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Neural correlates of the attentional bias towards pain-related faces in fibromyalgia patients: An ERP study using a dot-probe task

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ABSTRACT

Background: One of the major cognitive deficits in fibromyalgia has been linked to the hypervigilance phenomenon. It is mainly reflected as a negative bias for allocating attentional resources towards both threatening and pain-related information. Although the interest in its study has recently grown, the neural temporal dynamics of the attentional bias in fibromyalgia still remains an open question.

Method: Fifty participants (25 fibromyalgia patients and 25 healthy control subjects) performed a dot-probe task. Two types of facial expressions (pain-related and neutral) were employed as signal stimuli. Then, as a target stimulus, a single dot replaced the location of one of these two faces. Event-related potentials (ERP) in response to facial expressions and target stimulation (i.e., dot) were recorded. Reaction time (RT) and accuracy measures in the experimental task were collected as behavioural outcomes.

Results: Temporal dynamics of brain electrical activity were analysed on two ERP components (P2 and N2a) sensitive to the facial expressions meaning. Pain-related faces elicited higher frontal P2 amplitudes than neutral faces for the whole sample. Interestingly, an interaction effect between group and facial expressions was also found showing that pain-related faces elicited enhanced P2 amplitudes (at fronto-central regions, in this case) compared to neutral faces only when the group of patients was considered. Furthermore, higher P2 amplitudes were observed in response to pain-related faces in patients with fibromyalgia compared to healthy control participants. Additionally, a shorter latency of P2 (at centro-parietal regions) was also detected for pain-related facial expressions compared to neutral faces. Regarding the amplitude of N2a, it was lower for patients as compared to the control group. Non-relevant effects of the target stimulation on the ERPs were found. However, patients with fibromyalgia exhibited slower RT to locate the single dot for incongruent trials as compared to congruent and neutral trials.

Conclusions: Data suggest the presence of an attentional bias in fibromyalgia that it would be followed by a deficit in the allocation of attentional resources to further process pain-related information. Altogether the current results suggest that attentional biases in fibromyalgia might be explained by automatic attentional mechanisms, which seem to be accompanied by an alteration of more strategic or controlled attentional components.

1. Introduction

Current clinical positions establish that fibromyalgia is characterized by the presence of widespread and diffuse chronic pain along with a wide variety of affective and cognitive symptoms (Okifuji and Turk, 2002; Wolfe et al., 2010; Bell et al., 2018; Wu et al., 2018). As a part of these cognitive symptoms, previous evidence has shown that fibromyalgia patients exhibit deficits involving attentional processes (Duschek

et al., 2014). The idea that chronic pain patients selectively attend to pain-related information at the cost of other information in the environment (i.e., the allocation of attentional resources towards threatening events is notably higher than other stimulation) has been discussed in terms of attentional biases or hypervigilance phenomena (Bar-Haim et al., 2007). What is most important is to know under which specific conditions, this mechanism might initiate, exacerbate and maintain certain clinical symptoms in chronic pain patients (Pincus and

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Morley, 2001; Crombez et al., 2013; Mercado et al., 2013).

However, the hypervigilance phenomenon in fibromyalgia is still under debate. Whereas some studies describe the presence of general hypervigilance towards any type of information in the environment (McDermid et al., 1996; Geisser et al., 2003, 2008; Hollins et al., 2009; González et al., 2010; Wilbarger and Cook, 2011), growing research has indicated that fibromyalgia patients are characterized by an augmented allocation of attentional resources towards negative, threatening and/or nociceptive events. Negative words (Duschek et al., 2014), aversive tones (Carrillo-De La Peña et al., 2015), sensory painful stimuli (Kosek et al., 1996; Lorenz, 1998; Peters et al., 2000; Davis et al., 2001; Desmeules et al., 2003; Burgmer et al., 2009; de Tommaso et al., 2011) and fear/pain-related faces (Khatibi et al., 2009; González-Roldán et al., 2013) have been reported as different kinds of potential threatening signals for eliciting an attentional bias in these patients. Due to its specificity, facial expressions of pain might be a stimulus of special relevance for the patient who suffers from it and an important emotional signal for external observers (Prkachin and Craig, 1995; Williams, 2002). It has been found that observing painful faces activated similar brain areas as the own experience of pain (Saarela et al., 2006; Xiong et al., 2019). Furthermore, the use of emotional faces has led to obtaining more solid results than those obtained with symbolic information such as words (Pishyar et al., 2004; Staugaard, 2009). In this line, the inclusion of pain-related faces to investigate attentional bias in chronic pain patients has been previously recommended (Khatibi et al., 2009).

Although evidence supporting the presence of an attentional bias to threat in fibromyalgia seems to be solid, the different phases or stages characterizing such attentional processing have been scarcely studied in chronic pain patients (Khatibi et al., 2009). In line with Posner and Petersen models (Posner, 1980; Posner and Petersen, 1990), several independent but interrelated components have been suggested to explain attentional processing to threatening information (Van Damme et al., 2004a, 2006; Cisler et al., 2009; Cisler and Koster, 2010): 1) Initial orienting or engagement to threat; 2) Disengagement attention from threat; 3) Attentional avoidance or directing attention away from threat. Briefly, while the first component has been related to the automatic orientation of attentional resources towards where or when an important event occurs for further enhancing sensory processing, disengaging and avoidance processes would involve more controlled processing resources to reorienting the attention away from potential threats (Petersen and Posner, 2012; Carretié, 2014). Accordingly, attentional bias could involve both automatic and controlled processing (Legrain et al., 2009).

Experimental paradigms as the spatial cueing (Van Damme et al., 2004b; Koster et al., 2006) or the dot-probe task (MacLeod et al., 1986; Vervoort et al., 2011) have been shown as the more suitable tools for studying attentional biases in several clinical conditions such as anxiety (Bar-Haim et al., 2007), depression (Neshat-Doost et al., 2000; Gotlib et al., 2004), eating disorders (Brooks et al., 2011) or substance addictions (Ehrman et al., 2002; Field and Cox, 2008). A recent meta-analysis (Todd et al., 2018) has reported evidence supporting the existence of attentional biases in chronic pain patients towards pain-related information (sensory pain stimuli and pictures) using the dot-probe task. As a rule, participants performing the dot-probe task have to indicate the location or orientation of a single target stimulus (i.e., a dot) that replaces one of the two simultaneous stimuli previously presented (i.e., the signals). Usually, one of these two signal stimuli is neutral, while the other one conveys emotional (threat-related) meaning. Typically, participants' processing benefits if the target stimulus replaces the emotional signal (congruent trials). However, in the case that target replaces the neutral signal stimulus, a longer response time is normally detected (incongruent trials). The explanation at the behavioural level is twofold. On the one hand, congruent trials produce an engagement towards emotional stimulation, reflected by shorter reaction times to target detection. But on the other hand, the increase of reaction times to

the target stimulus during incongruent trials might be attributed to an effect of attentional disengaging (Koster et al., 2004; Carlson and Reinke, 2008).

