | | |
| | 0 | 1 | 2 | 3 | 4 | 5 | 6 |
| | <i>nunca</i> | | | | | | <i>muy frecuentemente</i> |
| 15. Ir de viaje: | | | | | | | |
| a. ¿Con qué frecuencia usted participa en esta actividad? | 0 | 1 | 2 | 3 | 4 | 5 | 6 |
| | <i>nunca</i> | | | | | | <i>muy frecuentemente</i> |
| b. El dolor reduce mi participación en esta actividad: | | | | | | | |
| | 0 | 1 | 2 | 3 | 4 | 5 | 6 |
| | <i>nunca</i> | | | | | | <i>muy frecuentemente</i> |
| 16. Ir a un parque o una playa: | | | | | | | |
| a. ¿Con qué frecuencia usted participa en esta actividad? | 0 | 1 | 2 | 3 | 4 | 5 | 6 |
| | <i>nunca</i> | | | | | | <i>muy frecuentemente</i> |
| b. El dolor reduce mi participación en esta actividad: | | | | | | | |
| | 0 | 1 | 2 | 3 | 4 | 5 | 6 |
| | <i>nunca</i> | | | | | | <i>muy frecuentemente</i> |
| 17. Lavar las ropas: | | | | | | | |
| a. ¿Con qué frecuencia usted participa en esta actividad? | 0 | 1 | 2 | 3 | 4 | 5 | 6 |
| | <i>nunca</i> | | | | | | <i>muy frecuentemente</i> |
| b. El dolor reduce mi participación en esta actividad: | | | | | | | |
| | 0 | 1 | 2 | 3 | 4 | 5 | 6 |
| | <i>nunca</i> | | | | | | <i>muy frecuentemente</i> |
| 18. Hacer reparos necesarios en el hogar: | | | | | | | |
| a. ¿Con qué frecuencia usted participa en esta actividad? | 0 | 1 | 2 | 3 | 4 | 5 | 6 |
| | <i>nunca</i> | | | | | | <i>muy frecuentemente</i> |
| b. El dolor reduce mi participación en esta actividad: | | | | | | | |
| | 0 | 1 | 2 | 3 | 4 | 5 | 6 |
| | <i>nunca</i> | | | | | | <i>muy frecuentemente</i> |

Protocol 4.2.8. Section 3 of MPI-SCI questionnaire (Questions 13 to 18, Spanish version).

STATISTICAL ANALYSIS: PAIN INTENSITY AND UNPLEASANTNESS, CSQ-R AND MPI-SCI

	Observed Power Tests of Within-Subjects Contrasts; factor1 * cervthorac
7day VAS	
7day VAS gral	.456
7day VAS cerv/thorac	.445
Unpleasantness VAS gral	.181
Unpleasantness VAS cerv/thorac	.383

Appendix Table 4.1. Observed Power for Pain intensity and Unpleasantness, computed using alpha = .05

CSQ factor	Observed Power Tests of Within-Subjects Contrasts; factor1 * cervthorac
Ignoring pain	.138
Distancing	.519
Coping Self Statements	.426
Praying	.687
Catastrophizing	.369
Distraction	.318

Appendix Table 4.2. Observed Power for CSQ-R Questionnaire comparing cervical versus thoracic SCI, computed using an alpha = .05.

MPI factor	Observed Power Tests of Within-Subjects Contrasts; factor1 * cervthorac
Interference	.289
support	.147
pain severity	.545
life control	.134
affective distress	.516
negative responses	.416
solicitous responses	.115
distracting responses	.113
household chores	.242
outdoor work	.197
activities away from home	.210
social activities	.203

Appendix Table 4.3. Observed Power for MPI-SCI Questionnaire comparing cervical versus thoracic SCI, computed using an alpha = .05.

	VAS			CSQ-R							MPI-SCI									
	7VAS	Unpl	Ign	Dsta	Cop	Pra	Cat	Dstr	Int	Sup	Sev	LCo	Aff	NeR	SoR	DiR	HCh	OWo	AAw	
Unpl	.847																			
Ign	.872	.922																		
Dsta	.452	.545	.49																	
Cop	.848	.974	.897	.621																
Para	.848	.974	.897	.621	.848															
Cat	.755	.867	.726	.583	.899	.755														
Dstr	.842	.802	.663	.489	.835	.91	.847													
Int	.827	.875	.876	.439	.916	.884	.988	.775												
Sup	.784	.95	.943	.579	.941	.725	.837	.657	.821											
Sev	.924	.908	.991	.469	.893	.73	.903	.705	.887	.917										
Lco	.77	.893	.888	.624	.951	.812	.921	.681	.921	.917	.877									
Aff	.966	.888	.837	.543	.885	.833	.896	.883	.831	.792	.879	.77								
NeR	.687	.59	.571	.716	.628	.778	.702	.696	.667	.457	.6	.584	.759							
SoR	.507	.796	.689	.558	.755	.692	.667	.497	.68	.764	.638	.68	.66	.539						
DiR	.368	.712	.618	.597	.686	.534	.522	.359	.538	.769	.549	.634	.511	.342	.943					
HCh	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
Owo	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
Aaw	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
Sac	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	

Appendix Table 4.4. Correlational analysis between *spontaneous* pain intensity (VAS), CSQ-R and MPI-SCI factors at 2 months time for cervical SCI.

Note. 7VAS= Intensity of pain 7 day spontaneous pain intensity ; Unpl= Unpleasant intensity; CSQ-R Factors: Ign=Ignoring pain; Dsta=Distancing; Cop=Coping Self Statements; Pra=Praying; Cat=Catastrophizing; Dstr=Distraction. MPI-SCI Factors: Int=Interference; Sup=Support; Sev=Pain Severity; LCo=Life Control; Aff=Affective Distress; NeR=Negative Responses; SoR=Solicitous Responses; DiR=Distracting Responses; HCh=Household Chores; OWo=Outdoor work; AAw=Activities away from home; Sac=Social Activities Data in bold represent significant correlation at $\alpha = .0001$; Unformatted data represent non-significant correlations ($\alpha = .005$).

	VAS			CSQ-R							MPI-SCI									
	7VAS	Unpl	Ign	Dsta	Cop	Pra	Cat	Dstr	Int	Sup	Sev	LCo	Aff	NeR	SoR	DiR	HCh	OWo	AAw	
Unpl	.974																			
Ign	.842	.966																		
Dsta	.842	.966	1																	
Cop	.855	.974	.993	.993																
Para	.855	.974	.993	.993	1															
Cat	.589	.848	.708	.708	.716	.716														
Dstr	.651	.697	.846	.846	.785	.785	.347													
Int	.842	.966	1	1	.993	.993	.708	.846												
Sup	.829	1	.971	.971	.978	.978	.846	.708	.971											
Sev	.829	1	.971	.971	.978	.978	.846	.708	.971	1										
Lco	.855	.974	.993	.993	1	1	.716	.785	.993	.978	.855									
Aff	.718	.877	.891	.891	.878	.878	.69	.752	.891	.878	.718	.878								
NeR	.849	.991	.978	.978	.993	.993	.785	.716	.978	.993	.849	.993	.871							
SoR	.842	.966	1	1	.993	.993	.708	.846	1	.971	.971	.993	.891	.978						
DiR	.842	.966	1	1	.993	.993	.708	.846	1	.971	.971	.993	.891	.978	1					
HCh	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
Owo	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
Aaw	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
Sac	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	

Appendix Table 4.5. Correlational analysis between *spontaneous* pain intensity (VAS), CSQ-R and MPI-SCI factors at 2 months time for thoracic SCI.

Note. 7VAS= Intensity of pain 7 day spontaneous pain intensity ; Unpl= Unpleasant intensity; CSQ-R Factors: Ign=Ignoring pain; Dsta=Distancing; Cop=Coping Self Statements; Pra=Praying; Cat=Catastrophizing; Dstr=Distraction. MPI-SCI Factors: Int=Interference; Sup=Support; Sev=Pain Severity; LCo=Life Control; Aff=Affective Distress; NeR=Negative Responses; SoR=Solicitous Responses; DiR=Distracting Responses; HCh=Household Chores; OWo=Outdoor work; AAw=Activities away from home; Sac=Social Activities Data in bold represent significant correlation at $\alpha = .0001$; Unformatted data represent non-significant correlations ($\alpha = .005$).

	VAS				CSQ-R				MPI-SCI											
	7VAS	Unpl	Ign	Dsta	Cop	Pra	Cat	Dstr	Int	Sup	Sev	LCo	Aff	NeR	SoR	DiR	HCh	OWo	AAw	
Unpl	.716																			
Ign	.228	.494																		
Dsta																				
Cop	.400	.041	.034																	
Para	.353	.633	.704	.061																
Cat	.556	.864	.494	.066	.647															
Dstr	.47	.441	.017	.385	.271	.266														
Int	-.061	.056	.561	.442	.584	.05	.055													
Sup	.574	.645	.182	.283	.447	.359	.466	.059												
Sev	.653	.411	.485	.503	.356	.143	.294	.236	.638											
Lco	.711	.705	.533	.478	.582	.583	.3	.18	.685	.799										
Aff	-.163	.168	.022	.343	.104	.229	.222	.146	.223	.431	.407									
NeR	.403	.266	.059	.42	.133	.176	.36	.188	.383	.464	.476	.488								
SoR	.218	.045	.336	.372	.211	.17	.318	.399	.013	.448	.406	.262	.699							
DiR	.327	.196	.672	.341	.555	.226	.054	.506	.347	.785	.716	.388	.447	.723						
HCh	.52	.234	.524	.632	.411	.317	.274	.422	.319	.777	.777	.344	.432	.735	.885					
OWo	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
AAw	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
Sac	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	

Appendix Table 4.6. Correlational analysis between *spontaneous* pain intensity (VAS), CSQ-R and MPI-SCI factors at 6 months time for cervical SCI.

Note. 7VAS= Intensity of pain 7 day spontaneous pain intensity ; Unpl= Unpleasant intensity; CSQ-R Factors: Ign=Ignoring pain; Dsta=Distancing; Cop=Coping Self Statements; Pra=Praying; Cat=Catastrophizing; Dstr=Distraction. MPI-SCI Factors: Int=Interference; Sup=Support; Sev=Pain Severity; LCo=Life Control; Aff=Affective Distress; NeR=Negative Responses; SoR=Solicitous Responses; DiR=Distracting Responses; HCh=Household Chores; OWo=Outdoor work; AAw=Activities away from home; Sac=Social Activities Data in bold represent significant correlation at $p \leq .0001$; Unformatted data represent non-significant correlations ($p \leq .005$).

	VAS			CSQ-R						MPI-SCI									
	7VAS	Unpl	Ign	Dsta	Cop	Pra	Cat	Dstr	Int	Sup	Sev	LCo	Aff	NeR	SoR	DiR	HCh	OWo	AAw
Unpl	.861																		
Ign	.124	.118																	
Dsta	.418	.462	.085																
Cop	.408	.525	.202	.254															
Pra	.421	.654	-.08	-.016	.816														
Cat	.503	.63	.294	-.317	.509	.616													
Dstr	.462	.613	.297	.298	.92	.659	.576												
Int	.696	.467	.194	.223	.654	.455	.395	.603											
Sup	.096	.161	.653	.021	.547	.256	.47	.539	.665										
Sev	.573	.45	.158	.266	.429	.376	.465	.386	.715	.693									
LCo	.47	.694	.327	-.143	.401	.456	.911	.522	.525	.736	.663								
Aff	.401	.519	.06	0	.572	.643	.531	.628	.556	.48	.653	.584							
NeR	.241	.451	.207	-.345	.36	.46	.839	.376	.392	.689	.454	.918	.361						
SoR	-.018	.33	.343	.266	.706	.554	.368	.65	.39	.791	.553	.66	.519	.636					
DiR	.012	.376	.345	.203	.645	.589	.403	.561	.38	.792	.55	.696	.507	.681	.984				
HCh	.271	.615	-.191	.125	.159	.593	.257	.055	-.036	.009	.321	.319	.44	.193	.359	.456			
OWo																			
AAw	.271	.615	-.191	.125	.159	.593	.257	.055	-.036	.009	.319	.44	.193	.359	.456	1			1
Sac	.271	.615	-.191	.125	.159	.593	.257	.055	-.036	.009	.321	.44	.193	.359	.456	1			1

Appendix Table 4.7. Correlational analysis between *spontaneous* pain intensity (VAS), CSQ-R and MPI-SCI factors at 6 months time for thoracic SCI.

Note. 7VAS= Intensity of pain 7 day spontaneous pain intensity ; Unpl= Unpleasant intensity; CSQ-R Factors: Ign=Ignoring pain; Dsta=Distancing; Cop=Coping Self Statements; Pra=Praying; Cat=Catastrophizing; Dstr=Distraction. MPI-SCI Factors: Int=Interference; Sup=Support; Sev=Pain Severity; LCo=Life Control; Aff=Affective Distress; NeR=Negative Responses; SoR=Solicitous Responses; DiR=Distracting Responses; HCh=Household Chores; OWo=Outdoor work; AAw=Activities away from home; Sac=Social Activities Data in bold represent significant correlation at $\alpha = .0001$; Unformatted data represent non-significant correlations ($\alpha = .005$).

	Mean	Std. Deviation	N
ignoring pain CSQ factor 2m	1,5620	2,88512	12
ignoring pain CSQ factor 3m	2,6078	3,27711	12
ignoring pain CSQ factor 4m	3,5383	4,02029	12
ignoring pain CSQ factor 6m	3,4567	4,12074	12
ignoring pain CSQ factor 12m	3,8505	2,95939	12

Appendix Table 4.8. General descriptive statistics for ignoring pain CSQ-R factor from 2 to 12 months after SCI

	Mean	Std. Deviation	N
distancing CSQ factor 2m	,0000	,00000	12
distancing CSQ factor 3m	,1650	,57158	12
distancing CSQ factor 4m	,0000	,00000	12
distancing CSQ factor 6m	,9625	2,03166	12
distancing CSQ factor 12m	1,2696	3,07940	12

Appendix Table 4.9. General descriptive statistics for distancing CSQ-R factor from 2 to 12 months after SCI

	Mean	Std. Deviation	N
Coping Self Statements CSQ factor 2m	2,2800	4,47213	12
Coping Self Statements CSQ factor 3m	5,8683	5,53352	12
Coping Self Statements CSQ factor 4m	7,0517	7,05947	12
Coping Self Statements CSQ factor 6m	9,3650	6,94730	12
Coping Self Statements CSQ factor 12m	8,8683	5,35193	12

Appendix Table 4.10. General descriptive statistics for Coping Self Statements CSQ-R factor from 2 to 12 months after SCI

	Mean	Std. Deviation	N
praying CSQ factor 2m	1,5700	3,90353	12
praying CSQ factor 3m	3,5614	4,82738	12
praying CSQ factor 4m	4,2575	4,93883	12
praying CSQ factor 6m	5,5092	5,49926	12
praying CSQ factor 12m	4,4531	5,18187	12

Appendix Table 4.11. General descriptive statistics for praying CSQ-R factor from 2 to 12 months after SC

	Mean	Std. Deviation	N
catastrophizing CSQ factor 2m	1,6900	4,63121	12
catastrophizing CSQ factor 3m	3,0350	4,53540	12
catastrophizing CSQ factor 4m	3,5900	5,13706	12
catastrophizing CSQ factor 6m	4,3158	4,96943	12
catastrophizing CSQ factor 12m	5,8250	6,06726	12

Appendix Table 4.12. General descriptive statistics for catastrophizing CSQ-R factor from 2 to 12 months after SCI

	Mean	Std. Deviation	N
distraction CSQ factor 2m	2,7530	6,48751	12
distraction CSQ factor 3m	5,3000	7,85809	12
distraction CSQ factor 4m	6,4683	7,25989	12
distraction CSQ factor 6m	7,0315	8,77780	12
distraction CSQ factor 12m	8,1340	8,46477	12

Appendix Table 4.13. General descriptive statistics for distraction CSQ-R factor from 2 to 12 months after SCI

	Mean	Std. Deviation	N
interference MPI factor 2m	7,3283	14,81888	15
interference MPI factor 3m	13,8103	17,01855	15
interference MPI factor 4m	13,7448	15,78315	15
interference MPI factor 6m	14,6970	17,06054	15
interference MPI factor 12m	24,7895	16,90976	15

Appendix Table 4.14. General descriptive statistics for interference MPI-SCI factor from 2 to 12 months after SCI

	Mean	Std. Deviation	N
support MPI factor 2m	2,5333	4,83465	15
support MPI factor 3m	6,3833	6,44334	15
support MPI factor 4m	9,5667	6,93044	15
support MPI factor 6m	8,4833	6,47831	15
support MPI factor 12m	9,3889	3,75286	15

Appendix Table 4.15. General descriptive statistics for support MPI-SCI factor from 2 to 12 months after SCI

	Mean	Std. Deviation	N
pain severity MPI factor 2m	3,3333	5,78612	15
pain severity MPI factor 3m	6,6667	7,27623	15
pain severity MPI factor 4m	7,2667	6,49414	15
pain severity MPI factor 6m	7,0333	5,90918	15
pain severity MPI factor 12m	10,0500	5,32196	15

Appendix Table 4.16. General descriptive statistics for pain severity MPI-SCI factor from 2 to 12 months after SCI

	Mean	Std. Deviation	N
life control MPI factor 2m	2,6333	5,78319	15
life control MPI factor 3m	5,8889	8,30105	15
life control MPI factor 4m	9,5111	7,64580	15
life control MPI factor 6m	9,9669	6,97257	15
life control MPI factor 12m	10,3778	4,34680	15

Appendix Table 4.17. General descriptive statistics for life control MPI-SCI factor from 2 to 12 months after SCI

	Mean	Std. Deviation	N
affective distress MPI factor 2m	,8000	1,42428	15
affective distress MPI factor 3m	1,4889	1,45769	15
affective distress MPI factor 4m	1,5331	1,37902	15
affective distress MPI factor 6m	1,3553	1,34186	15
affective distress MPI factor 12m	2,9331	1,44336	15

Appendix Table 4.18. General descriptive statistics for affective distress MPI-SCI factor from 2 to 12 months after SCI

	Mean	Std. Deviation	N
negative responses MPI factor 2m	1,6333	5,10765	15
negative responses MPI factor 3m	3,8833	6,36176	15
negative responses MPI factor 4m	3,1667	4,93590	15
negative responses MPI factor 6m	2,1667	3,91958	15
negative responses MPI factor 12m	3,0500	3,77279	15

Appendix Table 4.19. General descriptive statistics for negative responses MPI-SCI factor from 2 to 12 months after SCI

	Mean	Std. Deviation	N
solicitous responses MPI factor 2m	3,6111	9,13820	15
solicitous responses MPI factor 3m	11,0933	12,80215	15
solicitous responses MPI factor 4m	11,9400	10,52635	15
solicitous responses MPI factor 6m	10,4600	9,29192	15
solicitous responses MPI factor 12m	15,2378	10,54896	15

Appendix Table 4.20. General descriptive statistics for solicitous responses MPI-SCI factor from 2 to 12 months after SCI

	Mean	Std. Deviation	N
distracting responses MPI factor 2m	2,5333	6,68812	15
distracting responses MPI factor 3m	5,0500	6,64146	15
distracting responses MPI factor 4m	5,9000	6,03250	15
distracting responses MPI factor 6m	6,0333	5,28633	15
distracting responses MPI factor 12m	7,0667	5,41943	15

Appendix Table 4.21. General descriptive statistics for distracting responses MPI-SCI factor from 2 to 12 months after SCI

	Mean	Std. Deviation	N
household chores MPI factor 2m	,0000	,00000	14
household chores MPI factor 3m	,0000	,00000	14
household chores MPI factor 4m	5,6250	6,16188	14
household chores MPI factor 6m	2,3357	6,04160	14
household chores MPI factor 12m	4,8071	6,05976	14

Appendix Table 4.22. General descriptive statistics for household chores MPI-SCI factor from 2 to 12 months after SCI

	Mean	Std. Deviation	N
outdoor work MPI factor 2m	,0000	,00000	15
outdoor work MPI factor 3m	,0000	,00000	15
outdoor work MPI factor 4m	,0000	,00000	15
outdoor work MPI factor 6m	,0000	,00000	15
outdoor work MPI factor 12m	,3333	,89974	15

Appendix Table 4.23. General descriptive statistics for outdoor work MPI-SCI factor from 2 to 12 months after SCI

	Mean	Std. Deviation	N
activities away from home MPI factor 2m	,0000	,00000	15
activities away from home MPI factor 3m	,0000	,00000	15
activities away from home MPI factor 4m	,0333	,12910	15
activities away from home MPI factor 6m	,3667	1,28823	15
activities away from home MPI factor 12m	5,0833	4,21378	15

Appendix Table 4.24. General descriptive statistics for outdoor work MPI-SCI factor from 2 to 12 months after SCI

	Mean	Std. Deviation	N
social activities MPI factor 2m	,0000	,00000	15
social activities MPI factor 3m	,0000	,00000	15
social activities MPI factor 4m	,3778	1,46313	15
social activities MPI factor 6m	,8444	2,24268	15
social activities MPI factor 12m	4,1111	4,57647	15

Appendix Table 4.25. General descriptive statistics for social activities MPI-SCI factor from 2 to 12 months after SCI

CERVICAL VS THORACIC LESIONS

	cervical or thoracic lesion	Mean	Std. Deviation	N
ignoring pain CSQ factor 2m	cervical	3,7488	3,55577	5
	thoracic	,0000	,00000	7
	Total	1,5620	2,88512	12
ignoring pain CSQ factor 3m	cervical	2,9828	3,98028	5
	thoracic	2,3400	2,98771	7
	Total	2,6078	3,27711	12
ignoring pain CSQ factor 4m	cervical	5,4356	5,25542	5
	thoracic	2,1831	2,46504	7
	Total	3,5383	4,02029	12
ignoring pain CSQ factor 6m	cervical	4,2588	5,93107	5
	thoracic	2,8837	2,60000	7
	Total	3,4567	4,12074	12
ignoring pain CSQ factor 12m	cervical	4,7676	3,04436	5
	thoracic	3,1954	2,94552	7
	Total	3,8505	2,95939	12

Appendix Table 4.26. Descriptive Statistics for ignoring pain CSQ-R factor in the cervical and thoracic SCI subject groups.

	cervical or thoracic lesion	Mean	Std. Deviation	N
distancing CSQ factor 2m	cervical	,0000	,00000	5
	thoracic	,0000	,00000	7
	Total	,0000	,00000	12
distancing CSQ factor 3m	cervical	,3960	,88548	5
	thoracic	,0000	,00000	7
	Total	,1650	,57158	12
distancing CSQ factor 4m	cervical	,0000	,00000	5
	thoracic	,0000	,00000	7
	Total	,0000	,00000	12
distancing CSQ factor 6m	cervical	,0000	,00000	5
	thoracic	1,6500	2,49878	7
	Total	,9625	2,03166	12
distancing CSQ factor 12m	cervical	3,0020	4,43117	5
	thoracic	,0321	,08504	7
	Total	1,2696	3,07940	12