The use of high-temporal resolution brain measures, such as eventrelated potentials (ERPs) could complement behavioural studies. ERPs are considered as an excellent option for exploring the time course of rapid neural processes such as those involved in the attentional processing (Carretié, 2014). Different phases reflecting the attentional response to emotional faces are frequently described in ERPs components comprised between 100 and 300 ms to the stimulus onset (Torrence and Troup, 2018). Thus, early posterior components as P1 and N1, have been associated with the allocation of automatic attentional resources towards attended emotional stimuli (Mangun, 1995; Halit et al., 2000; Itier and Taylor, 2004; Eimer and Holmes, 2007; Luck, 2014). In this line, N170 has been considered as a face-specific ERP component related to the rapid structural facial encoding (Eimer and Holmes, 2007). Around 180-200 ms from the stimulus onset, the P2 component has been linked to engagement and sustained perceptual processing of emotional facial expressions (Schupp et al., 2004; Bar-Haim et al., 2005; Eldar et al., 2010; Yang et al., 2012; Carretié et al., 2013). The emotional meaning conveyed by the stimulus seems to modulate P2 amplitude (Bar-Haim et al., 2005; Eldar et al., 2010). Notably, greater amplitudes and shorter latencies of this component have been interpreted as the reflection of a negativity bias to emotional information (Carretié et al., 2001, 2013). Finally, the anterior N2a component, a negative deflection observed just after P2, seem to be reflecting cognitive control mechanisms (Eldar and Bar-Haim, 2010), involved in the regulation of attentional engagement and the subsequent disengagement (Price et al., 2014; Fu et al., 2017). In sum, whereas early ERPs to attentional face processing (i.e., P1, N1, N170 and P2) has been related to bottom-up attentional mechanisms, N2a component has been involved in controlled top-down mechanisms (Thai et al., 2016). On the other hand, brain responses to target location are frequently described in ERPs components related to posterior P1 and a lesser extend to anterior P3 (Torrence and Troup, 2018). However, inconclusive ERP findings to target location have been displayed up to date (Pourtois et al., 2004; Mueller et al., 2009; Eldar et al., 2010; O'Toole and Dennis, 2012; Rossignol et al., 2013; Torrence and Troup, 2018).

Therefore, the present investigation was aimed to characterize the temporal dynamics of the attentional bias towards pain-related information in fibromyalgia at both behavioural and neural levels, as complementary measures. Based on previous literature, we hypothesized that the configuration of the electric field corresponding to ERPs components involved in automatic attention to pain-related information (e. g., P1, N1, N170 and/or P2), would be associated with higher amplitude and shorter latency in fibromyalgia patients as compared to the control participants. In addition, we expected to find a poor distribution of attentional resources in fibromyalgia patients (i.e., difficulties in reorienting the attention from facial expressions to target dot, in order to prepare a quickly motor response), reflected in more controlled attentional processing stages (e.g., lower amplitude of N2a), which could contribute to lower performance in the ongoing task (i.e., poor performance for detecting the target locations).

2. Methods

2.1. Participants

Fifty women (25 healthy control participants and 25 fibromyalgia patients), took part in this experiment. The whole sample was aged between 29 and 69 (mean age \pm SD of 51.50 \pm 9.05 years). Patients fulfilled the American College of Rheumatology diagnostic criteria for fibromyalgia (ACR: Wolfe et al., 1990, 2016). They were recruited from the Fibromyalgia and Chronic Fatigue Syndrome Association of Mostoles (AFINSYFACRO). Healthy control participants were recruited by posting advertisements at the Rey Juan Carlos University (School of

Health Sciences) and among the friends of patients in order to balance the age and sociodemographic status between both groups. Finally, only data from 46 subjects (24 healthy control participants and 22 fibromyalgia patients) were analysed (as it will be explained later). No group differences were found on age [F $_{(1.44)} = 1.09$; p = 0.302] or educational level [F $_{(1,44)} = 2.339$; p = 0.133]. Patients who were taking medications that could be affecting cognition (antidepressants and benzodiazepines), were asked to stop it 48 h before starting the study. The intake of other medication, such as general analgesic (i.e., ibuprofen or paracetamol) was continued because of both medical prescription and ethical considerations. Participation in the study required the absence of neurological disorders that impair cognitive functions (i.e., stroke and other brain damage), psychosis and substance abuse/dependence, so these conditions were set as exclusion criteria. All participants had normal or corrected-to-normal eyesight and hearing. Data regarding sociodemographic and psychological variables are shown in Table 1.

Before starting the experimental session, all participants were instructed about the procedure and signed the informed consent. The study was approved by the Rey Juan Carlos University Research Ethics Board and it followed all requirements from this committee. Subsequently, they completed the State-Trait Anxiety Inventory (STAI) (Spielberger, 2010), and the Beck Depression Inventory (BDI) (Beck, 1961) to measure both state-trait anxiety and depressive symptoms. The Pain Catastrophizing Scale (PCS) (Sullivan et al., 1995) was also applied to the whole sample of participants, with the aim of measure catastrophic thoughts about pain. The Fibromyalgia Impact Questionnaire (FIQ) (Burckhardt et al., 1991), a specific questionnaire to assess the current health and functional status in fibromyalgia patients, was only administered to the patients. Additionally, other clinical variables such as pain and fatigue symptoms were measured by two Visual Analogue Scales (VAS).

2.2. Stimuli and procedure

As mentioned in the Introduction section, the experimental paradigm used in this experiment was a dot-probe task (Fig. 1), where two types of facial expressions were included as signal stimuli: pain-related faces (PF) and neutral faces (NF). A probe (i.e., a single dot) was used as the target stimulus

Facial expressions were selected based on the results from an independent study (conducted several weeks prior to the experiment), in which forty participants took part (17 men and 23 women; aged between 18 and 67 years old). Facial expressions were recorded in response to somatosensory stimulation applied using both a CO_2 laser

Table 1
Mean and standard deviations (in parenthesis) of age, level of anxiety, depression, catastrophism, impact of fibromyalgia, pain and fatigue. Information about the percentage of participants (healthy controls and fibromyalgia patients) who were taking medications is also included.

Variables	НС	FM	p-value
Age	50.17 (9.12)	52.95 (8.94)	0.302
Months of Diagnosis	_	91.95 (51.07)	
Medication			
Antidepressants (%)	4.2	77.3	0.01
Anxiolytics (%)	0	68.2	0.01
Analgesics (%)	0	40.9	0.01
Others (%)	0	27.3	0.01
STAI State	26.10 (12.13)	53.59 (14.58)	0.01
STAI Trait	17.60 (17.87)	75.10 (17.75)	0.01
BDI	4.92 (5.54)	17.59 (7.18)	0.01
PCS Total	23.50 (19.85)	55.86 (28.79)	0.01
PCS Rumination	25.67 (18.63)	49.41 (28.95)	0.01
PCS Magnification	38.67 (21.31)	64.95 (26.47)	0.01
PCS Helplessness	24.62 (19.55)	58.09 (29.94)	0.01
VAS Pain	.761 (1.99)	5.12 (2.86)	0.01
VAS Fatigue	1.17 (1.83)	5.90 (2.97)	0.01
FIQ	_	60.08 (13.85)	_

(Neurolas, Electronic Engineering; wavelength of 10.6 µm) and a pressure algometer. The laser pulse was set at a supra-threshold intensity (it was always perceived as painful), with a power of 9 W and a duration of 30 ms. This painful stimulus was delivered via a mean beam diameter of 2.8 mm (density = 30.70 mJ/mm2) (see Peláez et al., 2019 for a more detailed description). Participants were asked to introduce their right hand into a box (only opened at the top) to prevent them from seeing the laser beam direction and to avoid distractions. Subsequently, while participants kept their right hand on the box an additional painful stimulus was also applied by a pressure algometer. This method was carried out to get a second facial expression in response to a more durable painful stimulation. Finally, participants were asked to make a neutral baseline expression lasting for 1 s. This session was recorded through a camcorder (Sony Handycam HDR-XR550VE) located at eye level. The distance between the camcorder and participants was set at 50 cm. Video sequences were segmented in epochs of 1000 ms and it was scanned frame by frame to extract the single images belonging to each face where the most representative expression (i.e., painful or neutral) was displayed.

A total of 120 facial pictures (80 PF and 40 NF) were enrolled in a validation procedure. Eighty-two participants (mean age \pm SD of 29.48 \pm 12.70 years) were instructed for rating the whole set of facial expressions in pain intensity, valence and arousal (see Simon et al., 2008), by means a three-dimensional scaling test of nine positions: how much pain intensity is represented (from 0, any pain, to 8, most imaginable pain), how the person might feel with respect to valence (from 0, highly unpleasant, to 8, highly pleasant), and arousal (from 0, highly relaxed, to 8, highly arousing). Thus, 40 facial expressions (20 PF and 20 NF) were chosen among which complied with the following inclusion criteria: 1) facial expressions rated with pain intensity scores and levels of arousal higher than 5 points and ratings of valence below 2, comprised the PF category; 2) the NF category was comprised by faces rated with pain intensity and arousal scores lower than 2 points and mean valence ranged between 3.5 and 5.5 points. Finally, these facial expressions representing twenty different personal identities (8 men and 12 women; aged between 18 and 63 years old) were included in the dot-probe task (mean of pain intensity \pm SD of 6.33 \pm 0.57 for PF and 0.55 ± 0.76 for NF; mean level of valence \pm SD of 1.23 ± 0.43 for PF and 3.41 \pm 0.59 for NF; mean level of arousal \pm SD of 5.27 \pm 0.53 for PF and $1.20\,\pm\,0.74$ for NF). The whole set of facial expressions used in the experimental study is displayed in Fig. 2. Additionally, the mean of pain intensity, valence and arousal for every single picture are showed in

The Gentask module of the STIM2 package (NeuroScan Inc) was used as the software for the stimuli presentation and behavioural data acquisition (Fig. 1). It includes a dedicated visual system and a fourbutton response pad for data collection. Each trial began with a fixation cross during 500 ms. Then, the fixation cross was followed by a signal stimulus made up of a pair of faces located at the right and left sides of the fixation cross (8.7, 8.30° width x 11, 10.50° height, visual angle degrees). Facial expression stimuli were presented in black and white colour and they were matched in luminance. In order to remove non-facial features, all images were cropped within an oval frame (3.50 cm \times 5 cm). This pair of facial expressions was presented for 500 ms. Three different types of right-left pairs of faces were employed: Neutral-Neutral (named from now as "neutral baseline") and Pain-Neutral and Neutral-Pain (both boards named from now as "pain-related"). Fifty repetitions were set for each condition. After a regular interval of 300 ms, a target stimulus (i.e., dot) appeared during 200 ms. Target stimulus replaced the location of one of the two facial expressions establishing three different experimental conditions (congruent, incongruent and neutral). The congruent condition was constituted when the target stimulus replaced the location of a PF in the pain-related condition, and the incongruent condition was constituted when the target stimulus replaced the location of the NF in the pain-related condition. Finally, the neutral condition was formed by a target stimulus that replaced the

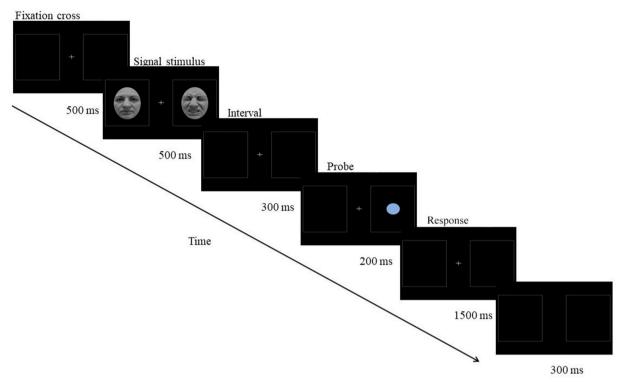


Fig. 1. Illustration shows a trial of the dot-probe task belonging to the pain-related condition (signal stimulus: Neutral-Pain) followed by the target stimulus (dot) replacing pain-related expression (congruent condition).



Fig. 2. The whole set of facial expressions used in the dot-probe task.

Table 2Mean and standard deviations (in parenthesis) of intensity of pain scores and levels of valence and arousal in each facial picture.