Appendix Table 4.27. Descriptive Statistics for distancing CSQ-R factor in the cervical and thoracic SCI subject groups.

	cervical or thoracic lesion	Mean	Std. Deviation	N
coping self statements CSQ factor 2m	cervical	5,4720	5,75904	5
	thoracic	,0000	,00000	7
	Total	2,2800	4,47213	12
coping self statements CSQ factor 3m	cervical	7,4880	4,94034	5
	thoracic	4,7114	6,00978	7
	Total	5,8683	5,53352	12
coping self statements CSQ factor 4m	cervical	9,8020	6,68836	5
	thoracic	5,0871	7,12301	7
	Total	7,0517	7,05947	12
coping self statements CSQ factor 6m	cervical	6,4320	8,27417	5
	thoracic	11,4600	5,52769	7
	Total	9,3650	6,94730	12
coping self statements CSQ factor 12m	cervical	9,8340	6,04849	5
	thoracic	8,1786	5,17598	7
	Total	8,8683	5,35193	12

Appendix Table 4.28. Descriptive Statistics for coping self statements CSQ-R factor in the cervical and thoracic SCI subject groups.

	cervical or thoracic lesion	Mean	Std. Deviation	N
praying CSQ factor 2m	cervical	3,7680	5,61700	5
	thoracic	,0000	,00000	7
	Total	1,5700	3,90353	12
praying CSQ factor 3m	cervical	5,0240	5,25422	5
	thoracic	2,5167	4,61114	7
	Total	3,5614	4,82738	12
praying CSQ factor 4m	cervical	5,0507	5,28134	5
	thoracic	3,6910	5,02245	7
	Total	4,2575	4,93883	12
praying CSQ factor 6m	cervical	3,1533	5,43872	5
	thoracic	7,1919	5,27210	7
	Total	5,5092	5,49926	12
praying CSQ factor 12m	cervical	2,6980	5,08189	5
	thoracic	5,7067	5,25460	7
	Total	4,4531	5,18187	12

Appendix Table 4.29. Descriptive Statistics for praying CSQ-R factor in the cervical and thoracic SCI subject groups.

	cervical or thoracic lesion	Mean	Std. Deviation	N
catastrophizing CSQ factor 2m	cervical	4,0560	6,85468	5
	thoracic	,0000	,00000	7
	Total	1,6900	4,63121	12
catastrophizing CSQ factor 3m	cervical	1,8000	2,83464	5
	thoracic	3,9171	5,49325	7
	Total	3,0350	4,53540	12
catastrophizing CSQ factor 4m	cervical	3,9600	7,02099	5
	thoracic	3,3257	3,91435	7
	Total	3,5900	5,13706	12
catastrophizing CSQ factor 6m	cervical	1,5660	2,24604	5
	thoracic	6,2800	5,57757	7
	Total	4,3158	4,96943	12
catastrophizing CSQ factor 12m	cervical	4,7360	4,92069	5
	thoracic	6,6029	7,04640	7
	Total	5,8250	6,06726	12

Appendix Table 4.30. Descriptive Statistics for catastrophizing CSQ-R factor in the cervical and thoracic SCI subject groups.

	cervical or thoracic lesion	Mean	Std. Deviation	N
distraction CSQ factor 2m	cervical	6,6072	9,16022	5
	thoracic	,0000	,00000	7
	Total	2,7530	6,48751	12
distraction CSQ factor 3m	cervical	6,8124	9,19054	5
	thoracic	4,2197	7,32320	7
	Total	5,3000	7,85809	12
distraction CSQ factor 4m	cervical	7,2076	7,17239	5
	thoracic	5,9403	7,84548	7
	Total	6,4683	7,25989	12
distraction CSQ factor 6m	cervical	3,5460	7,92910	5
	thoracic	9,5211	9,05478	7
	Total	7,0315	8,77780	12
distraction CSQ factor 12m	cervical	6,6644	8,78022	5
	thoracic	9,1837	8,76827	7
	Total	8,1340	8,46477	12

Appendix Table 4.31. Descriptive Statistics for distraction CSQ-R factor in the cervical and thoracic SCI subject groups.

	cervical or thoracic lesion	Mean	Std. Deviation	N
interference MPI factor 2m	cervical	10,7792	15,06818	6
	thoracic	5,0278	15,08333	9
	Total	7,3283	14,81888	15
interference MPI factor 3m	cervical	15,9091	19,24234	6
	thoracic	12,4111	16,42958	9
	Total	13,8103	17,01855	15
interference MPI factor 4m	cervical	10,3333	17,08411	6
	thoracic	16,0192	15,45878	9
	Total	13,7448	15,78315	15
interference MPI factor 6m	cervical	7,3333	16,08312	6
	thoracic	19,6061	16,73059	9
	Total	14,6970	17,06054	15
interference MPI factor 12m	cervical	20,5000	14,56560	6
	thoracic	27,6492	18,56872	9
	Total	24,7895	16,90976	15

Appendix Table 4.32. Descriptive Statistics for interference MPI-SCI factor in the cervical and thoracic SCI subject groups.

	cervical or thoracic lesion	Mean	Std. Deviation	N
support MPI factor 2m	cervical	4,0833	5,31429	6
	thoracic	1,5000	4,50000	9
	Total	2,5333	4,83465	15
support MPI factor 3m	cervical	6,6667	5,02908	6
	thoracic	6,1944	7,53303	9
	Total	6,3833	6,44334	15
support MPI factor 4m	cervical	9,5833	6,89686	6
	thoracic	9,5556	7,37053	9
	Total	9,5667	6,93044	15
support MPI factor 6m	cervical	7,2917	7,16313	6
	thoracic	9,2778	6,29291	9
	Total	8,4833	6,47831	15
support MPI factor 12m	cervical	8,3056	3,24580	6
	thoracic	10,1111	4,07376	9
	Total	9,3889	3,75286	15

Appendix Table 4.33. Descriptive Statistics for support MPI-SCI factor in the cervical and thoracic SCI subject groups.

	cervical or thoracic lesion	Mean	Std. Deviation	N
pain severity MPI factor 2m	cervical	6,7083	7,35258	6
	thoracic	1,0833	3,25000	9
	Total	3,3333	5,78612	15
pain severity MPI factor 3m	cervical	7,4167	6,47624	6
	thoracic	6,1667	8,10767	9
	Total	6,6667	7,27623	15
pain severity MPI factor 4m	cervical	6,2083	6,47383	6
	thoracic	7,9722	6,79780	9
	Total	7,2667	6,49414	15
pain severity MPI factor 6m	cervical	4,6667	5,86231	6
	thoracic	8,6111	5,71198	9
	Total	7,0333	5,90918	15
pain severity MPI factor 12m	cervical	8,0000	4,68775	6
	thoracic	11,4167	5,52975	9
	Total	10,0500	5,32196	15

Appendix Table 4.34. Descriptive Statistics for pain severity MPI-SCI factor in the cervical and thoracic SCI subject groups.

	cervical or thoracic lesion	Mean	Std. Deviation	N
life control MPI factor 2m	cervical	3,0000	3,34664	6
	thoracic	2,3889	7,16667	9
	Total	2,6333	5,78319	15
life control MPI factor 3m	cervical	6,7500	10,17718	6
	thoracic	5,3148	7,41125	9
	Total	5,8889	8,30105	15
life control MPI factor 4m	cervical	9,5278	6,17289	6
	thoracic	9,5000	8,85924	9
	Total	9,5111	7,64580	15
life control MPI factor 6m	cervical	8,1667	7,07578	6
	thoracic	11,1670	7,05242	9
	Total	9,9669	6,97257	15
life control MPI factor 12m	cervical	8,0833	5,09111	6
	thoracic	11,9074	3,20710	9
	Total	10,3778	4,34680	15

Appendix Table 4.35. Descriptive Statistics for life control MPI-SCI factor in the cervical and thoracic SCI subject groups.

	cervical or thoracic lesion	Mean	Std. Deviation	N
affective distress MPI factor 2m	cervical	1,1667	1,83485	6
	thoracic	,5556	1,13039	9
	Total	,8000	1,42428	15
affective distress MPI factor 3m	cervical	1,8889	1,48573	6
	thoracic	1,2222	1,46249	9
	Total	1,4889	1,45769	15
affective distress MPI factor 4m	cervical	1,5000	1,58815	6
	thoracic	1,5552	1,32295	9
	Total	1,5331	1,37902	15
affective distress MPI factor 6m	cervical	,2778	,38968	6
	thoracic	2,0737	1,26678	9
	Total	1,3553	1,34186	15
affective distress MPI factor 12m	cervical	3,0556	1,75647	6
	thoracic	2,8515	1,30338	9
	Total	2,9331	1,44336	15

Appendix Table 4.36. Descriptive Statistics for affective distress MPI-SCI factor in the cervical and thoracic SCI subject groups.

	cervical or thoracic lesion	Mean	Std. Deviation	N
negative responses MPI factor 2m	cervical	3,2500	7,96084	6
	thoracic	,5556	1,66667	9
	Total	1,6333	5,10765	15
negative responses MPI factor 3m	cervical	4,0833	7,45933	6
	thoracic	3,7500	6,00000	9
	Total	3,8833	6,36176	15
negative responses MPI factor 4m	cervical	2,0833	3,88158	6
	thoracic	3,8889	5,63487	9
	Total	3,1667	4,93590	15
negative responses MPI factor 6m	cervical	,2917	,60035	6
	thoracic	3,4167	4,71865	9
	Total	2,1667	3,91958	15
negative responses MPI factor 12m	cervical	,6250	1,11524	6
	thoracic	4,6667	4,09649	9
	Total	3,0500	3,77279	15

Appendix Table 4.37. Descriptive Statistics for negative responses MPI-SCI factor in the cervical and thoracic SCI subject groups.

	cervical or thoracic lesion	Mean	Std. Deviation	N
solicitous responses MPI factor 2m	cervical	5,0278	11,28737	6
	thoracic	2,6667	8,00000	9
	Total	3,6111	9,13820	15
solicitous responses MPI factor 3m	cervical	8,4833	8,25116	6
	thoracic	12,8333	15,35415	9
	Total	11,0933	12,80215	15
solicitous responses MPI factor 4m	cervical	11,8500	9,57784	6
	thoracic	12,0000	11,68600	9
	Total	11,9400	10,52635	15
solicitous responses MPI factor 6m	cervical	8,9000	11,36151	6
	thoracic	11,5000	8,20823	9
	Total	10,4600	9,29192	15
solicitous responses MPI factor 12m	cervical	14,0333	12,27056	6
	thoracic	16,0407	9,94099	9
	Total	15,2378	10,54896	15

Appendix Table 4.38. Descriptive Statistics for solicitous responses MPI-SCI factor in the cervical and thoracic SCI subject groups.

	cervical or thoracic lesion	Mean	Std. Deviation	N
distracting responses MPI factor 2m	cervical	3,0833	7,55259	6
	thoracic	2,1667	6,50000	9
	Total	2,5333	6,68812	15
distracting responses MPI factor 3m	cervical	3,2917	3,90005	6
	thoracic	6,2222	7,98871	9
	Total	5,0500	6,64146	15
distracting responses MPI factor 4m	cervical	4,8750	4,01793	6
	thoracic	6,5833	7,23058	9
	Total	5,9000	6,03250	15
distracting responses MPI factor 6m	cervical	4,5000	5,53173	6
	thoracic	7,0556	5,18076	9
	Total	6,0333	5,28633	15
distracting responses MPI factor 12m	cervical	5,4583	4,45089	6
	thoracic	8,1389	5,98189	9
	Total	7,0667	5,41943	15

Appendix Table 4.39. Descriptive Statistics for distracting responses MPI-SCI factor in the cervical and thoracic SCI subject groups.

	cervical or thoracic lesion	Mean	Std. Deviation	N
household chores MPI factor 2m	cervical	,0000	,00000	5
	thoracic	,0000	,00000	9
	Total	,0000	,00000	14
household chores MPI factor 3m	cervical	,0000	,00000	5
	thoracic	,0000	,00000	9
	Total	,0000	,00000	14
household chores MPI factor 4m	cervical	,0000	,00000	5
	thoracic	1,6111	4,83333	9
	Total	1,0357	3,87529	14
household chores MPI factor 6m	cervical	,0000	,00000	5
	thoracic	3,6333	7,34915	9
	Total	2,3357	6,04160	14
household chores MPI factor 12m	cervical	1,8000	2,04939	5
	thoracic	6,4778	6,98423	9
	Total	4,8071	6,05976	14

Appendix Table 4.40. Descriptive Statistics for household chores MPI-SCI factor in the cervical and thoracic SCI subject groups.

	cervical or thoracic lesion	Mean	Std. Deviation	N
outdoor work MPI factor 2m	cervical	,0000	,00000	6
	thoracic	,0000	,00000	9
	Total	,0000	,00000	15
outdoor work MPI factor 3m	cervical	,0000	,00000	6
	thoracic	,0000	,00000	9
	Total	,0000	,00000	15
outdoor work MPI factor 4m	cervical	,0000	,00000	6
	thoracic	,0000	,00000	9
	Total	,0000	,00000	15
outdoor work MPI factor 6m	cervical	,0000	,00000	6
	thoracic	,0000	,00000	9
	Total	,0000	,00000	15
outdoor work MPI factor 12m	cervical	,0000	,00000	6
	thoracic	,5556	1,13039	9
	Total	,3333	,89974	15

Appendix Table 4.41. Descriptive Statistics for outdoor work MPI-SCI factor in the cervical and thoracic SCI subject groups.

	cervical or thoracic lesion	Mean	Std. Deviation	N
activities away from home MPI factor 2m	cervical	,0000	,00000	6
	thoracic	,0000	,00000	9
	Total	,0000	,00000	15
activities away from home MPI factor 3m	cervical	,0000	,00000	6
	thoracic	,0000	,00000	9
	Total	,0000	,00000	15
activities away from home MPI factor 4m	cervical	,0000	,00000	6
	thoracic	,0556	,16667	9
	Total	,0333	,12910	15
activities away from home MPI factor 6m	cervical	,0000	,00000	6
	thoracic	,6111	1,65412	9
	Total	,3667	1,28823	15
activities away from home MPI factor 12m	cervical	3,4167	2,74165	6
	thoracic	6,1944	4,78568	9
	Total	5,0833	4,21378	15

Appendix Table 4.42. Descriptive Statistics for activities away from home MPI-SCI factor in the cervical and thoracic SCI subject groups.

	cervical or thoracic lesion	Mean	Std. Deviation	N
social activities MPI factor 2m	cervical	,0000	,00000	6
	thoracic	,0000	,00000	9
	Total	,0000	,00000	15
social activities MPI factor 3m	cervical	,0000	,00000	6
	thoracic	,0000	,00000	9
	Total	,0000	,00000	15
social activities MPI factor 4m	cervical	,0000	,00000	6
	thoracic	,6296	1,88889	9
	Total	,3778	1,46313	15
social activities MPI factor 6m	cervical	,0000	,00000	6
	thoracic	1,4074	2,81256	9
	Total	,8444	2,24268	15
social activities MPI factor 12m	cervical	2,3333	3,41931	6
	thoracic	5,2963	5,03927	9
	Total	4,1111	4,57647	15

Appendix Table 4.43. Descriptive Statistics for social activities MPI-SCI factor in the cervical and thoracic SCI subject groups.

STATISTICAL ANALYSIS: MAXIMUM PAIN INTENSITY

	Mean	Std. Deviation	N
Max pain 7day VAS either at/below 2m	2,071	3,6525	14
Max pain 7day VAS either at/below 3m	3,214	3,3438	14
Max pain 7day VAS either at/below 4m	3,750	3,9455	14
Max pain 7day VAS either at/below 6m	3,929	4,0849	14
Max pain 7day VAS either at/below 12m	5,036	3,2490	14

Table Appendix 4.44. General Descriptive Statistics for Maximum 7day *spontaneous* pain intensity either at/below level of SCI.

	cervical or thoracic lesion	Mean	Std. Deviation	N
Max pain 7day VAS either at/below 2m	cervical	3,417	4,2710	6
	thoracic	1,063	3,0052	8
	Total	2,071	3,6525	14
Max pain 7day VAS either at/below 3m	cervical	4,833	4,0083	6
	thoracic	2,000	2,3146	8
	Total	3,214	3,3438	14
Max pain 7day VAS either at/below 4m	cervical	3,333	4,0456	6
	thoracic	4,063	4,1182	8
	Total	3,750	3,9455	14
Max pain 7day VAS either at/below 6m	cervical	1,750	4,0466	6
	thoracic	5,563	3,4891	8
	Total	3,929	4,0849	14
Max pain 7day VAS either at/below 12m	cervical	3,500	2,7568	6
	thoracic	6,188	3,2617	8
	Total	5,036	3,2490	14

Appendix Table 4.45. Descriptive Statistics for Maximum 7day *spontaneous* pain intensity in the cervical and thoracic SCI subject groups.

--VERSIÓN RESUMIDA EN ESPAÑOL--**CAPÍTULO 4****CALIDAD DE VIDA E INTENSIDAD DEL DOLOR ESPONTÁNEO
EN PACIENTES LESIONADOS MEDULARES AGUDOS Y CRÓNICOS
CON DOLOR NEUROPÁTICO.****4.1. Introducción**

El DN Central es un problema persistente en pacientes con LM tanto aguda como crónica, asociada con cambios en el ánimo y en la función independientemente de la evolución de la lesión. Un diagnóstico de éxito y una estrategia de tratamiento deberían depender de un procedimiento de evaluación que refleje factores físicos y psicosociales, así como los signos fisiopatológicos presentes en el paciente (Yeziarski et al., 1996; Siddall et al., 1997; Bryce, 2000). Estos factores están unidos a la gravedad del dolor y de los síntomas depresivos y también el estrés percibido (Siddall et al., 2003) y las características personales relacionadas con la adaptación y habilidades de afrontamiento son cruciales para mejorar la Calidad de Vida (QoL) (Haythornthwaite et al., 2000). Este concepto engloba numerosos temas y factores como las auto-percepciones de salud física general, salud psicológica y emocional, relaciones interpersonales, relaciones sexuales satisfactorias, espiritualidad, etc (Schumaker, 1990; Renwick et al., 1996).

Algunos autores como Turk (1992; 2001) han mencionado que la mayoría de instrumentos no son apropiados para su uso con pacientes lesionados medulares por las limitaciones asociadas a otras consecuencias de la lesión que influyen la percepción del dolor y las consiguientes respuestas en diferentes maneras (Widerström-Noga et al., 1999). Factores como el nivel de lesión (Putzke et al., 2002) y los mecanismos del dolor tienen diferente impacto.

El Cuestionario de Estrategias de Afrontamiento del CSQ-R (versión revisada) (Riley et al., 1997), consiste en 27 preguntas, midiendo 6 dimensiones de técnicas de afrontamiento en modo auto-informe de estrategias de afrontamiento cognitivas y conductuales (*Rezo, Ignorancia de las Sensaciones Dolorosas, Distanciamiento del Dolor, Catastrofismo, (Auto-)Afrontamiento y Distracción de la Atención*) y se ha convertido en la medida más frecuente de afrontamiento en pacientes crónicos y objeto de considerable investigación (Jensen et al., 1991). Este último autor encontró que los pacientes que creen que pueden controlar su dolor y evitan el Catastrofismo (la expectativa o preocupación acerca de enormes consecuencias negativas de una situación) y creen que no se encuentran gravemente disminuidos poseen una mejor función que quienes no lo piensan. Estas creencias pueden mediar algunas de las relaciones entre gravedad del dolor y su adaptación a él. Los coeficientes de consistencia van desde 0,57 a 0,89 (Gil et al., 1989; Keefe et al. 1987; Spinhoven et al., 1989) y la fiabilidad test-retest de las subescalas desde 0,68 to 0,91 (Rosenstiel and Keefe, 1983; Main and Waddell, 1991). La validez concurrente ha sido ampliamente estudiada y apoyada. Las escalas del CSQ han explicado la varianza significativa en ajuste en numerosos estudios (Rosenstiel and Keefe, 1983; Beckham et al., 1991; Main and Waddell, 1991). El CSQ-R ha mostrado robustas propiedades psicométricas pero ha tenido limitada exposición en poblaciones de pacientes por su reciente desarrollo (Riley et al., 1997; Riley et al. 1999; Robinson et al. 1997).

Algunos autores (Affleck et al., 1992) han hipotetizado que el Catastrofismo es un constructo cognitivo independiente, mientras que las otras subescalas reflejan un factor de segundo orden de afrontamiento activo del dolor. Esta escala es el predictor más potente de depresión, minusvalía y gravedad del dolor en pacientes crónicos (Tan et al., 2001), consistente con los modelos cognitivo-conductuales del dolor. Altos niveles de Catastrofismo han sido asociados con alta severidad del dolor y estrés psicológico (Turner et al., 2002). El dolor intenso puede causar pensamientos catastrofistas (Sullivan et al., 2001), aunque es necesaria más investigación. Los factores y metas sociales juegan un papel en su mantenimiento, mientras que los procesos evaluativos relacionados apuntan a los mecanismos que unen el Catastrofismo con la experiencia de dolor (Sullivan et al., 2001).

El factor Rezo-Esperanza, evaluado con el CSQ, ha sido considerado previamente una estrategia pasiva y maladaptativa, aunque podría ser adaptativa para algunos individuos en ciertas circunstancias. El afrontamiento ha sido definido como los esfuerzos intrapsíquicos orientados a la acción para manejar el ambiente estresante y las demandas internas que ponen a prueba los recursos de la persona (Robinson et al., 1997). De hecho, Turner and Clancey (1986) informaron de que el aumento del uso del Rezo y Esperanza se relacionaba con auto-informe de

dolor bajo; en algunas muestras de pacientes crónicos fue la estrategia más informada (**Ashby and Lenhart, 1994; Haythornthwaite et al., 2000**).

La conducta de Afrontamiento siempre ocurre en un contexto social y es afectada por el contexto y contribuye a su cambio. Así, el Rezo-Esperanza “activo” podría ser realmente un mecanismo de afrontamiento adaptativo para algunas comunidades (**Hastie et al., 2004**). **Turner et al. (2000)** encontró que las puntuaciones en Afrontamiento significativa e independientemente predijeron invalidez física pero no depresión, mientras que el Catastrofismo predijo depresión pero no invalidez.