Nº	Type	Sex	Intensity	Valence	Arousal
1	Pain	Women	6.81 (1.16)	1.79 (1.93)	6.53 (1.27)
2	Pain	Women	7.20 (1.48)	1.33 (1.96)	7.10 (1.42)
3	Pain	Men	7.47 (0.98)	1.20 (2.25)	7.07 (1.45)
4	Pain	Women	6.75 (1.74)	1.74 (1.96)	6.54 (1.42)
5	Pain	Men	6.51 (1.72)	1.82 (1.94)	6.37 (1.35)
6	Pain	Women	6.02 (1.49)	2.29 (1.85)	6.00 (1.44)
7	Pain	Women	6.14 (1.39)	2.08 (1.70)	6.02 (1.38)
8	Pain	Women	7.18 (1.79)	1.27 (1.57)	7.10 (1.79)
9	Pain	Men	6.14 (1.62)	1.98 (1.58)	5.91 (1.63)
10	Pain	Women	7.13 (1.55)	1.26 (1.95)	6.82 (1.52)
11	Pain	Women	6.04 (1.53)	2.12 (1.64)	5.95 (1.37)
12	Pain	Women	5.45 (1.59)	2.54 (1.59)	5.36 (1.56)
13	Pain	Women	5.24 (1.75)	2.67 (1.72)	5.27 (1.74)
14	Pain	Men	5.73 (1.92)	2.73 (1.94)	5.37 (1.85)
15	Pain	Men	6.38 (1.37)	2.08 (1.91)	6.22 (1.39)
16	Pain	Men	6.58 (1.38)	1.87 (1.77)	6.41 (1.23)
17	Pain	Men	5.97 (2.12)	2.14 (1.93)	6.00 (1.86)
18	Pain	Women	5.66 (1.63)	2.44 (1.55)	5.58 (1.41)
19	Pain	Women	7.08 (1.54)	1.23 (1.96)	6.73 (1.56)
20	Pain	Men	5.93 (1.46)	2.35 (1.65)	5.79 (1.30)
21	Neutral	Women	3.43 (1.98)	3.40 (1.46)	3.95 (1.79)
22	Neutral	Women	0.57 (1.18)	4.05 (1.70)	1.65 (1.73)
23	Neutral	Men	1.37 (1.85)	3.89 (1.95)	1.88 (1.77)
24	Neutral	Women	1.01 (1.52	4.54 (1.91)	2.17 (1.72)
25	Neutral	Men	1.95 (1.80)	3.94 (1.67)	2.84 (1.78)
26	Neutral	Women	0.58 (1.26)	5.39 (2.16)	1.70 (1.81)
27	Neutral	Women	0.60 (1.18)	5.44 (2.11)	1.46 (1.60)
28	Neutral	Women	2.43 (1.39)	3.86 (2.12)	3.62 (1.31)
29	Neutral	Men	0.72 (1.46)	4.97 1.95)	1.85 (1.74)
30	Neutral	Women	0.66 (1.31)	5.51 (2.11)	1.75 (1.74)
31	Neutral	Women	1.36 (1.65)	4.39 (1.71)	2.74 (1.82)
32	Neutral	Women	0.69 (1.38)	4.42 (2.19)	1.20 (1.55)
33	Neutral	Women	0.67 (1.57)	5.05 (2.16)	1.97 (1.82)
34	Neutral	Men	0.86 (1.53)	4.46 (2.15)	1.88 (1.92)
35	Neutral	Men	0.62 (1.47)	4.72 (1.99)	1.60 (1.76)
36	Neutral	Men	0.55 (1.18)	4.50 (1.89)	1.42 (1.72)
37	Neutral	Men	0.67 (1.24)	5.05 (2.16)	1.97 (1.82)
38	Neutral	Women	0.57 (1.07)	4.92 (1.94)	1.31 (1.56)
39	Neutral	Women	0.59 (1.32)	5.47 (2.22)	1.52 (1.76)
40	Neutral	Men	0.65 (1.12)	4.52 (2.06)	1.68 (1.52)

location of any facial expressions in the neutral baseline condition. Participants were instructed to respond by pressing different key buttons as quickly and accurately as possible to indicate the side where the dot appeared. The inter-trial interval was set at 3500 ms. A total of 150 pseudorandomized trials were presented (the same pair of facial expression category was not displayed in more than three consecutive trials). Trials were counterbalanced across emotional facial expressions, target location and face gender. The experiment was carried out in optimal conditions of acoustic, electromagnetic and air conditioning insulation room. The distance between participants and screen (19" flatpanel monitor, refresh rate 60 Hz), was approximately 70 cm. Before starting the experiment, participants completed a practice block of 10 trials to familiarize themselves with the task.

After the recording session, in the same way that occurred with the procedure for selecting the facial expression stimulation, all participants whose data were finally analysed, completed a similar scaling test for each facial expression. As it mentioned, assessments of pain intensity, valence and arousal were given by each participant. The results of this assessment are described in the Results section.

2.3. Electrophysiological recording

Brain Vision Recorder software (Brain Products) was employed for neural data acquisition. Brain electrical activity was recorded using an electrode cap (QuikCap-Neuroscan) that included sixty homogeneously distributed scalp electrodes (10-10 system). The electroencephalography (EEG) recording took as reference two electrodes located on both

mastoids. Eye movements were controlled through a vertical and horizontal electrooculographic recording (EOG), by placing two electrodes located infra- and supraorbitally in the left eye (vertical EOG), as well as at the left and the right orbital rim (horizontal EOG). All electrode impedances were kept below 5 k Ω . A bandpass filter of 0.1–40 Hz was applied for the recording amplifiers. Channels were continuously digitizing data at a sampling rate of 500 Hz. Brain Vision Analyzer software was used for data processing. In order to isolate the brain response to facial expressions from the one related to the single dot, two different epochs of 1000 ms (-200 ms-800 ms) were selected for each category of stimulus (signal/faces and target/dots). Gratton, Coles and Donchin algorithm (Gratton et al., 1983) was applied to reduce eye movements artefacts. Baseline correction was performed using 200 ms before stimulus onset. EEG epochs whose signal exceeded $\pm 75~\mu v$ were excluded. Data from seven participants were removed from further analyses because of the high rates of artefact-contaminated trials (over 50%). In the fibromyalgia group, this artefact rejection procedure for facial expressions led to a trial average admission of 74% (mean = 37; SD = 5) in neutral baseline condition, and 73% (mean = 73; SD = 8) for the pain-related condition. The artefact rejection procedure for targets led to a trial average admission of 70% (mean = 35; SD = 6) for congruent condition, 72% (mean = 36; SD = 6) for incongruent condition, and 72% (mean = 36; SD = 6) for neutral condition. With respect to the healthy control group, the average of admitted trials related to faces was the 80% (mean = 40; SD = 5) in neutral baseline condition, and 76% (mean = 76; SD = 10) for pain-related condition. Finally, the percentage of trials processed in further analyses for the target stimulation reached the 72% (mean = 36; SD = 7) for congruent condition, 74% (mean = 37; SD = 6) for incongruent condition, and 74% (mean =37; SD = 6) for neutral condition.

2.4. Data analyses

2.4.1. Detection and characterization of ERPs: temporal principal component analysis

Temporal principal component analysis (tPCA) performed using a covariance matrix was applied to detect and quantify the ERP components explaining most of the brain electrical activity variance. The application of this technique has been strongly recommended for these kind of tasks because it allows avoiding the subjectivity of selecting time windows based only on visual inspection of grand-averaged ERPs (this can lead to several types of misinterpretation, especially when high-density montages are employed), representing each ERP component free of the influences of adjacent or subjacent components (see Dien and Santuzzi, 2005, for a more detailed description of tPCA procedure and advantages). This technique has already demonstrated its ability to disentangle and characterize ERP components and it has been previously used in experiments focused on the study of attention to emotional processing by means of ERPs (Carretié et al., 2005, 2009, 2013; Delplanque et al., 2005).

In brief, the tPCA computes the covariance between all ERP time points, which tends to be high between those time points involved in the same component, and low between those belonging to different components. The tPCA based on a covariance matrix was performed on the averaged waveforms, each being represented by 512 time points (from -200 to 800 ms averaged epoch). The solution is therefore a set of different factors made up of highly covarying time points, which ideally correspond to ERP components. The temporal factor (TF) score, the tPCA-derived parameter in which extracted temporal factors (TFs) may be quantified, is linearly related to the amplitude of ERP components. Forty-six subjects, two stimulus categories (pain-related and neutral faces: PF and NF) and sixty electrode sites yielded a total of 5520 averaged waveforms which served as the database for the tPCA related to the facial expressions. Besides, forty-six subjects, three stimulus categories (congruent, incongruent and neutral baseline) and sixty electrode sites yielded a total of 8280 averaged waveforms which served as the database for the tPCA related to the single dot. The decision on the number of factors to extract was carried out through the application of the scree test (Cliff, 1987). Promax rotation was applied in order to select temporal factors as recommended (Dien, 2010, 2012).

2.4.2. Detection and characterization of ERPs: spatial principal component analysis

Considering that signal overlapping may occur also at the space domain, a spatial principal component analysis (sPCA) was also applied for decomposing the TFs into their main spatial regions or spatial factors (SFs). At any given time point, different neural processes (and hence, different electrical signals) may concur, and the recording at any scalp location at that moment represents the electrical balance of these distinct neural processes. While tPCA allows representing a complex superposition of different overlapping electrical potentials in time, the sPCA separates the ERP components along the electrodes located on the scalp (and hence, different regions). In this sense, each SF would ideally reflect one of the concurrent neural processes underlying each TF. This configuring and quantifying scalp regions system is preferable to an a priori subdivision into fixed scalp regions for all components, since sPCA demarcates scalp regions according to the real behaviour of each scalppoint recording. Frequently, the components fluctuate differently depending on the scalp area analysed, which can produce an opposite polarity, even react differently to experimental manipulation. This regional grouping was also determined through a covariance matrixbased sPCA and the decision on the number of factors to extract also was carried out through the application of the scree test (Cliff, 1987). Also, Promax rotation was applied in order to select spatial factors (Dien, 2010, 2012). Therefore, the pre-processing analyses of ERPs comprised both the tPCA and sPCA.

2.4.3. Analyses on the experimental effects

To test whether the emotional meaning conveyed by the selected set of facial expressions (PF and NF) was that supposed a priori, each group of participants (fibromyalgia and healthy control) filled out a three-dimensional scaling test for each type of facial expression, assessing its levels of valence, arousal and pain intensity. Analyses were carried out by means of a series of 2×2 repeated-measures ANOVAs, where the type of facial expression (two levels: PF and NF) was included as a within-subject factor and the group of participants (two levels: healthy control and fibromyalgia) did so as the between-subject factor.

Experimental effects related to the dot-probe task were computed for both the signal (i.e., facial expressions) and target stimuli (i.e., dot) at both neural and behavioural levels. In all contrasts described below, Greenhouse-Geisser (GG) epsilon correction was applied to adjust degrees of freedom of the F statistic where necessary. Effect sizes were computed through the eta-square $(\eta^{\ 2}_p)$ technique. Moreover, we also computed post-hoc statistical power (1- β) observed for the ANOVAs using SPSS. Post-hoc comparisons were made to determine the significance of pairwise contrast, using Bonferroni test (alpha = .05). All statistical analyses described in this section were performed on SPSS Statistics 25 (IBM, Inc). Characteristics of the analyses according to each dependent variable were conducted as follows:

1. Neural response to facial expressions. A series of 2 × 2 repeated-measures ANOVAs including the group of participants (fibromyal-gia and healthy control) and facial expressions (PF and NF) as factors, were computed for exploring their effects on the ERP components elicited in response to facial expressions. Analyses were computed on the factor scores derived from the PCA application. As mentioned, this parameter is linearly related to the amplitude of ERP components. However, the latency of ERPs cannot be measured by tPCA-derived factor scores (Carretié et al., 2013). Thus, in this case the direct peak voltage-associated latencies of the P2 wave were computed. This procedure has been previously recommended (Clayson et al., 2013).

- 2. Neural response to target stimuli (i.e., dot). A series of 2 × 3 repeated-measures ANOVAs were conducted on the ERP components elicited in response to the dot. For these analyses, group of participants (fibromyalgia and healthy control) and target location (congruent, incongruent and neutral) were included as the betweensubjects and within-subject factors, respectively.
- 3. Behaviour. Performance in the dot-probe task (RT and accuracy: omissions plus errors) were also computed by a series of 2 × 3 repeated-measures ANOVAs. Group of participants and target location (congruent, incongruent and neutral) were also included as factors. Before conducting ANOVAs on the behavioural response, inaccurate responses or responses above 2000 ms or below 200 ms were identified to be removed from the analyses. Additionally, the attentional bias index score was calculated for each participant by subtracting the mean of RTs for congruent trials from the mean of RTs for the incongruent ones (Price et al., 2015; Thai et al., 2016). Whereas positive scores would indicate a bias towards threat, negative scores would suggest a bias away from threat. A series of one-way ANOVAs were conducted on these attentional bias index scores.

As it has been previously reported (Kappenman et al., 2014, 2015), different effects related to the visual field (i.e., right or left) where threat-related pictures or target location are presented relative to the hemisphere (i.e., electrodes at the scalp sites) were noticeable at posterior electrodes for attention-related ERP components (i.e., P1, N1, N2pc, and P3). Accordingly, a series of repeated-measure ANOVAs were performed to explore the potential effects of mentioned variables (see supplementary materials for a full description of the statistical results).

Finally, although patients who were taking medications were asked to stop it 48 h before starting the study, we performed several control analyses through ANOVAs in order to neutralise its potential effects. Thus, we introduced the group (patients with fibromyalgia using and not using particular medications) and type of medication (psychotropic drugs, benzodiazepines, and antidepressants) as factors, whereas ERP data (P2 and N2a amplitudes) and behavioural measures (RT) were used as dependent variables.