El Inventario Multidimensional de Dolor – Versión Lesión Medular (MPI-SCI) (**Widerström-Noga et al., 2002**) evalúa las valoraciones de dolor de los pacientes, el impacto en dominios específicos de sus vidas y conductas específicas que son llevadas a cabo o evitadas a causa del dolor (**Hadjistavropoulos et al., 1999**). El MPI-SCI fue derivado del Inventario Multidimensional de Dolor West Haven-Yale (WHYMPI), el cual posee buenas propiedades psicométricas (**Kerns et al., 1985; Bernstein, 1995**), buena fiabilidad (**Kerns et al., 1985; Bernstein, 1995**), y validez como herramienta de evaluación para numerosos pacientes (**Turk, 1998**), y es sensible al cambio (**Turk, 1998**). Aunque se ha demostrado una buena fiabilidad (**Kerns and Jacob, 1992**) y validez como herramienta de evaluación para numerosos pacientes crónicos (**Turk, 1998**), es sensible al cambio (**Turk, 1998**) y aparece como medida razonable para la evaluación del impacto de dolor crónico después de la LM, en ensayos clínicos, sin embargo, instrumentos suplementarios deben ser incluidos. El rango de respuestas es de 0 (en absoluto) a 6 (extremadamente). La consistencia interna de las subescalas del MPI-SCI fluctúan entre 0,60 para la Angustia Afectiva y 0,94 para Interferencia del Dolor en actividades; casi todas las subescalas muestran buena validez convergente, discriminante y convergente, por lo que aparece como una medida razonable para evaluar el impacto crónico tras la LM (**Widerström-Noga et al., 2006**).

Aunque la reducción de dolor relacionada con la reducción en actividades diarias no ha sido asociada con el nivel de lesión, la intensidad de dolor severa es probable que afecte estos niveles de actividad significativamente (**Widerström-Noga et al., 2002**). Además, factores físicos como el nivel de la lesión medular (**Putzke et al., 2002**) y diferentes mecanismos de dolor (presencia de alodinia, hiperalgesia, etc) puede ser afectar a la Calidad de Vida directamente.

Hasta la fecha no se han realizado estudios descriptivos longitudinales para examinar la intensidad de dolor y factores de Calidad de Vida en pacientes agudos con DN, aunque factores psicológicos han sido vinculados a la presencia e intensidad de dolor y síntomas depresivos hasta cinco años (**Siddall et al., 2003**). Aunque las escalas VAS ha sido ampliamente usada en pacientes para obtener medidas repetidas de la intensidad de dolor en el tiempo (**Price, 1999**), no han sido usadas con escalas de QoL estándar para identificar la relación con características psicosociales de pacientes con dolor crónico. Tal descripción longitudinal y asociación de intensidad de dolor y factores psicofísicos pueden proporcionar mejores medidas de los efectos de los tratamientos.

4.2. Objetivos

4.2.1. Objetivos del Estudio

Identificar cambios significativos en los factores más importantes involucrados en la Calidad de Vida (QoL), derivados del CSQ y MPI-SCI, y relacionar estos cambios con la intensidad de dolor espontáneo y desagradabilidad desde los 2 hasta los 12 meses después de la LM. La influencia de factores físicos como el nivel y naturaleza de la lesión fue también examinada en el desarrollo de factores cognitivo-conductuales.

4.2.2. Hipótesis de Estudio

Hipotetizamos que varios factores de QoL correlacionarían altamente con la intensidad de dolor espontáneo y desagradabilidad, y estaría influenciada por factores físicos asociados con la LM, como lesiones cervicales/torácicas y etiología traumática/ no traumática.

4.3. Métodos

4.3.1. Selección de Sujetos

4.3.1.1. Criterios de Selección

Pacientes con dolor neuropático (sensación de quemazón y/o presión principalmente, a cualquier nivel dermatómico) y lesión medular completa o incompleta sensitivo-motora (según la escala ASIA A-C) con un nivel por encima del cono medular (D10) evaluado a partir de los 2 meses después del trauma, es decir, en su fase aguda

(según la estabilidad neurológica). La etiología de la LM fue traumática o atraumática (enfermedad). Las edades estaban comprendidas entre los 18 y los 75 años. Comprenden y hablan Español. Los espasmos relativos al dolor neuropático se permitieron, independientemente del nivel de LM. Todos los pacientes fueron voluntarios y firmaron un informe de consentimiento. Manifestaron una intensidad mayor que 3 en la Escala Analógica Visual VAS (EVA) equivalente a “moderado” en la escala descriptiva de PPI de McGill (Ligero, Moderado, Angustioso, Horrible, Insoportable), a los dos meses después de la LM. Los pacientes pudieron manifestar cualquier otro dolor no Neuropático (nociceptivo, mecánico, osteomuscular, oncológico, etc) en cualquier estadio de la recogida de medidas.

4.3.1.2. *Criterios de Exclusión*

Se excluyeron los pacientes que sólo manifestaron dolor de tipo “síndrome de dolor complejo regional (CRPS)” o tipo mononeuropatía compresiva, dolor sólo periférico o sólo psicógeno. También se excluyeron el dolor asociado a esclerosis múltiple; aquellos que presentaron deterioro cognitivo: retraso mental, daño cerebral, pacientes sin lenguaje oral, hipoacusia severa, demencia. Los espasmos no relativos al dolor neuropático también se excluyeron del estudio.

4.3.1.3. *Grupos Experimentales*

El análisis longitudinal de Calidad de Vida se realizó en la población en general, seguido por un análisis temporal de estos factores de acuerdo con su nivel de lesión, cervicales versus dorsales y lesiones traumáticas y atraumáticas.

4.3.1.4. *Diseño General de Estudios con Pacientes.*

Todos los procedimientos fueron aprobados por el Comité Ético de Investigación Clínica del “Complejo Hospitalario de Toledo-SESCAM” y se informó al paciente de la naturaleza del estudio, permitiéndole abandonar a voluntad.

4.3.2. *Instrumentos*

4.3.2.1. *Escala Analógica Visual (VAS)*

Como fue descrita en la sección 3.1.5.2 (Capítulo 2), la escala VAS es una herramienta estándar que facilita y simplifica la valoración del dolor del paciente. Una puntuación es elegida entre un mínimo (“sin sensación de dolor en absoluto” ó “0”) y máximo (“el peor dolor imaginable” o “10”). En el presente estudio se utilizaron dos diferentes tasas de dolor: VAS de 7 días (la media de todos los valores VAS obtenidos durante la última semana) y de Desagradabilidad (grado de molestia que le produce el dolor al paciente).

4.3.2.2. *Cuestionario de Estrategias de Afrontamiento –Revisado (CSQ-R)*

Consiste en 27 cuestiones del CSQ original, midiendo 6 dimensiones de técnicas de afrontamiento en una medida auto-informada de estrategias de afrontamiento cognitivo-conductuales (Riley et al., 1997). A los pacientes se les pide que puntúen con qué frecuencia utilizan estas estrategias (0=nunca; 6=siempre). Recientes análisis de factores (Riley and Robinson, 1997; Robinson et al., 1997) sugieren que la escala se representa mejor por una solución de los ya nombrados 6 factores (Ver la versión española del CSQ-R en Appendix 4.2.1).

4.3.2.3. *El Inventario Multidimensional de Dolor – Versión Lesión Medular (MPI-SCI)*

El MPI-SCI (Widerström-Noga et al., 2002) es un cuestionario auto-informado que evalúa las valoraciones del dolor por parte del paciente mediante tres secciones: impacto de dolor, respuestas de las personas significativas y actividades comunes, e incluye 12 subescalas, 8 de ellas miden las respuestas cognitivas, afectivas, sociales y conductuales: Severidad del Dolor, Interferencia en su vida, Control de su vida, Angustia afectiva, Apoyo, Respuestas Negativas de los otros, Respuestas Solícitas de los otros, y Respuestas Distractoras de los otros. Las otras 4 escalas evalúan el grado de participación en actividades diarias: Actividades Domésticas, Actividades lejos de casa y Actividades fuera de casa (Widerström-Noga et al., 2002) (Ver la versión española del MPI-SCI en Appendix 4.2.2-4.2.9)

4.4. Resultados

4.4.1. Datos Demográficos y Diagnósticos

Un total de 30 pacientes fueron reclutados. La media de edad fue de 39 años (DE +/- 13) con edades comprendidas entre los 21 y 71 años. Un tercio de ellos fueron mujeres (33,3 %) y dos tercios hombres (66,7 %). La etiología más común fue traumática por accidente de tráfico en un 40 % seguido de cerca por lesión atraumática (causas médicas y tumores óseos) con un 36,7 %; traumatismo por caída en un 13,3 %; zambullida 6,7 % y arma de fuego en un 3,3%. Según el nivel vertebral afectado valorado mediante el diagnóstico, la mitad de los pacientes tenían lesiones cervicales y la otra mitad dorsales. Más específicamente, el 26,7 % presentaba lesión cervical alta (C2-C4), el 23,3 % lesión cervical baja (C5-C8), el 16,7 % lesión dorsal alta (D1-D4) y el 33,3 % lesión dorsal baja (D5-D10). Esta última, con 10 pacientes fue la más prevalente de entre todas en nuestro estudio. Incluimos tanto lesiones completas (ASIA A) como incompletas (ASIA B y C), siendo dos tercios del primer tipo (63,3%) y un 10 % y 36,7 % del segundo, respectivamente (**Ver sección 2.4.1**).

Las escalas del CSQ-R se compararon con las posibles puntuaciones, las cuales varían con cada factor: Ignorancia del dolor (min= 0, media= 9.82, max= 19.64); Distanciamiento (min= 0, media= 8.27, max= 16.53); Auto-afrentamiento (min= 0, media= 7.74, max= 15.48); Rezo (min= 0, media= 6.28, max= 12.56); Catastrofismo (min= 0, media= 11.85, max= 23.70); Distracción (min= 0, media= 10.37, max= 20.74). Los pacientes no parecieron usar ninguna de las estrategias CSQ-R a los 2 meses de la lesión (**Tabla 4.2**), ya que las puntuaciones son menores que los valores medios del rango posible. Sin embargo, a los 12 meses pudimos observar un incremento en su uso, aunque siguieron mostrando bajas puntuaciones: el Auto-afrentamiento parece ser la más usada, y también durante las siguientes evaluaciones (la media es de 3.93 (2m) y 9.27 (12m)). Después se sitúa Ignorancia del dolor (la media es de 2.26 (2m) y 4.45 (12m)). Desde los 3 meses, Rezo es también usada (con una creciente media de 2.53 (2m) y 5.69 (12m)); Algunos factores CSQ-R muestran puntuaciones bajas, como Distanciamiento (media de 1.18 (2m) and 2.09 (12m)) y Distracción (media de 4.03 (2m) y 8.09 (12m)). Catastrofismo muestra una media de 1.92 (2m) y 7.37 (12m). Las posibles puntuaciones de los factores MPI-SCI son: Interferencia (min= 0, media= 30, max= 60); Apoyo (min= 0, media= 12, max= 24); Severidad del dolor (min= 0, media = 12, max= 24); Control de su vida (min= 0, media = 18, max= 36); Angustia Afectiva (min= 0, media = 9, max= 18); Respuestas negativas (min= 0, media= 12, max= 24); Respuestas solícitas (min= 0, media= 15, max= 30); Respuestas distractoras (min= 0, media = 12, max= 24); Actividades domésticas (min= 0, media = 15, max= 30); Actividades fuera de casa (min= 0, media = 15, max= 30); Actividades lejos de casa (min= 0, media = 12, max= 24); Actividades sociales (min= 0, media = 12, max= 24).

Los factores MPI-SCI también aumentan progresivamente en el tiempo (**Tabla 4.3**), mostrando más del doble del valor a los 12 meses tras la lesión en todos ellos. Los pacientes comenzaron a dar puntuaciones en Actividades domésticas, Actividades lejos de casa y Actividades sociales a los 4 meses y Actividades fuera de casa a los 12 meses.

La tabla de estadísticos descriptivos (**Tabla 4.1**) muestra el progresivo incremento en la intensidad de DN en las medidas repetidas con el VAS de 7 días (descrito en el **Capítulo 2**) en una combinación al nivel y por debajo del nivel de lesión en intensidad de dolor (el rango de la escala fue 0-10). La media del VAS de 7 días es 2.73 a los 2 meses de la lesión y 5.36 a los 12 meses, algunas más pronunciadas y claras con la medida del VAS de Desagradabilidad (la media es de 3.24 a los 2 meses de lesión y 6.00 a los 12 meses). Los estadísticos descriptivos del CSQ-R, MPI-SCI y VAS se muestran en las **Tablas 4.2-4.7**. Las **Tablas en Appendix 4.8-4.45** contienen los estadísticos descriptores para el VAS de 7 días, CSQ-R y MPI-SCI, incluyendo los grupos de pacientes cervicales y dorsales.

4.4.2. Intensidad del Dolor

Se realizaron ANOVA de medidas repetidas (test de Greenhouse-Geisser). No hemos observado diferencias significativas en dolor medido con el VAS de 7 días (n=14) para ninguno de los meses evaluados ($F(3.059, 39.765) = 1.891$; $p=0.146$) ni tampoco para el VAS de Desagradabilidad ($F(2.162, 17.296) = 0.876$; $p=0.565$) (n=9). Sin embargo podemos observar una tendencia para el aumento en intensidad de dolor en las medidas repetidas, con una rampa aguda en el VAS de 7 días y dos picos a los 3 y 6 meses con el VAS de Desagradabilidad, siendo este ligeramente más alto en intensidad (**Fig 4.1. y 4.2**). (La potencia observada se encuentra en el **Appendix de este capítulo**)

4.4.3. Correlaciones entre Intensidad de Dolor, y factores CSQ-R y MPI-SCI.

Para examinar las relaciones entre intensidad de dolor, y factores CSQ-R y MPI-SCI llevamos a cabo correlaciones de Pearson (**Tables 4.8-4.12**). También están incluidas (a modo ilustrativo) las correlaciones de los grupos cervical y dorsal en las **Tablas 4.4.-4.7 en el Appendix** de este capítulo.

4.4.4. Correlaciones de VAS de 7 días y VAS de Desagradabilidad

Altas y significativas correlaciones fueron obtenidas (Spearman Rho) entre el VAS de 7 días y VAS de Desagradabilidad y todos los otros factores CSQ-R y MPI-SCI ($0.625 < r < 0.868$; $p=0.0001$) y ambos cuestionarios a los 2 meses después de la lesión ($0.603 < r < 0.924$; $p=0.0001$). Las Respuestas Solícitas y Distractoras parecen estar más correlacionadas con la medida de Desagradabilidad del VAS ($r=0.745$ and $r=0.676$ respectivamente; $p=0.0001$) pero las Respuestas Negativas están mejor correlacionadas con el VAS de 7 días ($r=0.613$; $p=0.0001$). La Severidad del dolor es el factor del MPI que está más altamente correlacionado a través de todas las medidas (2, 3, 4, 6 y 12 meses tras la LM) tanto con el VAS de 7 días como con el de Desagradabilidad, significando que puede ser considerada como la misma variable. Pero en el mes 3 después de la lesión, únicamente los factores CSQ-R Rezo y Afrontamiento están altamente correlacionados con la intensidad del dolor ($r=0.690$ en VAS de 7 días y $r=0.756$ en VAS de Desagradabilidad; $p=0.0001$). En el siguiente mes examinado, todas las correlaciones altas entre Intensidad de dolor y los cuestionarios desaparecen excepto la Severidad del Dolor del MPI-SCI ($r=0.704$ y 0.768). Similar en el mes 6°, existen ahora altas correlaciones con el VAS de Desagradabilidad y Afrontamiento y Rezo ($r=0.746$ and 0.700 ; $p=0.0001$) y la Interferencia ($r=0.658$; $p=0.0001$). En la última valoración a los 12 meses las correlaciones son las mismas que a los 4 meses.

4.4.5. Correlaciones de los Factores CSQ-R.

A los 2 meses tras la LM, la mayoría de los factores CSQ-R se encuentran altamente correlacionados entre ellos y también con los MPI-SCI, por ejemplo Ignorancia de dolor con Distanciamiento ($r=0.827$), y Afrontamiento ($r=0.767$), Rezo ($r=0.679$) y Distracción ($r=0.751$). A los 3 meses Afrontamiento está correlacionado positivamente con Ignorancia de dolor, Rezo y Distracción ($r=0.625$). Afrontamiento también está correlacionado con todos los factores MPI-SCI (menos Respuestas Negativas). A los 4 meses Distracción está correlacionada positivamente con Ignorancia de dolor ($r=0.642$) mientras Afrontamiento correlaciona con Respuestas Solícitas ($r=0.757$) y Respuestas de Distracción ($r=0.684$). A los 6 meses las únicas estrategias altamente correlacionadas son Afrontamiento y Distracción ($r=0.694$). Afrontamiento también está correlacionada con el factor MPI-SCI Severidad ($r=0.659$). A los 12 meses las únicas estrategias del CSQ-R altamente correlacionadas son Ignorancia del dolor y Distracción ($r=0.773$).

4.4.6. Correlaciones de los Factores MPI-SCI.

Los factores MPI-SCI también son muy altos correlacionados a los 2 meses, desapareciendo a lo largo de los meses. Del mes 2 al 6, Distracción y Afrontamiento están muy bien correlacionados ($r=0.694$ en el mes 6) como también Severidad y Afrontamiento ($r=0.659$ en el mes 6); Respuestas Solícitas y Apoyo ($r=0.846$ en el mes 6) y Respuestas Distractoras y Apoyo ($r=0.784$ en el mes 6), Severidad y Apoyo ($r=0.789$ en el mes 6), Respuestas Solícitas y Severidad ($r=0.696$ en el mes 6), Respuestas Distractoras y Severidad ($r=0.712$ en el mes 6) y Respuestas Solícitas y Distracción ($r=0.899$ en el mes 6). A los 4 y 6 meses los pacientes empezaron a realizar Actividades Domésticas y correlacionan perfectamente con Actividades lejos de casa (1.00) y Actividades Sociales (1.00) a los 4 meses más que a los 6 meses (0.865 y 0.998 respectivamente). Las Respuestas Negativas están positivamente correlacionadas con Actividades lejos de casa sólo a los 6 meses, coincidiendo con el regreso del paciente a casa.

4.4.7. Diferencias en el uso de Estrategias Cognitivas.

4.4.7.1. CSQ

Se realizaron ANOVA de medidas repetidas (test de Greenhouse-Geisser) para cada factor del cuestionario. No hubo diferencias entre los 5 momentos temporales en 5 de los factores ($n=6$): Ignorancia de dolor ($F(2.655, 29.207) = 1.152$; $p=0.341$) (**Fig 4.3**); Distanciamiento ($F(1.606, 25.317) = 1.435$; ; $p=0.261$) (**Fig 4.4**); Rezo ($F(2.367, 26.042) = 2.135$; $p=0.131$) (**Fig 4.5**); Catastrofismo ($F(2.471, 27.177) = 1.487$; $p=0.243$) (**Fig 4.6**) ; Distracción ($F(2.621, 28.830) = 1.056$; $p=0.376$) (**Fig 4.7**).

Sólo el factor Afrontamiento fue estadísticamente significativo (intra-sujetos) ($F(2.302, 25.317) = 4.027$; $p=0.026$) (**Fig 4.8**) y aplicando el test de diferencia significativa post-hoc Tukey, la diferencia entre la medida de 2 meses y el resto fue significativa ($F(4,8) = 9.110$; $p=0.004$). Los datos descriptivos muestran una tendencia general con un incremento en todos los factores en las medidas temporales sucesivas tanto positivas (Ignorancia del dolor, Distanciamiento, Rezo, Distracción, Afrontamiento) o negativas (Catastrofismo).

Así podemos observar que los pacientes no usan estrategias cognitivas a los 2 meses (valores cercanos a 0). Sin embargo, a los 12 meses hay un incremento en su uso (generalmente es la puntuación más alta), aunque siguen mostrando valores bajos en Ignorancia del dolor (aquí el máximo es 4 comparado con el máximo posible =19.64), Distanciamiento (máx. de 1.5 con el máx.posible=16.53), Rezo (máx. de 1.5 con el máx.posible=12.56) y Distracción (máx. de 8 con el máx.posible=20.74). Una estrategia muy usada es Afrontamiento (máx. de 9.5 con el máx.posible=15.48). El Catastrofismo se mostró con baja presencia (máx. de 5.8 con el máx.posible=23.70).

4.4.7.2. MPI-SCI

Se realizaron ANOVA de medidas repetidas (test de Greenhouse-Geisser o test de Esfericidad Asumida si fue apropiado) para cada factor del cuestionario y encontramos diferencias entre los momentos temporales en 9 de los factores ($n= 15$): Interferencia ($F(4, 34.496) = 3.578$; $p=0.031$) (**Fig 4.9**); Apoyo ($F(3.017, 42.232) = 5.573$; $p=0.003$) (**Fig 4.10**); Severidad del dolor ($F(4, 46.223) = 3.144$; $p=0.030$) (**Fig 4.11**); Control de su vida ($F(4, 38.311) = 4.258$; $p=0.013$) (**Fig 4.12**); Angustia Afectiva ($F(4, 40.121) = 5.033$; $p=0.005$) (**Fig 4.13**); Respuestas Solícitas ($F(4, 45.016) = 4.241$; $p=0.009$) (**Fig 4.15**); Actividades Domésticas ($F(4, 25.784) = 4.641$; $p=0.019$) (**Fig 4.17**); Actividades lejos de casa ($F(4, 16.477) = 19.726$; $p=0.000$) (**Fig 4.19**); Actividades Sociales ($F(4, 21.844) = 9.162$; $p=0.002$) (**Fig 4.20**). Pero no hubo significación entre los factores: Respuestas Negativas ($F(4, 38.690) = .742$; $p=0.524$) (**Fig 4.14**); Respuestas Distractoras ($F(4, 38.198) = 1.915$; $p=0.148$) (**Fig 4.16**) y Actividades fuera de casa ($F(4, 14.000) = 2.059$; $p=0.173$) (**Fig 4.18**).

4.4.7.3. Diferencias entre Grupos

El grupo total de 30 pacientes fue dividido en dos grupos de acuerdo con la etiología, resultando en el grupo traumático ($n=6$) y atraumático ($n=6$) para el CSQ-R; y traumático ($n=8$) y atraumático ($n=7$) para el análisis del MPI-SCI. También se realizó de acuerdo al nivel de LM, resultando en el grupo cervical ($n=6$) y dorsal ($n=9$) para el análisis del CSQ-R; y cervical ($n=6$) y dorsal ($n=9$) para el MPI-SCI excepto para Actividades Domésticas (grupo cervical $n=5$, grupo dorsal $n=9$).

4.4.7.3.1. Cervical y Dorsal

4.4.7.3.1.1. CSQ-R

Se realizaron ANOVA de medidas repetidas (test de Greenhouse-Geisser) para cada factor del cuestionario. No hubo diferencias entre los 5 momentos temporales en 5 de los factores: Ignorancia de dolor ($F(2.490, 24.901) = 0.987$; $p=0.403$) (**Fig 4.21**) ; Distanciamiento ($F(1.751, 17.508) = 2.063$; $p=0.161$) (**Fig 4.22**) ; Afrontamiento (estadísticamente significativo intra-sujetos) ($F(2.015, 20.153) = 3.685$; $p=0.043$) (**Fig 4.23**), muestra una tendencia a ser más usado por pacientes con lesiones cervicales; mientras que Rezo ($F(2.649, 26.488) = 1.796$; $p=0.177$) (**Fig 4.24**) ; Catastrofismo ($F(2.388, 23.881) = 1.225$; $p=0.317$) (**Fig 4.25**) y Distracción ($F(2.526, 25.265) = 0.751$; $p=0.511$) (**Fig 4.26**) son más vistos en el grupo dorsal. La potencia observada no es muy alta en general (**Ver Tablas Appendix 4.2**) debido a la falta de pacientes en todas las medidas temporales.

4.4.7.3.1.2. MPI-SCI

Se realizaron ANOVA de medidas repetidas (test de Greenhouse-Geisser o test de Esfericidad Asumida si fue apropiado) para cada factor del cuestionario y encontramos diferencias entre los momentos temporales en 7 de los factores : Interferencia ($F(2.606, 33.876) = 3.066$; $p=0.047$) (**Fig 4.27**); y Apoyo ($F(3.004, 39.046) = 4.625$; $p=0.007$) (**Fig 4.28**); son estadísticamente significativos y más presentes en pacientes con lesiones dorsales y desde el mes 4º en Apoyo. El Control de su vida ($F(2.794, 36.320) = 3.551$; $p=0.026$) (**Fig 4.30**) muestra niveles significativos desde el mes 4 en el grupo dorsal. La Angustia Afectiva ($F(3.157, 41.042) = 5.372$; $p=0.003$) (**Fig 4.31**) muestra más niveles en los pacientes dorsales pero a los 12 meses parece tener el mismo aumento. Las respuestas Solícitas ($F(3.189, 41.459) = 3.589$; $p=0.020$) (**Fig 4.33**) muestran un significativo y progresivo incremento en las respuestas dadas al grupo dorsal. Las Actividades lejos de casa ($F(1.188, 15.442) = 17.465$; $p=0.0001$) (**Fig 4.37**) y las Actividades Sociales ($F(1.574, 20.468) = 7.706$; $p=0.005$) (**Fig 4.38**) muestran un significativo y progresivo incremento en esta clase de actividades a partir del mes 4 y 3 respectivamente para el grupo dorsal mientras que el cervical empieza en el mes 6.

Pero no fueron significativos los siguientes factores: Severidad del dolor ($F(3,189, 41.462)= 2.446; p=0.074$) (**Fig 4.29**) con una tendencia mayor en el grupo dorsal; Respuestas Negativas ($F(4, 52)=0.698; p=0.597$) (**Fig 4.32**); Respuestas Distractoras ($F(2.698, 35.070)= 1.493; p=0.235$) (**Fig 4.34**) muestran una tendencia mayor en el grupo dorsal; Actividades Domésticas ($F(2.101, 25.213) = 3.177; p=0.057$) (**Fig 4.35**) muestran un significativo comienzo más temprano en el mes 3 para el grupo dorsal mientras que el cervical lo hace al mes 6; y Actividades fuera de casa ($F(1.000, 13.000)= 1.413; p=0.256$) (**Fig 4.36**) muestra una tendencia a comenzar en el mes 6 en el grupo dorsal (cuando vuelven a casa del hospital) pero el grupo cervical no parece desarrollar ninguna actividad. La potencia observada que debería obtenerse con diferente número de participantes es en general aceptable y es alta en algunos de los factores (**Ver Tablas Appendix 4.3**).

4.4.7.3.2. Lesiones Traumáticas y Atraumáticas.

4.4.7.3.2.1. CSQ-R

Se realizaron ANOVA de medidas repetidas (test de Greenhouse-Geisser) para cada factor del cuestionario y no hubo diferencias entre los momentos temporales en 5 de los factores: Ignorancia del dolor ($F(2.617, 26.167)= 1.085; ; p=0.367$) (**Fig 4.39**) y Distanciamiento ($F(1.519, 15.192)= 1.481; p=0.254$) (**Fig 4.40**) muestran una tendencia a ser más utilizados por los pacientes con lesiones traumáticas; Rezo ($F(2.274, 22.741) = 2.171; p=0.132$) (**Fig 4.41**) muestra una tendencia cambiante a ser más usada en pacientes con lesiones atraumáticas en los primeros meses pero no en el mes 12; Catastrofismo ($F(2.461, 24.610) = 1.423; p=0.261$) (**Fig 4.42**) muestra una mayor tendencia a estar más presente en pacientes con lesiones atraumáticas; Distracción ($F(2.706, 27.056)= 1.115; p=0.356$) (**Fig 4.43**) muestra una tendencia a un mayor uso en pacientes con lesiones traumáticas desde el mes 6. Sólo Afrontamiento fue significativo (entre-sujetos) ($F(2.236, 22.363) = 4.122; p=0.026$) (**Fig 4.44**) y muestra un cambio en el uso por los pacientes con lesiones atraumáticas en los primeros meses pero no en el mes 12.

4.4.7.3.2.2. MPI-SCI

Se realizaron ANOVA de medidas repetidas (test de Greenhouse-Geisser o test de Esfericidad Asumida si fue apropiado) para cada factor del cuestionario y encontramos diferencias entre los momentos temporales en 9 de los factores: Interferencia ($F(4, 52) = 3.661; p=0.011$) (**Fig 4.45**); Apoyo ($F(2.673, 34.749) = 6.278; p=0.002$) (**Fig 4.46**); y Severidad del dolor ($F(3.124, 40.610) = 3.366; p=0.026$) (**Fig 4.47**) son estadísticamente significativos y más presente en pacientes con lesiones traumáticas a partir del mes 4.

El Control de su vida ($F(4, 38.311) = 4.258; p=0.013$) (**Fig 4.48**) muestra niveles significativos en los meses 4 y 6 en pacientes traumáticos, pero no con el grupo de atraumáticos a los 12 meses. La Angustia Afectiva ($F(4, 52) = 5.059; p=0.002$) (**Fig 4.49**) muestra una fluctuación entre los grupos pero en el mes 12 parecen tener el mismo nivel de angustia. Las Respuestas Solícitas ($F(4, 52) = 4.622; p=0.007$) (**Fig 4.51**) muestran un incremento progresivo en las respuestas dadas al grupo traumático mientras que el atraumático presenta más en el mes 3 y decrece después. Actividades Domésticas ($F(2.019, 24.222) = 5.210; p=0.013$) (**Fig 4.53**) muestra un comienzo temprano en el mes 3 para el grupo atraumático mientras que el traumático lo hizo en el mes 6. Las actividades lejos de casa ($F(1.161, 1.161)= 18.383; p=0.0001$) (**Fig 4.55**) y las Actividades Sociales ($F(1.491, 19.386)= 8.876; p=0.004$) (**Fig 4.56**) muestran un incremento significativo y progresivo en estas actividades desde los primeros meses para el grupo atraumático, pero después el traumático presenta más tasa a los 12 meses.

Pero no hubo diferencias significativas entre los factores: Respuestas Negativas ($F(4, 52)= 0.797; p=0.553$) (**Fig 4.50**); Respuestas Distractoras ($F(4, 52)= 0.130; p=0.148$) (**Fig 4.52**) y Actividades fuera de casa ($F(1.000, 13.000)= 1.920; p=0.189$) (**Fig 4.54**) muestran una tendencia a empezar en el mes 6 por el grupo traumático pero el atraumático parece no desempeñar ninguna actividad.

4.5. Discusión

Este es el primer estudio que describe cambios de dolor espontáneo y desagradabilidad utilizando la escala VAS, combinada con escalas cognitivo-conductuales de Calidad de Vida (CSQ-R y MPI-SCI) durante la fase aguda y crónica de la LM en un grupo seleccionado de pacientes con DN. Nuestros resultados indican que la intensidad y desagradabilidad aumentan, pero con el último desarrollo e el último estadio y con mayor intensidad entre los meses 3 y 6 después de la LM. Observamos que la escala CSQ-R por sí sola puede no ser el cuestionario más adecuado para la predicción de una medida funcionamiento físico de ajuste como la invalidez, y por ello elegimos

el MPI-SCI también, que complementa tales factores. Es de importancia que la escala MPI-SCI incluye importantes correlaciones con la intensidad de dolor y desagradabilidad después de la LM. Como tal, el uso de MPI-SCI puede ser más útil como instrumento de evaluación del impacto del dolor en personas con LM y sus otros significativos. Podemos observar una tendencia al incremento en la intensidad de dolor a lo largo de las medidas repetidas, con una rampa aguda en el VAS de 7 días y dos picos a los 3 y 6 meses en el VAS de Desagradabilidad, siendo este ligeramente más alto en intensidad.

4.5.1. Utilización de Estrategias Cognitivas frente al Dolor.

Este estudio indica que los pacientes con LM usan estrategias cognitivas de afrontamiento del dolor activo (CSQ-R) y solicitan Apoyo y Respuestas Solícitas (MPI-SCI) durante los primeros 12 meses después de la LM; a los 2 meses los factores se encuentran cerca del cero con un ligero aumento en Ignorancia de dolor, Distanciamiento, Rezo y Distracción a lo largo del año. Es interesante que el análisis de factores negativos como Catastrofismo del dolor (CSQ-R) reveló sólo un nivel moderado, incluso cuando los pacientes experimentaron una Interferencia de dolor (MPI-SCI) significativa a los 12 meses sugiriendo que el paciente raramente magnifica o se siente impotente frente al dolor durante su desarrollo en el último año.

Generalmente los pacientes tienden a utilizar estrategias cognitivas (Respuestas Solícitas, Distractoras y Negativas) cuando la intensidad de dolor espontáneo es sobre 3 en la escala de VAS, pero estos tienden a fallar en la correlación cuando la intensidad de dolor alcanza un 5 ó un 6, lo cual puede ser interpretado como que el uso de estas estrategias depende directamente de una baja puntuación de dolor. A más alta intensidad de dolor otros factores como la personalidad, depresión, etc pueden mediar en las respuestas de dolor (Sullivan et al., 1990). Análisis correlacionales también mostraron que el apoyo para estos pacientes desde los meses 34 con dolor espontáneo fue ampliamente obtenido con el uso de Afrontamiento y no de sus familiares incluso cuando tuvieron acceso a ellos durante la fase aguda de la LM.

En contraste, la Interferencia, Apoyo, Angustia Afectiva y Respuestas Solícitas correlacionaron significativamente con intensidad de desagradabilidad, indicando que la familia atiende y proporciona apoyo cuando el paciente experimenta malestar como un componente “afectivo” del dolor de la LM.

Durante los meses 23 del periodo agudo tras la LM, la mayoría de los factores CSQ-R (Afrontamiento, Rezo, Distanciamiento, Ignorancia del dolor) están presentes y coexisten. A los 4 meses el Afrontamiento correlaciona con Respuestas Solícitas y Distractoras, lo cual puede reflejar la motivación por la utilización de estrategias de afrontamiento proporcionadas por los familiares. El Afrontamiento y Distracción también correlaciona con Severidad a los 6 meses, indicando que los pacientes usan estrategias de afrontamiento para encarar directamente la intensidad del dolor y la desagradabilidad. Esta relación no es mantenida a los 12 meses de la LM mientras que sólo las estrategias del CSQ-R altamente correlacionadas son Ignorancia del dolor y Distanciamiento. Es clara que la interrelación entre las estrategias de afrontamiento durante los 12 primeros meses medidas con el cuestionario CSQ-R no es estática, sino que evoluciona constantemente mes a mes.

Los factores de Calidad de Vida medidos con el MPI-SCI correlacionaron altamente durante el periodo de los 2 meses tras la LM, aunque estos rápidamente se perdieron después: durante los primeros 6 meses, pudieron sugerirse intentos del uso de algunas estrategias como Distracción y Afrontamiento a pesar del incremento en el dolor. Las relaciones entre Apoyo y otros factores como Respuestas Solícitas y Distractoras, Severidad, y esta última con Respuestas Solícitas y Distractoras mostraron que a una intensidad de dolor moderada, los familiares progresivamente desplegaron más respuestas hacia el paciente a medida que la intensidad de dolor se desarrolló.

Observamos en los meses 2 al 4, con una relación no significativa a los 12 meses y similarmente al estudio de **McColl et al. (1995)**, que las relaciones entre “apoyo social” y “afrontamiento” cambiaron específicamente en esta población en el tiempo, reflejando una asociación positiva en un momento temprano después de la LM.

En nuestra actual muestra los tratamientos físicos y psicológicos no parece que fueron efectivos para el alivio del dolor (la intensidad decrece de los 2 a los 12 meses) sin tener en cuenta las estrategias cognitivo-conductuales aprendidas mientras los pacientes estaban ingresados. Pudimos observar que no parece ser ese el caso, ya que aumentos en las diferentes estrategias positivas contra el dolor no significan un cambio en la gravedad del dolor, más bien lo contrario. Sin embargo, podría ser una cuestión de cambio cuantitativo, en términos de cuánto es necesario para inferir un cambio significativo en intensidad de dolor.

De los meses 4-6 los pacientes empezaron a realizar algunas Actividades Domésticas las cuales correlacionan con Actividades fuera de casa y Actividades Sociales, pero no se mantiene a los 12 meses después de la LM, lo que puede interpretarse como una motivación inicial para el paciente en las actividades diarias lo antes posible, seguido

por un periodo de frustración causado por la incapacidad en el impedimento del desarrollo de tales actividades. En contraste, las Respuestas Negativas son positivamente correlacionadas con Actividades lejos de casa sólo a los 6 meses, coincidiendo con la vuelta del paciente al ambiente en el hogar, probablemente debido al estímulo familiar, apoyo y un incremento en la confianza del paciente.

En general nuestro estudio reveló una asociación entre Catastrofismo e Interferencia de dolor a los 2, 6 y 12 meses pero no a los 3 y 4 meses después de la LM (probablemente debido a la alta expectativa de una recuperación funcional relacionada con la rehabilitación física). Son importantes los altos niveles de Catastrofismo asociados con una Severidad del dolor más alta a los 2, 3, 4 y 12 meses y alta correlación con Angustia Afectiva a cada momento temporal. En contraste, el Catastrofismo sólo correlacionó con Afrontamiento durante el 2º y 3er mes. Nuestros resultados son apoyados por una correlación diferencial del Catastrofismo y tanto los factores cognitivos como afectivos durante identificación del dolor por los demás (**Turner et al. 2002 and Jones et al. 2003**).

El Catastrofismo puede contribuir a incrementar la intensidad del dolor, pero también es posible que un aumento de dolor contribuya a un elevado Catastrofismo (**Tan et al., 2001**). De hecho nuestra observación de que el Catastrofismo se relaciona con la intensidad del dolor tan pronto como a los 2 meses después de la LM apoya en alguna medida esta inter-relación, pero no es posible establecer una causa y efecto de ello (**Sullivan et al., 2001**). Más aún, **Sullivan et al. (2001)** sugirió que el Catastrofismo puede contribuir a una experiencia aumentada de dolor mediante el incremento de focalización atencional en el dolor y/o mediante una reactividad emocional al dolor incrementada. De la misma manera, nuestro estudio no mostró correlación entre Ignorancia del dolor, Distanciamiento y Control de su vida y mostró una correlación positiva entre Angustia Afectiva y Respuestas Negativas en la mayoría de pacientes evaluados.

El Rezo no fue una de las estrategias más frecuentemente usadas en nuestra población de pacientes con LM. Aunque Rezo fue progresivamente adoptado hasta los 4 meses, no se eligió después de un año. De hecho a los 2 meses es altamente correlacionada con todos los factores; con Afrontamiento, Severidad de dolor y Distracción a los 3 meses, y sólo con Distracción a los 4 meses, similar a la reducción en correlaciones entre factores observada a través del tiempo por otros factores de Calidad de Vida como Afrontamiento y Catastrofismo.

Sin embargo, como propuso **Hastie et al. (2004)** proposed, las personas aprenden el fundamento del afrontamiento del contexto cultural, el cual es similar al factor Auto-afrontamiento, que está relacionado con Respuestas Solícitas y Distractoras, influidas por el ambiente.

4.5.2. Patrones en el uso de las Estrategias Cognitivas.

Varios intentos se han realizado para categorizar e identificar subgrupos de pacientes o patrones en relación con las estrategias de afrontamiento usadas. **Riley et al. (1999)** encontró una estructura de dos factores para las subescalas del CSQ-R a través de dos muestras de pacientes con dolor crónico: "cognitiva" y "distracción". Tres subgrupos homogéneos fueron identificados que consistieron en un grupo con una alta puntuación en afrontamiento, un grupo con una puntuación general baja para las preguntas del CSQ-R, y finalmente un grupo con frecuente apoyo a las preguntas de Catastrofismo y Distracción. Los análisis con estos subgrupos de pacientes pueden proporcionar una valiosa información con respecto a la respuesta diferencial al tratamiento de dolor.

Por lo tanto podemos observar diferentes patrones en el uso de estrategias comparando el tipo de gráficos por observación de tendencias, sin tener en cuenta la puntuación máxima (**ver los gráficos en la sección 4.4 Resultados**):

Tipo 1) CSQ-R Ignorancia del dolor, MPI-SCI Apoyo y Respuestas Solícitas, muestran un rápido incremento en el uso de la estrategia hasta los 4 meses seguido por una menor disminución a los 6 meses y un nuevo incremento a los 12 meses, lo cual indica que el apoyo de los familiares estaba aumentando.

Tipo 2) CSQ-R Distanciamiento con un incremento rápido desde el mes 4 con una puntuación de 0, significando que los pacientes empiezan a usar esta estrategia en ese momento.

Tipo 3) MPI-SCI Interferencia, Severidad del dolor, Angustia Afectiva, un incremento hasta el mes 3 después una meseta y aumento de nuevo en el mes 12, mostrando una estabilidad en la percepción de la intensidad de dolor y angustia e interferencia con la vida diaria, incluso conociendo que del mes 3 al 6 el VAS aumenta progresivamente.

Tipo 4) CSQ-R Rezo, Afrontamiento, con un incremento hasta el mes 6 y después una disminución en el mes 12 mostrando que los pacientes usan las estrategias principalmente en la fase aguda; y también MPI-SCI Control de su vida, aunque este último aumenta ligeramente otra vez en el mes 12.

Tipo 5) Catastrofismo y Distracción y MPI-SCI Respuestas Distractoras muestran un incremento progresivo en todas las medidas, indicando que las estrategias son utilizadas sin importar el periodo evaluado.

Tipo 6) MPI-SCI Respuestas Negativas incrementa hasta el mes 3 después baja hasta el 6° y aumenta en el mes 12, podemos ver dos grandes incrementos en esta respuesta, no relacionados con la intensidad de dolor. Tipo 7) MPI-SCI Actividades Domésticas, Actividades fuera y lejos de casa, comenzaron con una puntuación de 0, subieron en el mes 3, 6 y 4 respectivamente, de acuerdo con las primeras salidas del hospital como ingresados.

Estudios de afrontamiento y dolor presentan contradicciones al focalizarse en los comportamientos. Típicamente incluyen el descanso, excesiva pasividad (Brown and Nicassio, 1987; Jensen et al., 1991b) y Catastrofismo relacionado con el dolor (Turner et al., 2000; Tan et al., 2001). Geisser et al. (1999) han argumentado recientemente que la reducción de las estrategias de afrontamiento que no ayudan deberían ser el principal foco del tratamiento, más que el incremento de potenciales estrategias de ayuda. Particularmente ocluido por la dominancia del afrontamiento son aquellas clases de conductas *automáticas* y aquellas que no están en control directo de sensaciones y emociones (McCracken and Eccleston, 2003).

Existen sólo un pequeño número de estudios empíricos que demuestran una asociación positiva entre aceptación y adaptación con éxito al dolor crónico, y los pacientes informan de menos dolor (Jacob et al., 1993; Schmitz et al.; McCracken 2003). La aceptación psicológica del dolor crónico ha sido definida como la vivencia del dolor sin reacción, desaprobación o intentos de reducirlo o evitarlo (McCracken 1998, 1999).

McCracken and Eccleston (2003) mostraron en su estudio que los pacientes con dolor crónico que las variables de afrontamiento fueron relativamente débiles relacionadas con la aceptación del dolor y relativamente no fiables con el ajuste a las variables de dolor. Sin embargo, una mayor aceptación de dolor crónico fue asociada con menos dolor, invalidez, depresión y ansiedad relacionada con el dolor, mayor tiempo de funcionamiento diario, y mejor estatus de trabajo. Desviar la atención y el rezo y la esperanza fueron asociados consistentemente a un mayor dolor y menos funcionamiento saludable, lo cual hemos observado en nuestra población hasta el mes 4° tras la LM. La aceptación del dolor no está relacionada con la desviación de la atención o la reinterpretación del dolor, es sólo mínimamente relacionada con la ignorancia del dolor y negativamente con el rezo y la esperanza.

Se ha demostrado que cuando los sujetos sanos tratan de no experimentar dolor inducido experimentalmente, tienen retrasada la recuperación después de la exposición al dolor (Cioffi and Holloway, 1993) y el fallo ha sido mostrado el informe adversamente afectado y en la tolerancia al dolor (Levine et al., 1993; Van den Hout et al., 2000). Otros estudios han defendido que el objetivo para controlar los intentos debe ser esencial. Algunos han mostrado control percibido sobre los efectos del dolor o la vida en general son correlatos más importantes que las percepciones de control sobre el dolor en sí mismo (Tan et al., 2002 ; Jacob et al., 1993 and Geisser ,1992).

4.5.3. El Impacto de los Factores Físicos en la Calidad de Vida: LM Cervical versus Dorsal.

El análisis de los factores de Calidad de Vida obtenidos de pacientes con LM cervical y dorsal indica un patrón de estrategias contra el dolor distinto aparentemente no relacionado con la invalidez física de la para- o tetraplegia, ya que una menor fluctuación de medida se ha visto en el grupo cervical a través de la mayoría de los factores. No podemos afirmar, como sugirió Turner et al. (2000), que las puntuaciones de Afrontamiento predigan la invalidez física en nuestra población y estamos de acuerdo con Widerström-Noga, et al. (2002) que propuso que la reducción en los niveles de actividad por el dolor era independiente del nivel de lesión.

Los pacientes con lesiones cervicales tienden a adoptar diferentes estrategias cognitivas frente al dolor del CSQ-R que los del grupo dorsal, como Ignorancia del dolor, Distanciamiento, Afrontamiento; mientras Rezo, Catastrofismo y Distracción eran más frecuentemente utilizadas por los pacientes con lesión dorsal.