3. Results

3.1. Control analyses

Assessments given by the participants on the valence, arousal and pain intensity of the selected set of facial expressions were analysed. ANOVAs yielded significant differences in valence [F $_{(1,38)}=925.33;\,p=0.001;\,\eta^2_{\,p}=0.961;\,1\cdot\,\beta=1.00],$ arousal [F $_{(1,38)}=484.02;\,p=0.001;\,\eta^2_{\,p}=0.927;\,1\cdot\,\beta=1.00]$ and pain intensity [F $_{(1,38)}=2302.34;\,p=0.001;\,\eta^2_{\,p}=0.989;\,1\cdot\,\beta=1.00].$ PF showed lower valence (PF: mean = 1.57, sd = 0.083; NF: mean = 4.14, sd = 0.040, p < 0.01), higher arousal (PF: mean = 6.47, sd = 0.098; NF: mean = 3.79, sd = 0.064, p < 0.01) and higher intensity of pain (PF: mean = 6.21, sd = 0.126; NF: mean = 0.218, sd = 0.046, p < 0.01) as compared to NF. No statistically significant effects of group were found for valence [F $_{(1,38)}=3.316;\,p=0.076],$ arousal [F $_{(1,38)}=2.596;\,p=0.115]$ and pain intensity [F $_{(1,38)}=0.003;\,p=0.953]$ measures. Additionally, interaction effects between

Table 3Means and standard deviations (in parenthesis) of pain intensity, valence and arousal for each group (FM and HC) and type of facial expression.

		Pain Faces (PF)	Neutral Faces (NF)
HC	Intensity	6.23 (0.86)	0.19 (0.28)
	Valence	1.64 (0.54)	4.25 (0.28)
	Arousal	6.48 (0.64)	3.60 (0.20)
FM	Intensity	6.18 (0.69)	0.23 (0.28)
	Valence	1.51 (0.50)	4.03 (0.21)
	Arousal	6.46 (0.58)	3.98 (0.53)

Table 4Means and standard deviations (in parenthesis) of RTs and accuracy (average number of errors plus omissions) for each condition and group.

	Congruency	RT (ms)	Accuracy
Healthy Control	Congruent	396.82 (49.83)	1.57 (2.88)
	Incongruent	399.74 (52.184)	0.52 (0.84)
	Neutral	407.40 (52.653)	0.74 (0.80)
	Bias Score	2.91 (24.03)	
Fibromyalgia patients	Congruent	478.70 (86.75)	0.86 (2.16)
	Incongruent	501.97 (84.708)	1.05 (1.04)
	Neutral	484.41 (73.65)	0.95 (1.46)
	Bias Score	23.31 (54.02)	

group and emotional facial expression in valence [F $_{(1,38)} = 0.277$; p = 0.601], arousal [F $_{(1,38)} = 2.647$; p = 0.112] and pain intensity [F $_{(1,38)} = 0.143$; p = 0.707]) did to reach statistical significance. Data about mean values for valence, arousal and pain intensity, corresponding to each type of facial expression and group are displayed in Table 3.

3.2. Behavioural performance

Means of RTs and accuracy are shown in Table 4. ANOVA results showed a significant main effect of group [F $_{(1,44)}=20.70$; p = 0.001; $\eta^2_p=0.320$; 1- $\beta=0.99$], revealing slower RTs for patients with fibromyalgia as compared to healthy control participants. Moreover, significant effects regarding to the interaction between target location by group were also found [F $_{(1,44)}=3.498$; p = 0.043; $\eta^2_p=0.074$; 1- $\beta=0.60$]. Post-hoc contrasts showed slower RTs in fibromyalgia for the incongruent condition compared to both neutral [F $_{(1,44)}=7.473$; p = 0.009; $\eta^2_p=0.145$; 1- $\beta=0.76$], and congruent condition [F $_{(1,44)}=7.473$; p = 0.11; $\eta^2_p=0.137$; 1- $\beta=0.73$]. However, no differences were found for congruent condition compared to neutral condition [F $_{(1,44)}=0.783$; p = 0.381]. Other comparisons concerning accuracy failed to show statistically significant differences (p > 0.05). In the same line, ANOVAs computed on the attentional bias index score did not revealed a significant effect of group [F $_{(1,44)}=2.818$; p = 0.100].

3.3. ERP analyses in response to facial expressions

Fig. 4 shows a sample of grand averages (where effects are more clearly appreciable) are shown once the pre-stimulus recording (the baseline value) has been subtracted from each ERP. This selection highlights the most relevant experimental results (i.e., ERP responses for each group of participants: fibromyalgia patients and HC participants) related to the amplitude of P2 and N2a (it will be detailed below).

As a consequence of the tPCA application, seven TFs were extracted from ERPs and submitted to Promax rotation (see Fig. 3 to observe the correspondence between the ERP components and the TFs derived from the application of the tPCA). Extracted factors explained an 85% of the total variance (TF1: 43.2%, TF2: 13.6%, TF3: 10.6%, TF4: 6.2%, TF5: 4.5%, TF6: 3.7%, TF7: 2.6%, respectively). Peak latency and topography distribution of TF4 (peaking at 196 ms in fronto-central electrodes) and TF3 (peaking at 274 ms in fronto-central electrodes) were associated with the components signalled in the grand averages as P2 and N2a, respectively (Fig. 3). Furthermore, TF5 (peaking at 100 ms), TF6 (peaking around 150 ms), TF7 (peaking at 350 ms), TF2 (peaking at 420 ms) and TF1 (peaking around 700 ms) were related to P1/N1, N170, P3, P4 and LPC components, respectively. Following the inspection of the grand averages and in accordance with previous literature on the electrophysiological correlates of spatial attention (Mueller et al., 2009; Eldar et al., 2010; Rossignol et al., 2013; Torrence and Troup, 2018), ERP analyses were focused on the factor scores related to the P1/N1, N170, P2 and N2 waves. Due to the lack of significant effects in P1/N1 and N170, we will only describe experimental results for the P2 and N2a ERP components. Full statistical details associated with the rest of ERP components (main effects and their interactions) are summarized in Table 5.

As it previously mentioned, latency cannot be measured by tPCA-derived factor scores. For latency measures, the direct peak voltage-associated latencies on the 148–235 ms time window were computed for centro-parietal electrodes (CP2, CP4, CP6, C2, C6 and P4) by means repeated-measures ANOVAs.

3.3.1. P2 amplitude

As it can be observed in Table 5, a main effect of facial expression was found in frontal regions [F $_{(1,44)}=4.629$, p = 0.037, $\eta^2_p=0.095$; 1- $\beta=0.56$]. As expected, pain-related expressions elicited higher amplitudes than the neutral baseline condition. Moreover, fronto-central regions showed a clear significant interaction effect between facial expression and group [F $_{(1,44)}=6.841$, p = 0.012, $\eta^2_p=0.135$; 1- $\beta=0.73$]. Post-hoc comparisons revealed that P2 amplitude elicited by pain-related condition was higher for fibromyalgia patients as compared to healthy control participants [F $_{(1,44)}=6.377$, p = 0.015, $\eta^2_p=0.127$; 1- $\beta=0.70$]. Moreover, only patients exhibited enhanced P2 amplitudes to pain-related condition with respect to the neutral one [F $_{(1,44)}=9.341$, p = 0.004, $\eta^2_p=0.175$; 1- $\beta=0.85$] (see also Fig. 4). However, no effect of facial expression [F $_{(1,44)}=3.239$, p = 0.079] or group [F $_{(1,44)}=3.566$, p = 0.066] was found in this scalp site region. Mean factor scores are shown in Table 6.