La Interferencia, Apoyo, Control de su vida y Respuestas Solícitas del cuestionario MPI-SCI indicaron la presencia de estos factores después de una LM dorsal en los pacientes. Un significativo y progresivo incremento en los factores Actividades Sociales y Actividades lejos de casa fue observado en los meses 3-4, respectivamente, después de una lesión dorsal, y un retraso hasta el mes 6° después de una lesión cervical. La Angustia Afectiva fue generalmente mayor también después de una LM dorsal, pero a los 12 meses presentó el mismo aumento en angustia. Una tendencia no significativa también fue observada con altas tasas observadas por la Severidad de dolor, Respuestas Distractoras, Actividades Domésticas y Actividades fuera de casa en el grupo dorsal.

También es interesante que el nivel neurológico de la LM (ASIA) fue identificado en un estudio como la única variable que explica la Calidad de Vida relacionada con la salud, y que la LM causó más depresión y angustia en los pacientes con lesión motora incompleta que completa (Dahlberg et al. 2005).

En una población de dolor crónico (de media 9.8 años de lesión), **Widerström-Noga et al. (2004)** identificó grupos de pacientes basados en estrategias cognitivas: el “Disfuncional” y el “Afrontamiento Adaptativo”, donde la LM cervical se asoció con el primer subtipo. En contraste nosotros no identificamos esa tendencia entre los grupos cervicales y dorsales con el análisis de Afrontamiento, más bien la población con LM cervical aplicó esta estrategia más temprano en el tiempo que los del grupo dorsal.

La Interferencia, Apoyo, Control de su vida, Respuestas Solícitas (estadísticamente significativa) y Respuestas Negativas del MPI-SCI mostraron más presencia en pacientes con lesiones dorsales. Las Actividades lejos de casa y Actividades Sociales mostraron un significativo y progresivo aumento en esta clase de actividades desde el mes 4 y 3 respectivamente para el grupo dorsal mientras que el cervical empezó en el mes 6. La Angustia Afectiva fue más constante en los pacientes dorsales también pero en el mes 12 mostró el mismo incremento en angustia. Aunque no hubo diferencia significativa entre Severidad del dolor, Respuestas Distractoras, Actividades Domésticas y Actividades fuera de casa, aún tuvieron más presencia en el grupo dorsal.

4.5.4. Factores Físicos: LM Traumáticas versus Atraumáticas

En general el grupo de pacientes atraumático tendió a rechazar el uso de algunas estrategias CSQ-R después de un periodo de ensayo, quizá porque no pudieron percibirlos como útiles contra el dolor, como fue el caso del Afrontamiento, Rezo y Distracción; mientras que la población traumática tendió a usar la mayoría de las estrategias de afrontamiento hasta un año después de la LM, incluso cuando mostraron el nivel más alto de Catastrofismo.

La Interferencia, Apoyo, Severidad del dolor y Respuestas Solícitas del MPI-SCI son significativamente más prevalentes en pacientes con lesiones traumáticas hasta el mes 4º después de la LM. El Control de su vida mostró un nivel significativo a los 4 y 6 meses después de la LM en pacientes traumáticos, pero no hubo diferencia cuando se comparó con el grupo atraumático a los 12 meses. Los pacientes con LM traumática presentaron algunas particularidades como el trauma emocional y la negación de la realidad, algunas veces combinado con estrés post-traumático, y el apoyo social es proporcionado extensamente a pacientes con enfermedades crónicas como cáncer o lesiones causadas por la cirugía. La intensidad del dolor, debida a la implicación de tales factores psicológicos y sociales es experimentada como más intolerable que para el grupo de lesión atraumática.

La presencia de actividades como las Domésticas es significativa a los 3 meses por pacientes con LM atraumática, mientras que esta actividad no comenzó hasta los 6 meses en la población de lesión traumática. Similarmente, las Actividades lejos de casa y Actividades Sociales mostraron un aumento progresivo y significativo durante los primeros meses para los pacientes LM atraumáticos, comparados con los del grupo traumático con equivalentes puntuaciones a los 12 meses de LM. Estos resultados pueden interpretarse en la población traumática como que ellos necesitan más tiempo después de la experiencia post-traumática para volver a las actividades diarias y afrontar la realidad de su situación; mientras que los pacientes atraumáticos se han situado en la condición de la LM de un modo más gradual.

4.5.5. Beneficios del Estudio

Nuestro estudio es el primero que reúne escalas psicofísicas (VAS de 7 días y VAS de Desagradabilidad) y escalas cognitivo-conductuales para la evaluación psicológica (CSQ-R y MPI-SCI) con medidas repetidas a lo largo de la fase aguda y crónica de la LM en pacientes con DN.

Pudimos identificar cambios significativos de los factores más importantes involucrados en la Calidad de Vida (QoL), derivados de dos cuestionarios, y relacionados estos cambios con la intensidad de dolor y el nivel de LM en una muestra seleccionada de pacientes con DN desde los 2 meses a los 12 después de la LM. Varios factores de Calidad de Vida correlacionaron altamente con la intensidad del VAS y factores físicos asociados con la LM, principalmente en los primeros estadios de la lesión. Las tendencias mostraron que varias y diferentes estrategias cognitivas se usaron en pacientes con lesiones cervicales y dorsales. Esto es de gran interés para tratamientos futuros, ya que los programas de manejo del dolor podrían acercar la psicoterapia de una manera más precisa y personalizada dependiendo del nivel de lesión de cada paciente. Por otro lado, ambos cuestionarios CSQ-R y MPI-SCI han demostrado diferente utilidad en la valoración de estrategias en DN con LM, y más bien podrían utilizarse de forma complementaria. Todos los pacientes fueron incluidos (del 1 de Julio de 2003 al 1 de Marzo de 2005) en caso de cumplir los criterios de inclusión-exclusión requeridos. Así, en términos de edad, tipo de lesión, género y el resto de datos clínicos y demográficos, podemos generalizar los resultados obtenidos a la población española con LM. Estos datos son comparables con estudios previos en población lesionada medular en grupo étnico, estado civil y causa de la lesión, excepto en el nivel de lesión, que en nuestro caso fue por encima de D10 medular y la mayoría

de estudios también incluyen algunos pacientes con paraplejía baja (Turner et al., 2002 ; Widerström-Noga , 2002).

4.5.6. Limitaciones del Estudio

Como en el estudio del capítulo 2, la limitación más importante fue la cantidad de datos perdidos en el mes 12 tras la LM, ya que fue menos posible para los pacientes el completar la evaluación del VAS y de los cuestionarios. Por esta razón, el N total disminuido hizo difícil el análisis y en algunas ocasiones sólo hizo posible dibujar una tendencia de lo que podría haber ocurrido evolutivamente en nuestros pacientes con LM.

Una limitación potencial también es la proporción de hombres/ mujeres reclutados, donde se incluyó el doble de hombres (consistente con la distribución de los pacientes con LM en España) y el pequeño número de pacientes que alcanzaron el criterio de inclusión (N=30), lo cual podría comprometer la generalización de nuestros resultados a la población de LM. Sin embargo, la homogeneidad de la población LM con DN específica y la inclusión de una gran variedad de lesiones y etiologías refuerzan este estudio como verdadera representación de la situación en la escena aguda.

4.5.7. Conclusiones y Futuras Líneas de Investigación.

En resumen, altos niveles de Catastrofismo están asociados con mayores niveles en intensidad de dolor y alto estrés psicológico, y también a una tendencia general al aumento de factores de Calidad de Vida medidos con los cuestionarios CSQ-R y MPI-SCI desde los 2 a los 12 meses después de la LM. El grupo de pacientes con lesión cervical utiliza diferentes estrategias cognitivas, como Ignorancia del dolor, Distanciamiento, y Afrontamiento, mientras que Rezo, Catastrofismo y Distracción son más frecuentemente utilizadas por el grupo dorsal. Es importante decir que el incremento en Catastrofismo es acompañado por un paradójico incremento en varias estrategias cognitivas positivas, como Ignorancia del dolor, Distanciamiento, Rezo, Distracción y Afrontamiento. Mientras estas estrategias de afrontamiento puedan ser efectivas para la modulación de la gravedad del dolor, es probable que el entrenamiento proporcionado a los pacientes por la Unidad de Psicología y Psiquiatría de este hospital de rehabilitación facilite la adopción de estrategias aprendidas durante la LM crónica. Estos resultados tienen implicaciones para el diseño de protocolos de evaluación e intervenciones de tratamiento adecuados a los pacientes con LM con el objetivo general de afrontar los síntomas de dolor durante su proceso rehabilitador. Más aún, la identificación de aquellos factores de Calidad de Vida que correlacionan fiablemente con la severidad del dolor después de la LM serían capaces de ofrecer una medida efectiva de eficacia en los tratamientos.

La aplicación de escalas psicofísicas (VAS) combinadas con evaluación psicológica (CSQ-R and MPI-SCI) proporcionan una comparación verdadera de los datos obtenidos del paciente. La escala VAS ha sido ampliamente usada en pacientes con medidas repetidas (Price, 1999), pero las escalas QoL necesitan más investigación para trazar las características y perfiles de los pacientes con LM.

El cuestionario CSQ-R solo parece ser inadecuado para la predicción de la medida funcional física de ajuste como discapacidad, por lo cual también elegimos el MPI-SCI que complementa dichos factores.

El MPI-SCI modificado aparece como un instrumento razonable con el que evaluar el impacto del dolor en las personas con LM y la respuesta de sus otros significativos al dolor. Sin embargo, debido a que los niveles de actividad son diferentes, dependiendo de si se presenta para- o tetraplejía, y porque otras consecuencias de la LM disminuyen el nivel de actividad más que el dolor, la frecuencia con la que la persona participa en una actividad concreta puede no reflejar necesariamente daño del dolor en sí mismo (Widerström-Noga, et al. 2002).

¿Los cambios en las respuestas de afrontamiento reflejan meramente, o realmente influyen, ajuste al dolor crónico?. En nuestro estudio pudimos observar que no parece ser el caso, ya que incrementos en diferentes estrategias positivas contra el dolor no significan un cambio en la severidad del dolor, más bien lo contrario. Sin embargo, podría ser una cuestión de cantidad, en términos de cuánto cambio es necesario para inferir un cambio significativo en la intensidad de dolor.

La futura investigación debería estar focalizada en tratamientos individuales que atiendan a las propias necesidades de cada paciente. Por tanto, cuestionarios más apropiados pondrían su objetivo en el nivel de lesión y posibilidades prácticas y verdaderas de la práctica de actividades supondrían una gran mejora en estos cuestionarios. Una escala de medida de dolor como la VAS también es necesaria como hemos visto previamente (MPI-SCI), algo de los que el CSQ y CSQ-R carecen.

4.6. Agradecimientos

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CHAPTER 5.

GENERAL DISCUSSION

For the first time a longitudinal and transversal analysis of NP and QoL has been assessed in SCI patients in the acute and sub-acute phase for a year following SCI associated with several physical factors (cervical versus thoracic, incomplete versus complete). Acute and chronic NP and non-NP and healthy volunteers were compared together in the same study. Several different methodologies for SCI-NP diagnosis including pain questionnaires (Neuropathic Pain Based on Mechanisms Interview and DN4), four *spontaneous* pain intensity ratio scales, and finally Bedside and Quantitative Sensory Tests including a new thermal Peltier testing system were compared and contrasted for their utility at, below and above the level of the injury.

A complete description of the development of sensory dysfunction and pain along with its psychosocial impact after SCI was established, based on the patient's original clinical report and the measurement of development of *spontaneous* and *evoked* pain (**Chapter 2**), along with a detailed thermal psychophysical evaluation and spinothalamic and dorsal column function (**Chapter 3**) and repeated quality of life assessment (**Chapter 4**). Furthermore, the relatively recent hypothesis of the existence of a centre of hyperexcitability at the level of the lesion, the CPG (**Finnerup et al., 2003; 2004**), may have obtained further support from our results. Depending on the specific post-injury time different pathophysiological mechanisms may be operating during the initiation and maintenance of SCI NP.

5.1. Longitudinal Development of NP in SCI.

The study carried out in **Chapter 2** is the first that gathers information about the longitudinal evolution of NP from the acute phase of SCI (before 6 months) up to its chronic phase (a year after the lesion), analyzing the relation between *spontaneous* pain intensity and *evoked* pain signs, with the objective of identifying mechanisms or the adequate stimuli necessary to perform a successful early diagnosis. We have especially centred on the utility of *spontaneous* and *evoked* pain measures implicated in NP. An added advantage of our study was the clinical characteristics of the patients in our sample study, representing an extensive range of age, gender, aetiology and level of lesion; and thus includes several different factors in the study groups.

The vast majority of our patients began with signs of NP (either *spontaneous* or *evoked*) between the second and third month after SCI, and in general presented more *spontaneous* pain intensity at level than below the level of lesion. As the observed power in the analysis is rather low, very probably because of the low number of patients included in the analysis, significant results may be taken cautiously. However trend analysis using repeated measures ANOVA for the longitudinal measures supports the general conclusions.

Siddall et al. (1999, 2003) identified evidence for *spontaneous* and *evoked* NP at and below the level of SCI as early as 2 weeks after the spinal cord lesion, and 6 months later most of the people continued to experience NP. In our study pain was assessed from 2 months onwards mainly because the neurological state of the patients with trauma made the evaluation very difficult and did not permit an adequate evaluation in the very few patients that accepted to participate at this time. Furthermore in patients with SCI of atraumatic origin assessed at one month after the injury (n=3) the *spontaneous* pain intensity (even including maximum VAS) did not exceed "2", excluding them from the initial inclusion criteria of a VAS score greater than "3", not reached until 2 months after lesion.

5.2. Spontaneous pain development from 2 to 12 months after SCI.

Spontaneous pain may be assessed using different VAS ratio scales, but the most interesting for this thesis work was the 7 day pain and unpleasantness intensity scales. In general unpleasantness intensity was higher than the 7 day pain intensity: we observed a tendency for an increase in pain up to 12 months, much more considerable at level than below the level of SCI (consistent again with the slow development of a local CPG mechanism). As such we used the 7 day pain intensity measure, as it was more homogeneous associated with a smaller SD, more informative and reproducible following the analysis. Interestingly patients with thoracic SCI presented a progressive increment in pain intensity at level in all the temporal measures compared to a constant level of pain intensity following cervical lesion. Below the level of SCI, patients with either cervical or thoracic lesions eventually reached the same level of pain intensity, but with a larger degree of temporal.

5.3. Evoked pain from 2 to 12 months after SCI.

The most common *evoked* pain signs were, either at 3 or 6 months after the lesion, mechanical hyperalgesia/sensibility to pinprick which is the most prevalent either at or below level, and is present in at least half of the patients studied at the level of injury at 6 months. In general more *evoked* pain signs were observed at level than below the level at 6 months; whilst the thermal allodynia/sensibility prevalence below the level of SCI significantly decreased to half its value at 6 months, in contrast to a doubling at the level of the lesion during the same month. Allodynia was more common in people who had incomplete spinal lesions, and more prevalent following cervical rather than thoracic SCI and central cord syndrome. However no relationship between the presence of pain overall and level or completeness of lesion, or type of injury was identified.

These no significant observations may support the activation of the CPG at the level of the lesion, with a higher neuronal hyperexcitability in response to cold stimuli measured in the acute SCI phase. It is of interest therefore that in spinally injured rats a high proportion of wide dynamic range (WDR) neurons and high-threshold (HT) neurons responding to innocuous cold stimulation increased in allodynic animals after SCI, suggesting that this chronic pain may be generated and maintained by abnormalities in dorsal horn neurons at the level of injury (**Hao et al., 2004**). Preliminary observations from our laboratory with Wistar rats also indicates that cold is the only adequate stimuli (compared to heat and mechanical) to evoke a progressive reduction in flexor withdrawal latency below a mild contusion SCI at the thoracic level.

5.4. Evidence for the Central Pain Generator (CPG)

The role of CPG after SCI at the level of the lesion and its effect on NP development below the level of the lesion was presented as one of the study hypothesis for Chapters 2 and 3. Some authors have suggested previously the existence of a neuronal hyperexcitability at level of lesion that would affect normal nociception at sites remote from the original injury, specifically below the level of the lesion (**Vierck, 2000**) and above the level (**Finnerup and Jensen, 2004**), possibly through the activation of the propriospinal system, or even though diffuse glia cell activation (**Hains and Waxman, 2006**).

The CPG hypothesis and its subsequent action on nociception remote to the original injury site is supported by our results suggesting hyperexcitability at both levels of the lesion, reflected as a higher and significant increase in *spontaneous* pain intensity following thoracic group SCI (0>VAS>5) compared to a constant pain intensity level following cervical SCI (2>VAS>3) from 2 to 12 months after SCI; additionally supported by a significant interaction of *spontaneous* pain with a tendency for an increase in the thoracic group and a decrease in *spontaneous* pain intensity in the cervical group. Multiple correlations have been observed between the number of *spontaneous* and *evoked* painful dermatomes at different months of injury at the level of SCI, but more interesting was the positive and significant correlation at level between the number of dermatomes and mechanical allodynia.

Furthermore, at level thermal allodynia/sensibility was correlated with *spontaneous* pain intensity, which may also support the presence of a local CPG mechanism at 6 months after the injury. Of interest was a trend for a decrease in the number of dermatomes involved with *spontaneous* or *evoked* NP below patients with cervical SCI compared to an increase in *spontaneous* and *evoked* dermatomes below thoracic SCI. On the other hand, in the thoracic SCI group a significant correlation between the number of *spontaneous* dermatomes at the level of the lesion at 2 months and the number of *evoked* dermatomes below the lesion at 6 months post-SCI was observed, indicating that the presence of the CPG mechanism at the early stages of SCI associated with specific lesions may influence remote processes of nociception at a later time.

Significant differences were seen in temporal summation at the level of the lesion and also in thermal allodynia (to acetone) below the level of the lesion from 2 to 6 months after the lesion, it means that an early activation of the CPG at 2 months must be present with another pain mechanism, perhaps due to abnormal spinothalamic tract dysfunction that may operate below the level of the lesion. The CPG system might be operating already in the early stages of the SCI at and below levels, as we have observed with an increase in *spontaneous* and *evoked* levels of pain presented in the patients. On the other hand, latent supraspinal changes in the spinothalamic system may complicate the interpretation of the CPG system after the first 6 months of SCI.

Thus, the gradual development of *spontaneous* pain intensity presented at level after injury, when the CPG is presumably activate, and the high correlations between pain signs either at level (thermal allodynia/sensibility with *spontaneous* pain intensity at 6 months) or below the level seems to be in consonance with this theory. The additional functional effect of ascendant tract damage and activation of rostral targets by other sources of spinal activity (propiospinal system, **Vierck et al., 2000**), may be responsible for NP development in patients, with no distinction between the spinal level of injury or the grade of damage (complete versus incomplete lesions) presented.

5.5. Reliability of Semi-directive Pain Questionnaires

In contrast, the SCI Neuropathic Pain Based on Mechanisms Interview revealed that questions related to “continuous” pain and the number of descriptors for this pain had more significance than the other questions, either at or below the level of lesion, and at level “dynamic mechanical” *evoked* pain during the year. In addition the results suggested that the patients could not distinguish clearly between pain at and below the level of injury, and between *spontaneous* and *evoked* pain, even though we observed a difference and clear exponential increase at level *spontaneous* pain in the general population, or a significant interaction when subdivided between the cervical and thoracic groups. In addition, all patients with SCI, irrespective of its associated physical factors, answered the questions with higher scores at 2 months, followed by a decrease from 3 to 4 months possibly due to a worsening in their evaluation of their NP. At 12 months the scores increased again started to increment possibly associated with the end of their period of rehabilitation in the hospital and the return of some activity with all the emotional implications that this process involves (see **Chapter 4**). Importantly the use of this interview revealed that *evoked* pain tests like standard “Bedside Sensory Testing” are more informative of the state of pain mechanisms and dysfunction in sensory fibres. In addition, the interview could not distinguish between different levels of NP intensity associated with SCI physical factors while BST could; therefore reliable information could not be provided by the patients themselves or even with the help of such a semi-directive interview.

5.6. Sensory examination at 4-6 months at the levels of SCI: DN4 and QST

The DN4-Spanish version has recently been confirmed to be reliable, stable and valid for the differential diagnosis of neuropathic pain conditions, as it is able to differentiate the neuropathic and nociceptive component of pain, using the same cut-off score than that identified in the original version. The questionnaire is easy for the patient to complete for the examiner to calculate the total score, thanks to the scale of 10 questions (**Huelbes et al., 2006**). In our study the DN4 pain questionnaire was useful in identifying NP in both the SCI and SYR subject groups, both with mean scores of 4,

successfully identifying this condition in both the acute or chronic stage of SCI. The BST evaluation in the questionnaire provided more useful information, indicating significant hypoesthesia to and significant presence of painful brush during NP. It is possible that a larger subject group would reveal further significant results for the rest of the questionnaire, particularly as the instrument has been tested in several NP populations (including SCI).

In general, the QST showed itself as a useful comprehensive test for sensory fibre function following different SCI pathologies. Possible explanations for our results are related to different fibres and pathways involved in the pain process, like the impairment of A β fibres *at the level of injury*, revealed by a reduced mechanical threshold detection to von Frey stimulation and the brush test for mechanical allodynia did not present responses with longitudinal analysis, although patients reported painful brush with the DN4 at 4-6 months after SCI. Evidence for dorsal column-medial lemniscal pathway damage was obtained also with a reduction in the detection of vibratory stimuli. Furthermore chronic SYR patients presented reduced mechanical threshold detection and two point discrimination, which may also suggest further changes in the cortical representation of dermatomes. Two types of mechanical hyperalgesia have been described previously, the dynamic type being mediated by myelinated fibre activation, and the static type via unmyelinated fibres (Ochoa and Yarnitsky, 1993). In general evidence for Ad or C fibre dysfunction or hyperexcitability with mechanical tests was difficult to detect, particularly as no difference was found between the patient either with mechanical (static) hyperalgesia testing or with repeated pinprick stimulation with QST or tonic heat stimulation. In our current sample of patients, C fibres may have found lesser impairment than Ad fibres, since no differences were found between the groups either in mechanical (static) hyperalgesia or temporal summation, with the QST or TSAR (only in subgroups). An hyperexcitability on C and Ad fibres was shown by the differences in heat stimulation, both in QST and in the heat pain curve response, where the pain increased more rapidly (slope) in the thoracic group, and also was observed in SYR group in cold at the level of lesion. Interestingly, augmented responses were observed both with heat and cold stimuli with the QST in this group, whilst with TSAR system did not occurred, rather the opposite with heat (see *Limitations* in 5.8 from this Chapter). Our findings suggest, as in previous studies, a differential processing of repetitive thermal and mechanical stimuli in the central nervous system maintained by activity in heat-sensitive nociceptors and an abnormal operating spinothalamic pathways.