3.3.2. P2 latency

Repeated measures ANOVAs yielded differences for the interaction between facial expression by group [F $_{(1,44)}=4.831$, p = 0.033, $\eta^2_{p}=0.099$; 1- $\beta=0.57$]. Specifically, patients with fibromyalgia showed a shorter P2-related latency for pain-related condition relative to neutral baseline at centro-parietal regions [F $_{(1,44)}=6.673$, p = 0.013, $\eta^2_{p}=0.132$; 1- $\beta=0.71$] (Fig. 5). Main effects of facial expression [F $_{(1,44)}=2.352$, p = 0.132] or group [F $_{(1,44)}=1.176$, p = 0.284] did not show statistically significant differences. Mean peak latency values P2 are shown in Table 6.

3.3.3. N2a amplitude

Regarding the statistical analyses conducted on N2a, a main effect of group was found at fronto-central regions [F $_{(1,44)}=8.883$, p = 0.005, $\eta^2_p=0.167$; 1- $\beta=0.83$]. Fibromyalgia participants showed a decrease for N2a amplitude compared to healthy control participants. However, analyses did not reveal statistical effects related to facial expression [F $_{(1,44)}=1.535$, p = 0.222] or facial expression by group [F $_{(1,44)}=0.142$, p = 0.708]. Mean factor scores of N2a are shown in Table 6.

3.4. ERPs analyses on the dot

tPCA application on the ERPs related to the target stimulus led to the selection of five TFs. Extracted factors explained an 82.23% of the total variance (TF1: 50.9%, TF2: 15.4%, TF3: 7.2%, TF4: 5.2%, TF5: 3.6%, respectively). Peak latency time-locked to target location in dot-probe tasks are frequently described in ERPs components comprised from 100 to 300 ms with respect to the stimulus onset (Torrence and Troup, 2018). In this way, factor scores of ERPs in response to the dot was computed to the P1, P2, and P3. Weak effects were found in the results of the ERP activity towards the dot. Only in P1 was detected a significant effect of group [F $_{(1,44)}=5.025,\,p=0.030,\,\eta^2_{\,p}=0.592;\,1$ - $\beta=0.60$] in

parieto-occipital regions, where fibromyalgia participants exhibited higher amplitudes than control participants. However, analyses did not reveal statistical effects of target location [F $_{(1,44)} = 3.069$, p = 0.058] or target location by group [F $_{(1,44)} = 0.078$, p = 0.907]. No other significant effects were found to P2 and P3 components (p > 0.05).

3.5. Effects of visual field by hemisphere on the ERP components

Although a significant effect of visual field and hemisphere was found as a function of the emotional meaning of facial expressions and target location (see also supplementary material: Figures S1 and S2), ANOVAs did not yield any significant effect related to group (fibromyalgia patients vs healthy control participants) or between group and facial expression/target location related to the ERP components (P1, N1, N2pc and P3).

3.6. Results controlling the use of psychotropic drugs

As previously indicated, the use of psychotropic drugs could affect cognition. In this sense, ANOVAs including consumption of benzodiazepines and antidepressants as factors were carried within the fibromyalgia group. Analyses revealed that neither ERPs nor behavioral measures are significantly affected by drugs taken by patients with fibromyalgia (see Table 7).

4. Discussion

The main findings of the present study have highlighted the presence of a specific brain temporal pattern underlying the attentional bias to negative stimulation in fibromyalgia during a dot-probe task. More specifically, biased responses to pain-related facial expressions were detected within the first 200 ms after stimulus onset, which was reflected on the higher amplitudes and shorter latencies of P2. This neural response towards faces displaying pain was only characterized in patients with fibromyalgia. Subsequently, patients exhibited lower anterior N2a amplitudes than control participants. At the behavioural level, responses given by patients to the location of the target stimulus (i.e., dots) are in accordance to the presence of attentional disengagement deficits, as shown by the slower RTs for incongruent trials than congruent and neutral conditions. Unexpectedly, other early ERP components typically sensitive to facial stimulation (i.e., P1/N1 and N170) did not yield significant results for fibromyalgia patients. Although attentional modulations by emotion on early ERP components have been described in different studies (for an example see Torrence and Troup,

2018), these neural components may be insensitive to standard parameters of the dot-probe task (Thai et al., 2016). Weak effects of emotional modulation of N1/P1 components have been reported in other patients, such as those suffering from anxiety (Kolassa and Miltner, 2006; Eldar and Bar-Haim, 2010). On the other hand, the sensitivity of N170 to the emotional meaning of facial expressions still remains unclear (see an exhaustive review in Hinojosa et al., 2015). In this line, previous studies have failed to detect modulations of the N170 to fearful (Pourtois et al., 2004), angry (Santesso et al., 2008), disgust (Rossignol et al., 2013), and pain-related faces (Reicherts et al., 2012). It has been suggested that the requirements of encoding two faces simultaneously, as occurs in the dot-probe designs, may minimise the sensitivity of these components (i.e., N1/P1 and N170) to the emotional meaning of the stimulation (Rossignol et al., 2013; Thai et al., 2016). A careful functional interpretation of the data obtained in the present experiment is given as follows.

As indicated in the Results section, a positive wave peaking around 200 ms after the facial stimuli (i.e., P2) showed significant differences between both conditions (i.e. pain-related and neutral faces) at frontal regions. In addition, pain-related facial expressions elicited higher anterior P2 amplitudes in patients with fibromyalgia than those detected in healthy control participants at fronto-central scalp sites. Moreover, only the fibromyalgia group exhibited both enhanced P2 amplitudes (fronto-central scalp sites) and shorter latencies (centro-parietal scalp sites) to pain-related stimulation as compared to the neutral condition. A wide amount of research using different tasks requiring facial processing has interpreted the presence of the P2 component as a neural index of attentional capture or engagement towards negative information (Kenemans et al., 1992; Doallo et al., 2006; Huang and Luo, 2006; Dennis and Chen, 2007; Carretié et al., 2011, 2013). Several studies have pointed out that larger amplitudes of this component may reflect neural processes that would permit early detection of potentially dangerous stimulation by bottom-up mechanisms (Mercado et al., 2009; Carretié et al., 2013). In this line, not only higher amplitudes but also shorter latencies of P2 have been attributed to the presence of a negative bias (Carretié et al., 2001, 2013). More detailed explanations suggest that faster latencies of this component might be an index of the hypervigilance phenomenon to painful stimulation (Arendt-Nielsen, 1994; Bromm and Lorenz, 1998; Sarkar et al., 2001). Although a straightforward comparison with prior evidence is difficult to be done due to the lack of available empirical data focused on the brain mechanisms underlying attentional biases to pain-related information in fibromyalgia (e.g., both experimental paradigms and stimulus modalities were different), present results are in line with some previous findings pointing out that negative, threatening and painful information may disproportionately capture attentional processing resources in chronic pain conditions (Kosek et al., 1996; Peters et al., 2000; Davis et al., 2001; Desmeules et al., 2003; Khatibi et al., 2009; Vago and Nakamura, 2011; Schoth et al., 2012; Crombez et al., 2013; Duschek et al., 2014; Todd et al., 2018). Interestingly, P2 modulations in central scalp sites have been previously related to attentional capture processes towards negative words in patients with fibromyalgia. Hence, these patients seem to allocate attention not only to painful stimulation but also to pain-related events (Montoya et al., 2005). Related to these findings, González-Roldán et al. (2013) have reported a specific modulation of EEG oscillations to pain-related and anger faces compared to neutral ones in these patients. It has been suggested that biased attentional capture by pain-related faces in fibromyalgia would also lead to produce interference processes over other cognitive domains, such as those related to inhibitory control (Pidal-Miranda et al., 2019).