Below the level of the lesion, temporal summation neither obtained responses with the QST. High pain responses were observed differentially in NP (for heat) and SYR groups (for cold), which may mean that the CPG is operating also at this level of the lesion together with the spinothalamic pathways. As it is explained below, no comparison may be done with the TSAR. In addition, *Above the level of the lesion* the heat stimulation was also more painful in NP and SYR groups, with both methodologies, however in TSAR we could observe a lesser maintained response on the pain curve for SYR group in heat but not cold stimulation, which suggest that in SYR all the levels presented a noticeable level of spinothalamic impairment.

In summary, our data support significant dysfunction of the dorsal column system after SCI with NP and in turn the hypothesis that an imbalance between the temperature and pain system and large fibre-touch system can contribute may contribute to abnormal *spontaneous* sensations. Indeed abnormal thermal responses in the spinothalamic pathways may be important in chronic NP associated with Syringomyelia, although further investigation is needed to identify acute and chronic pain mechanisms involved with SCI. Our data also supports the hypothesis that SCI NP may be initiated by an at level hyperexcitability of the CPG, which possibly depends on the level of injury, as suggested using tonic thermal stimuli with the TSAR system. These data highlight the difficulties in previous studies have had in identifying possible NP mechanisms involved. Central NP symptoms are most probably sustained by distinct mechanisms and alterations in sensory perception that may be mediated by spinothalamic or dorsal column-medial lemniscal pathway damage and/or the activation of a local CPG depending on the post-injury time and the level at which SCI is located. Furthermore, the fact that all areas with damaged spinothalamic function supported *spontaneous* chronic pain whilst none of the areas with similar damage produce pathological pain in pain free patients is consistent with the

possibility that a genetic predisposition determines the emergence of chronic pain (**Defrin et al., 2001**).

5.7. Non-painful and painful responses to mechanical and thermal stimuli during NP after SCI.

The application of the visual analogue (VAS) scale is considered to be the most reliable instrument to measure pain intensity where traditionally “0” represents “no pain” and “10” as “the worst pain imaginable” (see **Chapters 1 and 2**). However, more recently other VAS scales have been developed to rate non-painful responses to classical experimental pain stimuli with the use of non-painful adjectives throughout the scale applied simultaneously with more classical pain intensity VAS scales (**Morin and Bushnell, 1998**). We considered these requirements, together with the list of pain descriptors used in our study, too much information to be processed and provided by the patients in such a short testing time. That is why we developed a *unique and continuous VAS scale* (with only two words at the beginning and ending of the scale) to measure and include “unpleasantness” and “pain” as it seems much more understandable and practical for patient testing.

In our VAS “0” to “10” represented a *continuous* rating of sensation and pain intensity, starting with abnormal sensations that become unpleasant and then painful until the end of the scale where the pain/sensation was referred to as “unbearable” by the subject (a level never tested in our studies). We believe that non-painful responses and paraesthesias all may be part of a construct of pain sensations that may be situated in the same spectrum of VAS (0-10), being unpleasantness 0-2 scores and being “pain sensations” (dysesthesias) from 2-10 in our scale. This is supported by their correlated figures between themselves (see **correlations in Chapter 2**) that may activate the same pathways in patients and healthy subjects and by the fact that in our longitudinal study (**Chapter 2**) the beginning of NP in SCI patients was given by lower scores in the VAS (reported paraesthesias) followed by a later increase of pain in the VAS (reported dysesthesias) according to the evolution in months of the NP.

Analysis of sensory function with BST and QST methods (see **Chapter 3**) indicated intensities higher than 0.5 on our VAS scale, so that we were able to study both non-painful and painful sensations. However, clear pain sensations above the threshold value of “2” were scarce and insufficient in all subject groups, including SCI-NP and SYR patients clearly identified with NP according to the DN4 questionnaire, highlighting the controversy of how standard pain signs such as allodynia and hyperalgesia should be defined in context to painful or non-painful responses to standard testing stimuli. The IASP’s definition of these terms (see Introduction **Chapter 2**) do not allude to any sensory rating score to distinguish between allodynia and hyperalgesia even though the stimuli has been accepted normally innocuous and noxious respectively. Moreover, the IASP emphasize that “the activity induced in the nociceptor and nociceptive pathways by a noxious stimulus is not pain, which is always a psychological state, even though we may well appreciate that pain most often has a proximate physical cause” (see Psychological mechanisms in **Chapter 4**). In addition the intensity of pain as tested using standard BST methods in NP is not always high (**Dr. Serra**, personal communication). It is possible that what we have categorized in this study cannot be defined as allodynia or hyperalgesia, according to those pain states activated and characterized after peripheral neuropathic pain initiation, but we believe that those sensations experienced by our central neuropathic pain patients with obvious sensory pathway dysfunction, are close to pain in quality but in intensity, and the documentation of these non-painful sensations may also be valid to study pain in terms of sensory fibre and pain processing pathologies and associated mechanisms.

The difficulty in measuring clear pain responses “2/10” with standard BST and QST testing methods in SCI neuropathic pain patients, may also be related to the poor spatiotemporal characteristics of the stimuli used, such as one drop of acetone, a 48°C test-tube applied at 1- 2 s. Sensory responses of the same subject groups to tonic heat/cold stimuli applied with the TSAR system *evoked* higher *evoked* pain intensities equal or greater than 1.45 in the majority of subjects, using e-VAS system. Indeed

responses to adequate stimuli not only depend on the conduction velocity of peripheral afferents but also the successful activation of deep cold receptors and thermal properties of the skin (Yeomans et al., 1996). Nevertheless, some subjects only produced moderate pain maximum pain intensities with an e-VAS of less than 1, data which will be analyzed in future investigations, as the information provided by non-painful sensory e-VAS curves may present similar information compared to clearly painful responses greater than “2”. Further support for this concept is provided by our data, in that clearly painful intensity responses to tonic cold and heat stimuli were not different when activated using the TSAR system, similar to the results obtained in Morin and Bushnell’s (1998) study.

5.8. Diagnosis of SCI-NP with QST/BST and tonic thermal stimuli

We think that the BST/QST and Peltier-TSAR tests are valid methodologies for the adequate assessment of NP in SCI. Standard QST has been demonstrated as to its utility and reliability in several studies over the last decades, and is easily available for clinical researchers and physicians working with acute and chronic NP patients. The TSAR thermal testing method provides good and new stimulus-response characteristics such as the slope of pain response, and short (10s) and long-term (30s) e-VAS integrals which may be useful to detect peripheral or central sensitization and in addition spinothalamic dysfunction. QST techniques such as the TSAR Peltier system are easy to use after appropriate training and with further development of a data analysis program, more accurate and detailed analysis of pain response curves.

The main *limitation* with the TSAR-Peltier system was the fact that patients failed to respond below the level of the lesion in contrast to positive responses with simple BST/QST. Indeed the SYR group failed to respond also with at level of injury, even though the high scores of pain at this level. So far we have identified a probable explanation for this phenomenon. *Habituation* of pain responses in both these cases due to cutaneous nociceptive fibre fatigue (Kleinböhl et al., 2006) is unlikely because subjects had a rest period of about 7-10 minutes after QST stimulation and TSAR assessment, excluding the possibility of cutaneous fibre sensitization. Another explanation may be a cumulative *stress-produced analgesia (SPA)* present in majority of the patients specifically with TSAR testing, but not in HV. Indeed the nociceptive flexion reflex threshold of the lower limb in man was progressively increased with the repetition of stressful stimuli in Willis’ et al. study (1991). Below level testing was actually the first level tested in patients, and possibly a high degree of anticipation was higher at the beginning of the QST session. Thus, patients could have had a higher response threshold to either heat or cold below the level of injury induced by their psychological state. Other limitations of the TSAR method (tolerance problems, some of these patients were medicated, etc) reflect the need to recruit a larger number of patients to identify changes in nociceptive processing.

However BST/QST appears to be more effective than the TSAR system when NP analysis of below level pain following SCI and in SYR chronic patients in general. In contrast at the level of the lesion, both BST/QST and TSAR could differentiate between NP pain patients and HV subjects, and even detect previously unidentified above level changes in nociception, using heat stimuli. Importantly whilst acetone and Tip-Therm cold testing provided poor results, the TSAR system was able to detect changes in cold nociception at and above the level of lesion in subject groups. Future developments in electrophysiological and functional brain imaging techniques, may provide a real improvement in pain measurement in the future.

5.9. QoL of SCI-NP patients during the first year

The QoL study presented in (Chapter 4) is the first to describe changes in *spontaneous* pain intensity and unpleasantness associated with several items of two cognitive-behavioural scales of QoL (CSQ-R and MPI-SCI) during the acute and chronic phase of SCI in a selected patient group according to a strict set of neurological and NP characteristics present from 2 to 3 months following injury. The combination of two standard pain measures (intensity and unpleasantness) with standard new

cognitive-behavioural items provides a real picture of the direct impact of the development of *spontaneous* pain on the daily life of the SCI patient, and therefore directly identifies not only important negative factors that may be used for diagnostic and measurement of treatment effect, but also describes how the individual copes in the face of a gradually developing pathology (see **Chapter 2**). This study is one of a very few that describes the longitudinal changes in selected QoL factors, using established scales specifically designed to examine the impact of NP from its beginning to its development one year after SCI.

In general we could identify significant changes in the most important factors involved in the Quality of Life (QoL), derived from the two questionnaires, and related these changes to both pain intensity in a selected sample of patients with NP from 2 up to 12 months after SCI. Several QoL factors correlated highly with *spontaneous* pain intensity and unpleasantness associated with SCI mainly in the early stage of injury.

Several positive cognitive strategies for pain, such as ‘Ignoring pain, Distancing, Praying, Distraction and Coping Self Statements’ increased from 2 to 12 months after SCI. Whether these coping strategies were effective in modulating pain severity is not known, although it is likely that training in these strategies provided by the Psychological and Psychiatric Unit of the Rehabilitation Hospital (Toledo, Spain) could facilitate learned strategies during chronic SCI. These results have important implications for designing assessment protocols and treatment interventions adequate for spinal cord injury patients with the overall objective of promoting coping strategies to pain symptoms during their psychosocial rehabilitation. Although an increase in the use of different positive strategies against pain do not always mean a successful decrease in pain severity, rather the opposite based on our results, the identification of those QoL factors that correlate with pain severity after SCI should be able to provide an insight into the efficacy or adoption of different cognitive-behavioural strategies.

We believe that the study group characteristics (age, gender, type of SCI), clinical data and demographics (the patients came from any region of Spain) may represent generalised data from the entire Spanish SCI population, though a higher number of patients would have been desirable. These data are comparable with previous studies in SCI population in ethnic group, marital status and cause of SCI (except the level of injury). As in the Chapter 2 study, the main limitation was the amount of missing data mainly encountered during the 12th month after injury. We observed that the CSQ-R alone was not an adequate tool by itself as it did not control for the impact of disability on successful physical function, compared to the MPI-SCI. Furthermore, the MPI-SCI scale included important correlations between several QoL factors with both pain intensity and unpleasantness after SCI. The modified SCI version of the MPI appears to be a reasonable instrument with which to evaluate the impact of pain in people with SCI and the response of their significant others to pain, even though a reduction in several items may reflect unrelated changes in physical activity levels depending on whether the person presents tetraplegia or paraplegia (**Widerström-Noga et al., 2002**).

5.9.1. Effect of SCI physical factors on QoL.

Although we only may speak about tendencies based on the significant repeated measure ANOVA statistic, the analysis of QoL factors obtained from thoracic and traumatic SCI patients indicates a distinct development of pain coping and negative factors apparently unrelated to the level of physical disability.

Trend analysis revealed several different coping strategies adopted by patients with cervical and thoracic lesions, combined with the development of different QoL negative factors. In the cervical SCI group patients utilized different cognitive strategies such as ‘Ignoring pain, Distancing, Coping Self Statements’, whilst ‘Praying, Catastrophizing and Distraction’ were more frequently utilized in the thoracic SCI group. ‘Interference, Support, Life Control, and Solicitous Responses’ from the MPI-SCI questionnaire indicated the presence of these factors after thoracic SCI. A significant and progressive increase in the factors associated with pain and ‘Social Activities and Activities away from home’ was observed from 3-4 months, respectively, following thoracic SCI, but was only observed after a delay

up to 6 months after cervical SCI. Interestingly “Affective Distress” was generally greater after thoracic SCI, but at 12 months reached the same level as those with SCI after cervical injury. A non-significant trend was also observed with higher ratings observed for “Pain Severity, Distracting Responses, Household Chores and Outdoor Work” in the thoracic SCI group.

This study in general indicates that our SCI sample of patients use cognitive strategies like active pain coping self statements (CSQ-R) and request support and solicitous responses during the first 12 months after injury; at 2 months these factors are close to zero with a slight increase in “Ignoring Pain, Distancing, Praying and Distraction” over the year. Interestingly the analysis of negative factors such as “Pain catastrophizing” (CSQ-R) revealed only a moderate level during NP development, even though patients experienced significant “Pain Interference” and “Pain Severity” (MPI-SCI) at 12 months. This suggests that the patient rarely magnifies or feels impotent against pain development over the first year.

Interestingly, the atraumatic patient group tended to neglect the use of some CSQ-R strategies after a trial period, perhaps because they did not perceive them as useful against pain relief; as was the case with “Coping Self Strategies, Praying and Distraction”. In contrast the traumatic SCI group tended to use most of the coping strategies up to one year after SCI, even though they also showed the highest level of “Catastrophizing”. In addition “Interference, Support, Pain Severity, Solicitous Responses” factors from the MPI-SCI were significantly more prevalent in patients with traumatic injuries up to 4 months after SCI. A reduction in “Life Control” showed a significant level at 4-6 months after SCI in traumatic patients, but there was no difference when compared to the atraumatic group at 12 months. Patients with traumatic SCI also presented some particularities such as emotional trauma and denial of the reality, sometimes combined with post-traumatic stress, and social support was provided to a greater extent to patients with chronic illness like cancer or lesions caused by surgery.

These different patterns in coping strategies depending on physical factors are very interesting for future treatments, as pain management programs could approach the psychotherapy in a more accurate and personalized way depending on the level of the lesion of each patient.

5.10. Future research on QoL during SCI neuropathic pain

Future research should be focussed on individual treatments which attend to the own necessities of each patient and the physical factors associated with SCI neuropathic pain. The development of QoL pain questionnaires that cater to these physical factors, that is sufficiently sensitive to identify important treatment effects and to assess the real possibilities of practising different cognitive-behavioural strategies would represent a substantial improvement in the current global measurement of SCI pain impact on daily life. Also a scale that includes a direct rating of pain intensity and unpleasantness, such as that performed with the VAS in this study, would be an step forward particularly for the CSQ. The application of both MPI-SCI and CSQ-R questionnaires to the patient would be adequate for identifying QoL factors involved in pain and the general process of recovery after SCI.

5.11. Final Conclusions

The longitudinal analysis of pain signs and symptoms from 2 to 12 months and a specific diagnosis performed at 45 months in patients with SCI using standard bedside and quantitative sensory testing revealed new information highlighting the evolution and relationship between *spontaneous* and *evoked* pain (1, 2, 3), the early presence of a spinal site of *neuronal hyperexcitability* (1, 4, 5) and changes in ascending sensory pathways (6) and/or a supraspinal centre function due to deafferentation (6, 7). Specifically:

1. A gradual increase in at level *spontaneous* pain intensity was observed in general and in patients with thoracic SCI.
2. No increase in *evoked* pain intensity was identified from 2 to 6 months post-SCI using standard bedside sensory testing methods at the level of injury. Moreover a decrease in at level temporal summation to repeated pinprick and a reduction in thermal allodynia/sensibility to cold stimuli below the level of SCI was identified from 2-6 months.
3. Negative relationship between *spontaneous* pain intensity and *evoked* pain sign intensity was observed at 2 months, but not at 6 months, following SCI. At 6 months at level cold sensibility correlated with *spontaneous* pain intensity and mechanical sensibility.
4. Tonic heat stimulation at the level of the lesion revealed general changes in local nociceptive processing, specifically with increased pain sensitivity in acute thoracic compared to cervical SCI-NP patients, suggesting differential development of local NP mechanisms following injury.
5. Correlational analysis between at and below SCI level *spontaneous* and *evoked* pain signs revealed that the number of dermatomes with *evoked* pain was related at 2 and 6 months after SCI, with an additional correlation identified at 6 months between cold allodynia/sensibility intensity at level and mechanical hyperalgesia/sensibility below the level of injury. The role of an at level spinal centre of hyperexcitability in mediating remote changes in nociception below the level of the original lesion could not be concluded, due to the low number of incomplete SCI patients recruited in this study.
6. A reduction in sensory detection to two-point discrimination, vibration, von Frey stimulation, and heat/cold stimulation supports the existence of abnormal spinothalamic and dorsal column-lemniscal pathway function.
7. Tonic heat stimuli above the level of the SCI revealed that the initial 10 and 30s integrated e-VAS pain response was significantly lower in SYR than in acute SCI-NP patients, while a non-significant ($p=0.06$) larger 10s integrated e-VAS response to tonic cold stimuli applied above level was observed in NP compared to the HV group.

The Quality of Life study is the first one to describe associated changes in *spontaneous* pain intensity and unpleasantness with the adoption of several cognitive-behavioural factors (8) measured with *Coping Strategy Questionnaire-Revised (CSQ-R)*, (9) and the *Multidimensional Pain Inventory–Spinal Cord Injury Version (MPI-SCI)*, (10, 11), in addition to identifying significant differences in the use of strategies in patients with either thoracic or cervical injury (12), from the 2 to 12 month period after SCI. Specifically:

8. *Spontaneous* pain intensity correlated significantly with the use of CSQ-R and MPI-SCI strategies factors after SCI some of which were, some of which were maintained up to 12 months.
9. Several positive cognitive strategies for pain were adopted during the first 6 months, such as *Ignoring pain, Distancing, Praying, Distraction* and *Coping Self Statements*, observed together with an increase in *Catastrophizing* over the same time period.
10. *Catastrophizing* as a cognitive strategy was only present at a moderate level after SCI, suggesting that the patient rarely magnifies his pain during its development in the early phase.
11. The MPI-SCI questionnaire showed that in general, the patients applied cognitive strategies in many areas of their daily life, such as *Coping self statements*, and requested *Support* and *Solicitous responses* during the first 12 months after injury.

12. Although differences in the use of strategies was observed between patients with cervical and thoracic lesions must be taken cautiously, we may suggest that the thoracic SCI group is associated with lower QoL according over the first year after injury, according to data obtained with the CSQ-R and MPI-SCI.

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GENERAL APPENDIX: POSTER PRESENTATIONS AND ABSTRACTS

- May 2004: Neuropathic Pain: Changing paradigms in Diagnosis and Treatment. International Congress of NeuPSIG (IASP), Madrid, Spain.

Bedside Sensory Examination of Neuropathic Pain after Spinal Cord Injury

S.Huelbes Alonso¹, J.R.Cabrera Feria², F.Calderón Muñoz, C.Fernández-Shaw Toda³, D.García Marco³, M.Nieto-Sampedro¹, J.S.Taylor¹. Sensorimotor Function Group (1), Pain and Spasticity Unit (2), Pharmacy Service (3), Hospital Nacional de Paraplégicos, Finca “La Peraleda” s/n, Toledo 45071, Spain. Email: jscott@sescam.org

Although the clinical history of neuropathic pain after spinal cord injury has been well documented (Siddall et al. *Pain* (2003) 103(3):249-57, Finnerup et al. *Brain* (2003) 126:67-70), the further characterization and documentation of symptoms and signs during the acute phase of spinal cord injury may lead to improved prognosis and treatment. Here we present preliminary data obtained using routine bedside sensory testing from a group of patients with a VAS of greater than 3 for ongoing pain below the level of lesion (above T10), with or without analgesic treatment. The majority of patients reported ongoing pain with a mean VAS of 5 below the level of injury. Bedside sensory examination revealed a greater prevalence of brush-evoked allodynia, sensitivity to pin-prick, cold and repetitive pin-prick with half of the patient population responding at level rather than below the level of injury, although the mean VAS for each sign was less than 3. In conclusion initial results indicate that the utility of bedside sensory examination for the identification of common symptoms and signs of neuropathic pain is limited to the level of injury, and that the characterisation of ongoing pain below the injury level is more important in regards to both prevalence and pain intensity in patients during acute spinal cord injury. Work sponsored by the Consejería de Sanidad (Exp:GC02029) and SESCAM.

- September 2005: XI Neuroscience Spanish Society National Congress (SENC, Neuroscience Spanish Society). Torremolinos (Malaga), Spain.

Huelbes Alonso S, Peñacoba Puente C, Cabrera Feria JR, Calderón Muñoz F, Taylor JS. “Examinación Sensitiva de los Signos de Dolor Neuropático al Nivel y por Debajo del Nivel de la Lesión Medular en Pacientes” (Sensitive Examination of *evoked* Neuropathic pain signs at and below level of the Spinal Cord Injury). *Rev Neurol*, 2005;41 (Supl.2): S1-S131, p.120.

Aunque la historia clínica del dolor neuropático después de la lesión medular ha sido bien documentada (Siddall et al. *Pain*, 2003; 103(3):249-57; Finnerup et al. *Brain*, 2003 126: 67-70), la posterior caracterización y documentación de sus signos durante la fase aguda de la lesión medular puede conducir a un mayor entendimiento de los mecanismos responsables para su inicio y mantenimiento. Estudios previos sugieren el papel de una zona de hiperexcitabilidad neuronal de la médula espinal en el área del trauma en el desarrollo del dolor neuropático después de la lesión medular, cuya localización exacta no es aún conocida (Finnerup et al. *Brain*, 2003 126: 67-70). Para el estudio de esta hipótesis utilizamos dos de las categorías de dolor neuropático después de la LM: al nivel (dolor en los dermatomas al nivel del trauma) y por debajo del nivel de lesión medular (dolor en los dermatomas por debajo del trauma). Aquí presentamos los datos preliminares obtenidos usando una examinación

sensorial cuantitativa en un grupo de pacientes que presentan una lesión medular entre C2-D10, completa o incompleta, con una intensidad de dolor usual mayor que 3 (máximo 10) y con la presencia de dolor neuropático al nivel/por debajo del nivel de lesión. Todos los pacientes firmaron el consentimiento informado previamente aprobado por el comité ético de investigación clínica del hospital. Presentaremos datos de prevalencia de alodinia, hiperalgesia y sumación temporal, examinando la interrelación entre dolor espontáneo y dolor evocado al nivel y por debajo del nivel de la lesión medular.

- 13-16 September 2006: 2 Posters presentations for the Pain in Europe V, 5th Congress of the European Federation of IASP chapters (EFIC) Istanbul 2006.

Validity of the DN4 scale for differential diagnosis of patient with peripheral, central Neuropathic or Mixed Pain.

Silvia Huelbes,¹ Concepción Pérez,² Rafael Gálvez,³ Joaquín Insausti,⁴ Didier Bouhassira,⁵ Silvia Díaz,⁶ Javier Rejas.⁷

¹National Paraplegic Hospital, Toledo, Spain; ²Pain Clinic, Hospital de la Princesa, Madrid, Spain; ³Pain Clinic and Palliative Care, University Hospital Virgen de las Nieves, Granada, Spain; ⁴Pain Clinic, Hospital Severo Ochoa, Leganés, Spain; ⁵INSERM E-332, AP-HP Hôpital Ambroise Paré, Boulogne and Université Versailles-Saint-Quentin, France; ⁶Health Outcomes Research, ArtacBioestudios, Madrid, Spain; ⁷Health Outcomes Research, Medical Unit, Pfizer España, Alcobendas, Spain.

Objective.- To explore the validity of the Spanish version of DN4 (*Douleur Neuropathique 4 questions*) scale in subjects with central/peripheral Neuropathic Pain (NP) and patients with Mixed (neuropathic and nociceptive) Pain (MP).

Material and Methods.- Patients with NP of broad origin or MP included in a cross-sectional study carried out to validate the DN4 scale into Spanish were included in this post-hoc analysis. Validity of scale for differential diagnosis against subjects with Non-neuropathic pain (NNP) was evaluated by means of ROC curves analysis, kappa's agreement with reference diagnosis and determination of sensitivity, specificity and positive and negatives predictive values for selected cut off points.

Results.- A total of 164 subjects (99 women, 60.4%; age: 60.4±16.0 years), 94 (57.3%) with NP [36 (38%) peripheral, 32 (34%) central], 26 (28%) with MP, and 70 (43%) with NNP, were included in the study. Diagnosis of type of pain was realized by pain experts using standard clinical practice criteria. A cut-off value ≥ 4 points was the best value to discriminate between types of pain. Kappa's agreement coefficients were 0.57 (IC 95%: 0.44-0.69), 0.58 (0.45-0.71) and 0.55 (0.40-0.71) in all patients, and after excluding MP and central NP subjects, respectively. Sensitivity and specificity values were 80.9% (72.9%-88.8%) and 75.7% (65.7%-85.8%) in the whole sample, 82.4% (73.3%-91.4%) and 75.7% (65.7%-85.8%) excluded MP patients, and 83.3% (71.2%-95.5%) and 75.7% (65.7%-85.8%) excluded central NP patients.

Conclusion.- The Spanish version of DN4 scale looks acceptable for the differential diagnosis of pain sufferers with a neuropathic component of pain.

Validity, inter-rater agreement and test-retest reliability of the Spanish version of DN4 scale for differential diagnosis of Neuropathic Pain.

Rafael Gálvez,¹ Concepción Pérez,² Silvia Huelbes,³ Joaquín Insausti,⁴ Didier Bouhassira,⁵ Silvia Díaz,⁶ Javier Rejas.⁷

¹Pain Clinic and Palliative Care, University Hospital Virgen de las Nieves, Granada, Spain; ²Pain Clinic, Hospital de la Princesa, Madrid, Spain; ³National Paraplegic Hospital, Toledo, Spain; ⁴Pain Clinic, Hospital Severo Ochoa, Leganés, Spain; ⁵INSERM E-332, AP-HP Hôpital Ambroise Paré, Boulogne and Université Versailles-Saint-Quentin, France; ⁶Health Outcomes Research, ArtacBioestudios, Madrid, Spain; ⁷Health Outcomes Research, Medical Unit, Pfizer España, Alcobendas, Spain.

Objective.- Linguistic adaptation and validation into Spanish of DN4 (Douleur Neuropathique 4 questions) scale to be used for differential diagnosis of Neuropathic Pain (NP).

Material and Methods.- Cross-sectional validation study carried out into two phases; cultural adaptation of the scale into Spanish language, including forward and backward translations in duplicate and review for experts panel, and validation study in patients with NP of broad origin and subjects with Non-neuropathic pain (NNP). Reliability included determination of internal consistency, inter-rater agreement and test-retest reliability by means of Cronbach's alpha, Cohen's kappa and Intraclass Correlation Coefficient calculation. Validity included ROC curves analysis, assessment of concordance with reference diagnosis and determination of sensitivity, specificity and positive and negatives predictive values.

Results.- A total of 164 subjects (99 women, 60.4%; age: 60.4±16.0 years), 94 (57.3%) with NP and 70 with NNP, were included in the study. Diagnosis of type of pain was realized by pain experts using standard clinical criteria. The scale showed good reliability estimators; Cronbach's alpha coefficient: 0.71, inter-rater agreement coefficient: 0.80 (0.71-0.89), and test-retest intraclass correlation coefficient: 0.95 (0.92-0.97). Validity for a cut-off value ≥ 4 points, which was the best value to discriminate between patients with NeP component of pain, was acceptable: kappa's agreement coefficient; 0.57 (0.44-0.69), area under the curve 0.846 ($p < 0.0001$), sensitivity; 80.9% (72.9%-88.8%), specificity; 75.7% (65.7%-85.8%), predictive positive value; 81.7% (72.4%-89.0%), and predictive negative value; 74.6% (64.5%-84.8%).

Conclusion.- The Spanish version of DN4 scale is reliable, stable and valid for the differential diagnosis of neuropathic pain conditions.

--VERSIÓN RESUMIDA EN ESPAÑOL--**CAPÍTULO 5.****DISCUSIÓN GENERAL**

Por primera vez un análisis longitudinal del diagnóstico de DN y evaluación de QoL fue llevada a cabo en pacientes con LM en la fase aguda y sub-aguda durante un año después de la lesión en varios tipos de lesiones; y pacientes agudos y crónicos con y sin DN y voluntarios sanos en el mismo estudio. Originalmente comparamos diferentes metodologías en el diagnóstico del DN y LM (diferentes tipos de VAS, BST, QST y Entrevista Basada en Mecanismos de Dolor Neuropático, TSAR y cuestionario DN4) mostrando las particularidades de cada una, en tres diferentes áreas del cuerpo (al nivel, por debajo y por encima de la lesión).

Pudimos conseguir un diagnóstico completo de la LM observando los informes de los pacientes y el curso del dolor y la evaluación psicofisiológica de las funciones espinotalámicas y de la columna dorsal mediante diferentes métodos, como el acercamiento neurofisiológico **Capítulos 2 y 3** y la evaluación psicosocial (**Capítulo 4**). Además, la relativamente reciente hipótesis de la existencia de un centro de hiperexcitabilidad al nivel de la lesión, el CPG (**Finnerup et al., 2003; 2004**), puede haber obtenido apoyo adicional con nuestros resultados. Pensamos que dependiendo del momento específico de la lesión medular diferentes mecanismos pueden estar operando en el comienzo y mantenimiento posterior del DN.

5.1. Desarrollo Longitudinal del DN en la LM.

El estudio llevado a cabo en el **Capítulo 2** es el primero que recoge la evolución longitudinal del DN desde la fase aguda de la LM (antes de los 6 meses) hasta su fase crónica (un año después de la lesión), analizando la relación entre la intensidad de dolor *espontáneo* y de signos de dolor *evocados*, con el objetivo de analizar los mecanismos implicados y su impacto en los pacientes. Especialmente nos hemos centrado en la utilidad de las medidas de dolor *espontáneas* y *evocadas* implicadas en el DN. Las características clínicas de los pacientes en nuestra muestra presentaban amplio rango de edad, género, etiología y nivel de lesión; lo que favorece la inclusión de una gran cantidad de factores en los grupos de estudio.

La gran mayoría de nuestros pacientes estudiados empezaron su DN (tanto *espontáneo* como *evocado*) entre los meses 2 y 3 después de la LM, y presentaron más intensidad de dolor al nivel que por debajo del nivel de lesión. Como la potencia observada en el análisis es más bien baja muy probablemente debido al bajo número de pacientes para el análisis, los resultados significativos deben ser tomados con cautela, sin embargo podemos observar las tendencias dadas, ya que el único análisis que proporciona medidas longitudinales con nuestros datos es el ANOVA de medidas repetidas.

Siddall et al. (1999, 2003) encontró evidencia para dolor *espontáneo* y *evocado* tanto al nivel como por debajo del nivel de lesión, que comenzaban muy temprano (2 semanas) después de la LM, y 6 meses más tarde, la mayoría de los pacientes continuaron su experiencia de dolor. En nuestro estudio se evaluó a partir de los 2 meses principalmente porque el estado neurológico del paciente con trauma hizo muy difícil la evaluación y no permitió una adecuada evaluación en los pocos pacientes que aceptaron participar en este momento. Además en los pacientes con origen atraumático evaluados un mes después de la lesión (n=3), la intensidad de dolor espontáneo (incluido el Max VAS) no excedió de “2”, excluyéndolos del criterio inicial de inclusión de una puntuación de VAS mayor que “3”, no alcanzada hasta 2 meses después de la lesión.

5.2. Desarrollo de Dolor Espontáneo desde los 2 a los 12 meses Después de la LM.

El dolor espontáneo puede ser evaluado por diferentes escalas VAS; pero las más interesantes son el VAS de desagradabilidad y VAS de 7 días. El de desagradabilidad mostró mayores tasas pero en la misma línea: pudimos observar una tendencia en el incremento de dolor hasta los 12 meses, mucho más considerable al nivel de la LM que por debajo de ésta (consistente de nuevo con el mecanismo de dolor de CPG). Usamos el VAS de 7 días para el resto de análisis estadístico ya que fue considerado más homogéneo (ver SD), informativo y fiable de las puntuaciones de VAS del informe de los pacientes. Los pacientes con lesiones dorsales presentaron un progresivo incremento del dolor al nivel en todas las medidas temporales frente a un dolor más constante en pacientes con nivel de lesión cervical. Por debajo del nivel de LM, los pacientes con lesiones cervicales y dorsales alcanzaron el mismo nivel de dolor, pero con más amplia variabilidad en todas las medidas.

5.3. Dolor Evocado desde los 2 a los 12 meses Después de la LM.

El más común de los signos *evocados* es, tanto a los 3 como a los 6 meses después de la lesión, la hiperalgesia mecánica la cual es la más prevalente tanto al nivel como por debajo, y está presente en la mitad de los pacientes al nivel a los 6 meses después de la lesión. En general se observan más signos de dolor al nivel que por debajo a los 6 meses; mientras la alodinia térmica por debajo del nivel decrece hasta la mitad a los 6 meses, aumenta al doble al nivel de la lesión en el mismo mes. Estos hallazgos pueden estar apoyando al mecanismo CPG al nivel de la lesión, con la hiperexcitabilidad aumentada medida por los signos de dolor *evocado* en la fase aguda de la LM. En ratas lesionadas medularmente se ha observado que la proporción de neuronas de rango dinámico ancho (WDR) y de alto umbral (HT) respondiendo a estimulación inocua al frío respectivamente en animales con alodinia tras la LM. Estos resultados sugieren que el dolor crónico puede ser generado y mantenido por anomalías en las neuronas del asta dorsal (**Hao et al., 2004**).

5.4. Evidencia del Generador de Dolor Central (CPG).

El papel del CPG (Generador de Dolor Central) después de la LM al nivel de la lesión y su efecto en el desarrollo de dolor por debajo del nivel de lesión se presentó como hipótesis de estudio para los **Capítulos 2 y 3**. Algunos autores han sugerido previamente la existencia de un hiperexcitabilidad que operaría al nivel de la lesión y puede así influenciar vías nociceptivas por debajo del nivel de lesión (**Vierck, 2000**) y por encima del nivel (**Finnerup and Jensen, 2004**), posiblemente a través del sistema propioespinal, o incluso la activación de neuroglía (**Hains and Waxman, 2006**).

Estas hipótesis están apoyadas por nuestros resultados significativos que sugieren hiperexcitabilidad a ambos niveles de lesión, ya que se observaron más niveles de dolor para el grupo dorsal ($0 > VAS > 5$) versus tasas más bajas de dolor y mayor constancia del dolor en el grupo cervical ($2 > VAS > 3$) para los meses 2 y 12 tras la LM; y observamos en la interacción significativa una amplia variabilidad longitudinal en dolor espontáneo, con una tendencia al incremento en el grupo dorsal y disminución en el cervical. Múltiples correlaciones se han observado entre el número de dermatomas de dolor *espontáneo* y *evocado* a diferentes meses de lesión, incluso más interesante es el hecho de que a los 6 meses algunas correlaciones fueron positivas y significativas al nivel entre el número de dermatomas y signos como alodinia mecánica. Es interesante la observación de que la alodinia térmica correlacionara al nivel con el dolor *espontáneo*, lo cual puede también ser apoyado por el mecanismo CPG a los 2 y 6 meses después de la lesión. Pensamos que también era necesario observar el número de dermatomas involucrado en el DN de estos pacientes, viendo una tendencia en el grupo cervical por debajo del nivel a lo largo de los meses que fue disminuyendo el número de dermatomas tanto en dolor *espontáneo* como *evocado* en el tiempo. Al nivel de la lesión, el grupo cervical tendió a ser más constante y el dorsal más heterogéneo a lo largo de las diferentes medidas temporales. Por otra parte, el grupo dorsal encontró una correlación entre dermatomas *espontáneos* al nivel de lesión a los 2 meses y *evocados* por debajo del nivel a los 6 meses, lo que significa que si el mecanismo de CPG está operando a etapas tempranas de la lesión podría estar también presente más tarde.

Como se vieron diferencias significativas en sumación temporal al nivel de la lesión y también en alodinia térmica (a la acetona) por debajo del nivel de lesión a lo largo de las medidas desde 2-6 meses después de la lesión, ello significa más apoyo si cabe para el CPG al nivel, pero también para los tractos espinotalámicos que pueden estar operando por debajo del nivel de lesión. El sistema CPG podría estar operando ya en estadios tempranos de la LM al nivel y por debajo de la lesión, como hemos observado en los incrementados niveles *espontáneos* y *evocados* de dolor presentados en los pacientes, ya que el dolor *espontáneo* aumenta en intensidad en la mayoría de pacientes. Por otro lado, los cambios a altos niveles del sistema espinotalámico pueden ocurrir más probablemente después de los primeros 6 meses de la lesión.

Así, cuanto más intensidad de dolor *espontáneo* presentada al nivel a lo largo del tiempo de lesión, cuando el CPG es activado, y las correlaciones altas entre los signos de dolor *evocado* tanto al nivel (alodinia térmica e intensidad del dolor *espontáneo* a los 6 meses) como por debajo del nivel de lesión parece estar más en consonancia con esta teoría. La desaferentación de los tractos ascendentes y la activación de los objetivos rostrales por otras fuentes de actividad espinal (sistema propioespinal) (**Vierck et al., 2000**), pueden ser las responsables del DN que afecta a los pacientes, sin distinción entre nivel espinal afectado o el grado de lesión completa (desaferentada/ no desaferentada) que presentaron.

5.5. Fiabilidad de los Cuestionarios de Dolor Semi-directivos

La Entrevista basada en mecanismos de DN reveló que las preguntas relacionadas con dolor continuo y número de descriptores tuvieron más significación, tanto al como por debajo del nivel de lesión, y el dolor mecánico evocado dinámico al nivel a lo largo de las medidas temporales. Los resultados nos hicieron pensar que los pacientes no distinguieron claramente entre áreas del cuerpo afectadas (al y por debajo del nivel) y ente dolor *espontáneo* y *evocado*, principalmente en los estadios más tempranos de la LM. Los pacientes no tuvieron en cuenta que los signos como la sensibilidad mecánica, la sumación temporal y la disestesia /alodinia son signos *evocados* de dolor que realmente incrementaron su presencia de los meses 3 al 6. Además, observamos que los pacientes respondieron a nuestras preguntas con mayores puntuaciones en el principio, posiblemente debido a un peor entendimiento de su DN, y al hecho de que hasta el mes 6 empezaron a incrementar sus puntuaciones puede ser debido al final de la rehabilitación y al retorno de su actividad, con todas sus implicaciones emocionales (**Ver Capítulo 4**). La entrevista reveló que los exámenes de dolor *evocado* como el BST son más que útiles para el estudio de las fibras implicadas y vías en el proceso de DN; ya que la información dada por los propios pacientes parece no ser apropiada para evaluar tales cuestiones.

5.6. Examen Sensitivo a los 4-6 meses en los niveles de la LM: DN4 y QST.

La versión española del DN4 ha sido recientemente confirmada como fiable, estable y válida para el diagnóstico de las condiciones neuropáticas de dolor, ya que es capaz de diferenciar el componente neuropático del nociceptivo de dolor, con el mismo punto de corte que en la versión original. Es fácil de contestar por el paciente y fácil de calcular la puntuación total, gracias a la escala de 10 cuestiones (**Huelbes et al., 2006**). El cuestionario DN4 de dolor obtuvo puntuaciones entre 4 y 6 (de 10) en los grupos NP y SYR, y por ello es capaz de caracterizar los signos de DN en LM tanto aguda como crónica contrastada con sujetos sin DN. Las secciones de BST del cuestionario proporcionaron más significación (Hipoestesia al pinchazo de alfiler y cepilladura dolorosa). Pensamos que se necesitan más pacientes para obtener resultados significativos en el resto de preguntas, ya que el instrumento se probó con varias poblaciones (LM entre ellas) y fue válido para la evaluación del DN, como pudimos ver en el total de puntuaciones.

En general el QST se mostró a sí mismo como una batería de exámenes capaces de excitar diferentes tipos de fibras como hemos visto, teniendo en cuenta el nivel de LM y los grupos de pacientes examinados. Posibles explicaciones para nuestros resultados se relacionan con diferentes fibras y vías involucradas en el proceso de dolor, como el daño a las fibras A β , apuntando a un umbral de detección mecánico y vibración reducidos *al nivel de la lesión*, por tanto las vías de la columna dorsal medial lemniscal serían los mecanismos más implicados. El grupo de SYR crónico de pacientes presentados redujo su umbral de detección mecánico y los umbrales de discriminación entre dos puntos, mediados por las vías dorso mediales lemniscales de la columna.

El examen de la cepilladura no presentó respuestas a las fibras A β , probablemente debido al tratamiento con Gabapentina, ya que la alodinia mecánica es disminuida específicamente por la toma de esta medicación. Es de interés que los pacientes aún informaran de la presencia de cepilladura dolorosa; sin embargo, el informe del paciente puede ser influido por la alodinia sufrida antes de la medicación. Dos tipos de hiperalgesia mecánica se describieron previamente; el tipo dinámico estaría mediado por fibras mielínicas, mientras que el subtipo estático lo estaría por fibras amielínicas (**Ochoa and Yarnitsky, 1993**). En nuestra actual muestra de pacientes, las fibras C pueden haberse encontrado menos dañadas que las fibras Ad, ya que no se encontraron diferencias entre los grupos tanto en hiperalgesia mecánica (estática) como en sumación temporal, con el QST y TSAR (sólo en subgrupos). Se mostró hiperexcitabilidad en las fibras C y Ad por las diferencias en estimulación con calor, para el QST y la curva de respuesta al dolor, donde el dolor aumentó más rápidamente (pendiente) en el grupo dorsal, y también fue observado en el grupo SYR al frío al nivel de lesión. Es interesante que las respuestas aumentadas fueran observadas tanto con estímulos de calor como con frío en el QST en este grupo, mientras que el sistema TSAR no ocurrió, más bien lo contrario con el calor (**ver Limitaciones en este Capítulo**). Nuestros hallazgos sugieren, como en previos estudios, un procesamiento diferencial de los estímulos térmicos y mecánicos en el SNC mantenidos por actividad en los nociceptores sensibles al calor y unas vías espinotalámicas que operan anormalmente.

Por debajo del nivel de lesión, la sumación temporal tampoco obtuvo respuestas con el QST. Las altas respuestas de dolor fueron observadas diferencialmente en los grupos NP (con calor) y SYR (con frío) lo cual puede significar que el CPG está operando también a este nivel de la lesión junto con las vías espinotalámicas. Como se explica abajo, no se puede realizar ninguna comparación con el TSAR. Además, por encima del nivel de lesión la estimulación con calor fue más dolorosa en los grupos NP y SYR, con ambas metodologías, sin embargo en el

TSAR podemos observar menor respuesta mantenida en la curva de dolor para el grupo SYR para la estimulación al calor pero no al frío, lo que sugiere que en SYR todos los niveles presentaron un notable nivel de daño espinotalámico.

Aunque se asume que el “wind-up” no puede explicar plausiblemente los cambios perceptuales duraderos en el dolor crónico (p.e. **Woolf, 1999**) y que el “wind-up” no es central para el desarrollo del dolor crónico, permanece la observación clínica de una sensibilización aumentada como marcador clínico en algunos síndromes cónicos de dolor, como hemos observado en nuestras muestras de pacientes con DN. Sin embargo, pensamos que la sumación temporal puede presentar diferentes características por sí misma, ya que no se comportó como los otros signos de DN como la alodinia o la hiperalgesia. De hecho, el “wind-up” ha sido observado en voluntarios sanos en otros estudios, donde la estimulación repetida de fibras Ad and C causó sumación temporal con dolor secundario aumentado y dolor que perdura a la estimulación (**Price, 1991**).

La diferencia aparente significativa entre pacientes NP y HV en alodinia dinámica puede ser explicada diciendo que los pacientes NP estaban medicados así que la alodinia no estuvo presente en el momento del examen. La mitad de nuestros voluntarios sanos presentaron algo de desagradabilidad con la cepilladura pero sin llegar a niveles de alodinia en ningún punto (El VAS máximo fue de 0.50) (ver la sección 3.4.3).

En nuestra actual muestra de pacientes los exámenes realizados al nivel de la lesión generaron menos respuestas de dolor con frío pero no con estimulación de calor, lo que podría ser explicado probablemente por la hipótesis de que el dolor al calor, la sensación de frescor y de calor inocuo parecieron depender de la temperatura cutánea superficial, mientras que el dolor al frío fue relacionado con la temperatura subcutánea, sugiriendo diferentes receptores para el calor nociceptivo y para el frío nociceptivo (**Morin and Bushnell, 1998**), ya que las temperaturas nociceptivas usadas mostraron que el estímulo se comportó de modo diferente para las distintas muestras de sujetos. Observamos más respuestas con dolor al calor y al frío que al dolor evocado mecánicamente, lo cual es consistente con la relación inversa entre la diferencia de dolor a estas temperaturas y el grado de dolor evocado mecánicamente (**Gottrup et al., 1998**), y sugiere que el dolor anormal mecánicamente evocado en lesión traumática es en parte mantenida o generada por la actividad en los nociceptores térmicosensitivos (**Rowbotham and Fields, 1996**).

La anormal sensibilidad que creemos puede ser debida a la hiperexcitabilidad desde el CPG fue también observada con el método TSAR, y la respuesta anormal de las vías espinotalámicas podría estar más involucrada en patologías crónicas como la Siringomielia, aunque se necesita más investigación para separar los cambios agudos y crónicos en la LM.

Las observaciones en el sistema espinotalámico sin tener en cuenta el nivel de lesión puede producir disestesias y dolor mientras que las lesiones del sistema de la columna dorsal produce sólo parestesias (**Pagni, 1976**), sugiriendo que un desequilibrio entre el sistema de temperatura y dolor y el sistema táctil de fibras largas puede contribuir a las sensaciones espontáneas anormales. Además, hemos observado que considerando el nivel de lesión, al nivel de la LM podemos encontrar sensibilidad anormal que pensamos que es debida a la hiperexcitabilidad desde el CPG.

Las dificultades que algunos estudios presentan para explicar los posibles mecanismos implicados en el DN pueden deberse a un punto equivocado en las vías implicadas, Los síntomas de dolor central están mantenidos por distintos mecanismos y la percepción sensorial puede estar mediada por vías espinotalámicas o de la columna dorsal medial lemniscal y /o por el CPG dependiendo del punto evolutivo de la LM y del sitio del cuerpo afectado por el DN. Además, el hecho de que todas las áreas con función espinotalámica dañada apoyaron la existencia del dolor espontáneo crónico, mientras que ninguna de las áreas con similar daño produjo dolor patológico en pacientes son dolor, es consistente con la posibilidad de que la predisposición genética determine la emergencia del dolor crónico (**Defrin et al., 2001**).

5.7. Respuestas Dolorosas y No Dolorosas a estímulos mecánicos y térmicos en la LM.

La escala VAS está considerada como el instrumento más usado en la medida del dolor (Ver Capítulos 1 y 2). Algunas investigaciones recientes se han desarrollado utilizando más de un VAS al mismo tiempo para mediar la tasa de intensidad de dolor por el sujeto, añadiendo respuestas no dolorosas a la clásica escala de intensidad de dolor y situando palabras descriptoras no sólo en los extremos de la escala sino también en la mitad de ésta (**Morin and Bushnell, 1998**). Sin embargo, nosotros consideramos estos requisitos junto con la lista de descriptores de dolor demasiada información para ser procesada y proporcionada a los pacientes en tal corto espacio de tiempo de examen. Por ello es por lo que preferimos una *única y continua escala VAS* (con sólo dos

palabras al inicio y final) para medir desagradabilidad y dolor ya que parece mucho más comprensible, práctica y fiable.

Entendemos la escala de dolor (0 a 10) como una tasa continua que empieza con sensaciones extrañas que se convierten en desagradables, después dolorosas y más tarde más dolorosas hasta el final de esta escala donde la sensación se refiere como dolor insoportable por el sujeto. Creemos que las respuestas no dolorosas y las parestesias pueden ser parte de un constructo de sensaciones de dolor que puede ser situado en el mismo espectro que el VAS (0-10), siendo desagradabilidad las puntuaciones 0-2, y desde 210 “sensaciones de dolor” (disestesias) en nuestra escala. Esto se apoya en las cifras correlacionadas entre ellas (**ver correlaciones en Capítulo 2**) que pueden activar las mismas vías en sujetos sanos y pacientes y por el hecho de que en nuestro estudio longitudinal (**Capítulo 2**) el comienzo del DN en pacientes con LM se dio en bajas puntuaciones en el VAS (parestesias informadas) seguidas por un incremento más tarde del dolor en el VAS (disestesias informadas) de acuerdo con la evolución en meses del DN.

Para apoyar estos conceptos, nuestros hallazgos mostraron que la intensidad /desagradabilidad del dolor percibido no fue diferente para las temperaturas de calor y frío medidas con el sistema TSAR, como ocurrió en el estudio de **Morin y Bushnell (1998)**. Por tanto y basándose en ello, la desagradabilidad puede ser mediada por actividad neural similar en el área 24 cingulada anterior (ACC) para el dolor al calor y al frío, y también mostró correlación significativa con la intensidad de la sensación de dolor con independencia de la temperatura usada (**Craig et al., 1996**).

En los experimentos con psicofísica, analizamos cualquier sensación con la metodología QST percibida más que 0.5 en la escala VAS, así que pudimos estudiar las sensaciones dolorosas y no dolorosas. Sin embargo, las dolorosas fueron escasas e insuficientes en los grupos de pacientes, abriendo la controversia sobre cómo la intensidad de dolor es necesaria para considerar los signos de dolor como alodinia e hiperalgesia. Las definiciones de la IASP de estos términos (**ver Introducción del Capítulo 2**) no alude ninguna tasa de puntuación para distinguirlos entre ellos. Más aún, ellos pronuncian que la “actividad inducida en el nociceptor y vías nociceptivas por un estímulo nociceptivo no es dolor, lo cual siempre es un estado psicológico, incluso aunque podamos también apreciar que el dolor más frecuente tiene una causa física próxima” (**Ver Mecanismos psicológicos en Capítulo 4**). Quizá lo que hemos categorizado en este estudio no se puede llamar alodinia o hiperalgesia a la estimulación mecánica/ térmica, aunque creemos que aquellas sensaciones experimentadas por los pacientes están cerca del dolor en cualidad, solo que no en cantidad, y que pueden permitir el estudio del dolor en términos de fibras, vías y mecanismos implicados en el proceso de dolor.

Sin embargo, nosotros elegimos un VAS mayor o igual a 1.45 para la evaluación de las respuestas e-VAS ya que observamos que en la mayoría de los pacientes que respondieron a la estimulación térmica con el TSAR lo hicieron con el punto de corte. Sin embargo, algunos sujetos produjeron curvas moderadas de sensación con los VASes de menos de 1 en la escala, los cuales no se tomaron en cuenta para el análisis de las curvas de dolor, aunque no podemos descartarlas para futuras investigaciones, ya que la información proporcionada por las curvas de respuesta de sensación podría presentar similares patrones desde las respuestas de e-VAS.

5.8. Diagnóstico con QST/BST y estímulos térmicos tónicos

Creemos que los métodos BST/QST y TSAR son una metodología válida para una adecuada valoración del DN en LM. El QST ha demostrado su utilidad y fiabilidad en varios estudios en las últimas décadas, y es práctico y disponible para los investigadores clínicos y facultativos que trabajan con pacientes agudos y crónicos con DN. El método térmico TSAR proporciona características estímulo-respuesta sobre una configuración de intensidad y frecuencia de estímulos combinada, que el QST no puede conseguir (pendiente, modulus de 10 seg, modulus de 30 seg, etc) lo que es muy útil para detectar cambios espinotalámicos de dolor. El QST y el sistema informatizado TSAR son de fácil uso después del entrenamiento apropiado. La adecuada cantidad de datos informatizados necesarios para construir las curvas de dolor por el TSAR para medir sus fases supone datos más ajustados del dolor proporcionado por el paciente con los que trabajar.

Los exámenes BST/QST parecieron ser más efectivos que el TSAR para comparar a los pacientes crónicos SYR con los otros grupos de LM basados en la estimulación térmica principalmente por debajo del nivel de lesión. Sin embargo por encima del nivel, BST/QST y TSAR pudieron diferenciar entre sujetos de dolor crónico y HV con estímulos de calor. Mientras la acetona (BST/QST) mostró pobres resultados, el sistema TSAR fue capaz de detectar cambios térmicos entre grupos por encima del nivel y al nivel de lesión.

Los objetivos de nuestro estudio en el Capítulo 3 no han sido un campo exploratorio fácil ya que no ser capaces de evocar el signo de dolor no significa que estas fibras no jueguen un papel en el DN, puede ser debida a los métodos o a la selección de pacientes, y también se necesita una amplia muestra para concluir con resultados de manera más realista. La razón por la que no pudimos reclutar más respuestas dolorosas en nuestros pacientes fue probablemente debido a la falta de número suficiente de pacientes en cada grupo y que la mayoría de ellos estaban medicados.

La principal *limitación* que encontramos con el sistema TSAR fue el hecho de que los pacientes respondieron por debajo del nivel de lesión a sencillos exámenes realizados con el BST/QST pero no a ese nivel concreto con el sistema TSAR, lo que no tiene una explicación definitiva final. El grupo SYR tampoco respondió al nivel con las puntuaciones de dolor observadas al nivel. La *habituación* en forma de fatiga cutánea de fibras nociceptivas (Kleinböhl et al., 2006) no es probable ya que después de la estimulación con QST los sujetos tuvieron un descanso de cerca de 7-10 min., así que las fibras cutáneas no estaban sensibilizadas en el momento de la estimulación con el sistema TSAR. Otras explicaciones pueden ser posibles como los efectos acumulativos de una *anticipación del dolor inducida por estrés* informada por la mayoría de los pacientes específicamente a la máquina del TSAR, pero no por el grupo HV. El umbral de reflejo de flexión nociceptivo del miembro inferior en humanos fue progresivamente incrementado con la repetición del estrés en el estudio de Willis et al. (1991). Por otra parte, ese nivel fue siempre el primero examinado en pacientes, y la anticipación se supuso mayor al inicio del experimento doloroso. Así, los pacientes podrían haber presentado tal alto umbral inducido por el estado psicológico que no pudieron sentir ni el calor ni el frío por debajo del nivel de lesión. Otra explicación puede deberse al diferente método empleado, una superficie metálica pre-enfriada o pre-calentada frente a un tubo de cristal y gota de acetona, ya que las latencias al pico de comienzo de dolor elicitado están determinadas no sólo por la velocidad de conducción de los aferentes periféricos sino también por la profundidad de los receptores activados, las propiedades térmicas de la piel, los umbrales y utilización temporal de los nociceptores y el método de estimulación (Yeomans et al., 1996).

5.9. QoL de los pacientes con LM y DN durante el primer año.

El estudio de Calidad de Vida **Capítulo 4** es el primero que describe cambios en la intensidad de dolor espontáneo y desagradabilidad usando la escala VAS, combinada con las escalas cognitivo-conductuales de Calidad de Vida durante la fase aguda y crónica de la LM en un grupo seleccionado de pacientes con DN.

La aplicación de escalas psicofísicas (VAS) combinadas con escalas cognitivo-conductuales (CSQ-R y MPI-SCI) proporciona una comparación verdadera de los datos obtenidos del paciente. Aunque la escala VAS ha sido ampliamente usada en pacientes con medidas repetidas (Price, 1999), las escalas QoL necesitan más investigación para trazar las características de los pacientes con dolor crónico.

Hemos observado que los niveles de Catastrofismo estaban asociados con altos niveles de intensidad de dolor y alto estrés psicológico en nuestra muestra actual, así como una tendencia general para un incremento en factores QoL medidos por el CSQ-R y MPI-SCI desde los meses 2 al 12 después de la LM. Podemos identificar cambios similares en los factores más importantes involucrados en la Calidad de Vida (QoL), derivados de los dos cuestionarios, y relacionados estos cambios a la intensidad de dolor y al nivel de LM en una muestra seleccionada de pacientes con NP desde los 2 a los 12 meses tras la LM. Varios factores de QoL correlacionaron altamente con la intensidad del VAS y los factores físicos asociados con la LM principalmente en los estadios tempranos de la lesión.

Es de importancia que el incremento en Catastrofismo se acompaña por un incremento paradójico en varias estrategias cognitivas positivas para el dolor, tales como “Ignorancia de dolor, Distanciamiento, Rezo, Distracción y Afrontamiento”. Mientras que estas estrategias son efectivas en la modulación de la gravedad del dolor, es probable que el entrenamiento proporcionado a los pacientes por la Unidad de Psicología y Psiquiatría de este hospital de rehabilitación facilite la adopción de estrategias aprendidas durante la LM crónica. Estos resultados tienen implicaciones para los protocolos de evaluación y las intervenciones de tratamiento adecuadas para los pacientes con LM con el objetivo general del afrontamiento de los síntomas de dolor durante la rehabilitación psicosocial.

Así, la identificación de aquellos factores QoL que correlacionan con la gravedad del dolor después de la LM sería capaz de proporcionar una medida efectiva de la eficacia de los tratamientos.

Pudimos observar que las respuestas de afrontamiento no reflejan ajuste al dolor crónico, ya que incrementos en diferentes estrategias positivas contra el dolor no significan un cambio positivo en severidad de dolor, más bien lo contrario. Sin embargo, podría ser un problema de cuantitatividad, en términos de cuánto cambio se necesita para inferir un cambio significativo en la intensidad de dolor.

Aunque solo podemos hablar de tendencias en los resultados gracias al estadístico de medidas repetidas, el análisis de los factores QoL obtenido de los pacientes con lesión cervical y dorsal indica un patrón de afrontamiento distinto de dolor aparentemente no relacionado con el nivel de discapacidad asociada con la parálisis tetrapléjica, ya que se ha observado menos fluctuación en el grupo cervical a lo largo de la mayoría de los factores.

Los incrementos en estrategias positivas diferentes contra el dolor no siempre significan un cambio positivo en severidad de dolor, más bien lo contrario basado en nuestros resultados; podría ser cuestión de cuantitatividad como observamos.

5.9.1. Calidad de Vida en Población con LM Cervical y Dorsal.

Las tendencias proporcionadas por el estadístico de medidas repetidas mostró que varias y diferentes estrategias se usaron por pacientes con lesiones cervicales y dorsales: el grupo de pacientes cervical utilizó diferentes estrategias cognitivas como “Ignorancia de dolor, Distanciamiento y Afrontamiento”, mientras que “Rezo, Catastrofismo y Distracción” fueron más frecuentemente utilizadas en el grupo dorsal. La “Interferencia, Apoyo, Control de su vida y Respuestas Solícitas” del cuestionario MPI-SCI indicaron la presencia de estos factores después de la LM dorsal. Un significativo y progresivo incremento en los factores “Actividades Sociales y Actividades lejos de casa” fue observado en los meses 3-4, respectivamente, tras la LM dorsal, y un retraso hasta los 6 meses después de la lesión cervical. Interesantemente, la “Angustia Afectiva” fue generalmente mayor después de la LM dorsal, también pero a los 12 meses pareció el mismo aumento de angustia. Una tendencia no significativa también fue observada con altas tasas para “Severidad de dolor, Respuestas Distractoras, Actividades Domésticas y Actividades fuera de casa” en el grupo de LM dorsal.

No podemos afirmar, como sugirió **Turner et al. (2000)**, que las puntuaciones de Afrontamiento predicen la discapacidad en nuestra población y estamos de acuerdo con **Widerström-Noga et al. (2002)**, quien propuso que la reducción en los niveles de actividad por el dolor fue independiente del nivel de lesión.

Este estudio indica que nuestra muestra de pacientes usó estrategias cognitivas como estrategias de afrontamiento de dolor activo (CSQ-R) y solicitan Apoyo y Respuestas Solícitas (MPI-SCI) durante los primeros 12 meses después de la LM; a los 2 meses los factores se encuentran cerca del cero con un ligero aumento en Ignorancia de dolor, Distanciamiento, Rezo y Distracción a lo largo del año. Es interesante que el análisis de factores negativos como Catastrofismo del dolor (CSQ-R) reveló sólo un nivel moderado, incluso cuando los pacientes experimentaron una Interferencia de dolor (MPI-SCI) significativa a los 12 meses sugiriendo que el paciente raramente magnifica o se siente impotente frente al dolor durante su desarrollo en el último año. Caracterizamos diferentes patrones en el uso de estrategias comparando el tipo de gráficos mediante la observación de tendencias.

Estos patrones diferentes en estrategias de afrontamiento dependiendo de los factores físicos es de gran interés para tratamientos futuros, ya que los programas de manejo del dolor podrían acercar la psicoterapia de una manera más precisa y personalizada dependiendo del nivel de lesión de cada paciente.

En general el grupo de pacientes traumático tendió a rechazar el uso de algunas estrategias CSQ-R después de un periodo de ensayo, quizá porque no pudieron percibirlos como útiles contra el dolor, como fue el caso del Afrontamiento, Rezo y Distracción; mientras que la población traumática tendió a usar la mayoría de las estrategias de afrontamiento hasta un año después de la LM, incluso cuando mostraron el nivel más alto de Catastrofismo. La Interferencia, Apoyo, Severidad del dolor y Respuestas Solícitas del MPI-SCI son significativamente más prevalentes en pacientes con lesiones traumáticas hasta el mes 4° después de la LM. El Control de su vida mostró un nivel significativo a los 4 y 6 meses después de la LM en pacientes traumáticos, pero no hubo diferencia cuando se comparó con el grupo atraumático a los 12 meses. Los pacientes con LM traumática presentaron algunas particularidades como el trauma emocional y la negación de la realidad, algunas veces combinado con estrés post-traumático, y el apoyo social es proporcionado extensamente a pacientes con enfermedades crónicas como cáncer o lesiones causadas por la cirugía.

En términos de edad, tipo de lesión, género y el resto de datos clínicos y demográficos, podemos generalizar los resultados obtenidos a la población española con LM, aunque mayor número de pacientes podría ser deseable. Estos datos son comparables con estudios previos en población lesionada medular en grupo étnico, estado civil y causa de la lesión (excepto en el nivel de lesión). Como en el Capítulo 2, la limitación más importante fue la cantidad de datos perdidos en el mes 12 tras la LM, ya que fue menos posible para los pacientes el completar la evaluación del VAS y de los cuestionarios cuando fueron dados de alta médica. Observamos que la escala CSQ-R no es un cuestionario adecuado por sí mismo para la predicción de una medida de funcionamiento físico de ajuste como la discapacidad, y por eso escogimos también el MPI-SCI que complementa tales factores. Es importante reseñar que la escala de MPI-SCI incluye correlaciones con intensidad de dolor y desagradabilidad después de la LM. La versión modificada del MPI parece ser un instrumento razonable con el que evaluar el impacto del dolor en las personas con LM y la respuesta de sus otros significativos al dolor. Sin embargo, debido a que los niveles de actividad son diferentes, dependiendo de si se presenta para- o tetraplegia, y porque otras consecuencias de la LM disminuyen el nivel de actividad más que el dolor, la frecuencia con la que la persona participa en una actividad concreta puede no reflejar necesariamente daño del dolor en sí mismo (**Widerström-Noga, et al. 2002**).

5.10. Futuras Líneas de Investigación en Calidad de Vida y LM.

La futura investigación debería estar focalizada en tratamientos individuales que atiendan a las propias necesidades de cada paciente. Por tanto, cuestionarios más apropiados pondrían su objetivo en el nivel de lesión y posibilidades prácticas y verdaderas de la práctica de actividades supondrían una gran mejora en estos cuestionarios. Una escala de medida de dolor como la VAS también es necesaria como hemos visto previamente (MPI-SCI), algo de los que el CSQ y CSQ-R carecen.

Sin embargo, creemos que la aplicación de ambos cuestionarios a los pacientes sería muy adecuado para distinguir los factores involucrados en el dolor y el proceso de LM, y ambos deben ser usados para pacientes con LM cervical y dorsal.

5.11. Conclusiones Finales

El análisis longitudinal de los signos de dolor y síntomas desde los 2 a los 12 meses y un diagnóstico específico a los 4-5 meses en pacientes con LM utilizando BST y QST estándar con un nuevo sistema de estimulación Peltier-TSAR reveló nueva información que subraya la evolución y la relación entre el dolor espontáneo y evocado (1, 2, 3), apoyando la presencia temprana de un sitio espinal localizado de hiperexcitabilidad neuronal (4, 5) y cambios en las vías ascendentes sensoriales (6) y/o centros supraespinales de dolor debidos a desaferenciación espinal (6,7). Específicamente:

1. Desarrollo distintivo del dolor espontáneo en general y en subgrupos, dorsal versus cervical.
2. Un decremento significativo en la sumación temporal a la estimulación con pinchazo de alfiler al nivel y una reducción en la alodinia térmica/ sensibilidad a los estímulos fríos por debajo del nivel de los 2-6 meses.
3. Relación inversa entre intensidad del signo de dolor evocado y la intensidad de dolor espontáneo sólo a los 2 meses tras la LM, ausente a los 6 meses. A los 6 meses la intensidad de alodinia al frío / sensibilidad correlacionó con la intensidad de dolor espontáneo y con la hiperalgesia mecánica/ sensibilidad.
4. Los estímulos tónicos aplicados al nivel de la lesión revelaron cambios generales en el proceso nociceptivo local, específicamente en pacientes con LM dorsal aguda comparados con los cervicales, sugiriendo un desarrollo diferencial en los mecanismos de dolor locales.
5. Análisis correlacionales entre la LM al nivel y por debajo del nivel revelaron una relación en el número de dermatomas con dolor evocado a los 2 y 6 meses de la LM, con una correlación adicional entre la intensidad de alodinia térmica/ sensibilidad al nivel e hiperalgesia mecánica/ sensibilidad por debajo del nivel a los 6 meses. El papel de mecanismos espinales al nivel que median cambios remotos en la nocicepción por debajo del nivel de lesión no pudo concluirse debido al bajo número de pacientes con LM reclutados en este estudio.
6. Una reducción en el ratio de respuesta al calor, frío, discriminación entre dos puntos, vibración y estimulación con von Frey apoyan la existencia una función de las vías espinotalámicas y de la columna dorsal-lemniscal anormales.

7. Por encima del nivel de LM la estimulación térmica tónica de calor controlada reveló que los 10s y 30s iniciales de la respuesta integrada de dolor e-VAS por encima del nivel fue significativamente más baja para el grupo de SYR que para NP, mientras que una respuesta integrada no significativa ($p=0.06$) de e-VAS de 10s a estímulos tónicos de frío aplizados por encima del nivel se observaron en NP comparado con el grupo HV.

El estudio de Calidad de Vida es el primero en describir cambios asociados en intensidad de dolor y desagradabilidad con la evolución temporal de los factores cognitivo-conductuales (8) obtenidos del CSQ-R(9) y MPI-SCI (10,11) , también identificando diferencias en la estrategia de uso entre pacientes con lesión cervical y dorsal (12) desde los 2 a los 12 meses después de la LM. Específicamente:

8. La intensidad de dolor espontáneo correlacionó significativamente con los factores de Calidad de Vida del CSQ-R y MPI-SCI después de la LM, algunos de los cuales se mantuvieron hasta los 12 meses.
9. El incremento significativo en varias estrategias positivas contra el dolor, como Ignorar el dolor, Distanciamiento, Rezo, Distracción y Afrontamiento durante los 6 primeros meses fue observado con un incremento en catastrofismo sobre ese periodo de tiempo.
10. El Catastrofismo como estrategia cognitiva sólo estuvo presente a un nivel moderado, sugiriendo que el paciente raramente magnifica su dolor durante su desarrollo en la fase temprana.
11. El cuestionario MPI-SCI mostró que los pacientes stilizaron estrategias cognitivas, representando más aspectos de la vida diaria que el CSQ-R, como Afrontamiento, requirieron Apoyo y Respuestas solícitas durante los primeros 12 meses tras la LM.
12. Aunque los supuestos de nuestras muestras comparando pacientes con lesión cervical y dorsal deben tomarse con cautela, podemos sugerir que el grupo dorsal de LM se asocia con QoL más baja, de acuerdo con los datos longitudinales obtenidos con el CSQ-R y MPI-SCI.