In line with previous results, the N2a component, a negative deflection observed just after P2, reflected lower amplitudes in patients with fibromyalgia. It is important to note that whereas parieto-occipital scalp distribution of the N2 component (i.e., N2pc) has been related to preattention and sensory amplification processes (Carretié, 2014), anterior scalp distributions have been associated with attentional

 $^{^{1}}$ Reviewers suggested the possibility that attention effects emerged in early ERP components could be modulated as a function of visual field and hemisphere (electrode sites). In order to explore this possibility a series of ANOVAs were performed. Analyses revealed a main effect of visual field of facial expression by hemisphere in parieto-occipital regions, where contralateral conditions elicited higher amplitudes compared to ipsilateral conditions, for P1 in left hemisphere [F $_{(1,44)} = 4.375$, p = 0.042, $\eta^2_{p} = 0.090$; 1- $\beta = 0.53$] and N2pc in right hemisphere [F $_{(1,44)} = 8.154$, p = 0.007, $\eta^2_p = 0.156$; 1- $\beta = 0.80$]. Moreover, a main effect of visual field of target location by hemisphere in centro-parietal regions were found, where both congruent and incongruent trials in contralateral electrodes sites elicited higher N2 amplitudes compared to congruent and incongruent trials in ipsilateral electrode sites in both left [F $_{(1,44)} = 11.426, \, p = 0.001, \, \eta^2_{\,\, p} = 0.206; \, 1\text{-}\, \beta = 0.99]$ and right [F $_{(1,44)} = 19.033, \,$ $p=0.001,~\eta^2_{~p}=0.302;~1\mbox{-}~\beta=1.00]$ hemispheres. This effect was found reversed for P3 component in left hemisphere [F $_{(1,44)} = 7.710$, p = 0.002, η^2_p = 0.149; 1- β = 0.90]. However, should be noted that statistical analyses did not reveal any difference related to ERP components (P1, N1 and N2pc: facial expression; P1, N2 and P3: target location) between fibromyalgia and healthy control group (main effect of group: [F $_{(1,44)} = 0.241-1.786$, p = 0.18-0.42]; interaction effect group by facial expression/target location: [F (1,44) = 0.015-1.021, p = 0.36-0.90]).

control processes depending on top-down mechanisms (Falkenstein et al., 1999; Folstein and Van Petten, 2007; Eldar and Bar-Haim, 2010). N2a amplitudes seem to be modulated by the amount of available attentional resources with respect to those required by a given ongoing task (Van Veen and Carter, 2002). Lower amplitudes of N2a have been reported in patients with fibromyalgia when they had to deal with high demanding tasks (Samartin-Veiga et al., 2019). Indeed, decrements in N2a responses have been proposed as a neural index linked to the presence of cognitive control dysfunctions leading to a poor and inefficient redistribution of attentional resources in fibromyalgia (Dick et al., 2002; Samartin-Veiga et al., 2019). Some other studies have pointed out that cognitive impairment in chronic pain patients might be related to the interference caused by the concurrent pain, which impair for filtering out task-irrelevant stimuli resulting in a poor task performance (Legrain et al., 2009; Mao et al., 2014). Recently, it has been suggested that cognitive control is related to directing, correcting, and redirecting behaviour in line with current internal goals (Diamond, 2013) and its effectiveness might be modulated by affect (Pourtois et al., 2020). Thus, N2a modulations here detected would be supporting that patients with fibromyalgia may be characterized by a lower efficiency for regulating the allocation of attentional resources towards emotional stimuli such as facial expressions. Taken together, electrophysiological results (i.e., data on P2 and N2a in response to facial expressions) allow us to describe a neural pattern underlying the presence of a selective attentional bias in patients with fibromyalgia characterized by an initial attentional capture to pain-related faces (higher amplitudes and shorter latencies of P2) depending on bottom-up mechanisms followed by a decrease in the distribution of attentional resources (lower N2a amplitudes to pain-related faces) more closely related to top-down attentional control.

Regarding behavioural responses, patients with fibromyalgia showed slower RTs to dot location for incongruent trials compared to those representing congruent and neutral baseline conditions. Briefly, whereas some studies failed to report an abnormal attentional processing in fibromyalgia (Tiemann et al., 2012) or have suggested the only presence of a general hypervigilance to non-specific information as a symptom of this syndrome (Carrillo de la Peña et al., 2006; Geisser et al., 2008; González et al., 2010), large behavioural data have supported the existence of a threat-related bias that would characterize these patients (Schoth et al., 2012; Crombez et al., 2013; Todd et al., 2018; Broadbent et al., 2021). In this line, differences in RTs have been related to attentional capture processes towards pain-related scenes in a change detection paradigm (Schoth et al., 2015b). Other studies using the eve-tracking methodology have reported that very initial fixations in chronic pain patients were devoted towards pain-related faces when patients had to perform a visual search task (Schoth et al., 2015a). These findings lead to think that attentional bias in chronic pain patients could be guided by automatic mechanisms to rapidly mobilize cognitive resources to threatening and pain-related information (González-Roldán et al., 2013). It has been described that this abnormal attentional pattern in chronic pain (i.e., hypervigilance to pain and threat-related signals) might a contributing factor for its pathogenesis (Schoth et al., 2012; Crombez et al., 2013), leading to an augmentation of pain processing as a consequence of the perceived threat (Todd et al., 2015, 2018). Our results are not only agreed with prior research (i.e., attentional capture), but also may suggest an alteration involving more controlled attentional processing stages in fibromyalgia patients as it was previously reported (Roelofs et al., 2002; Broadbent et al., 2021). For example, using an emotional Stroop task Duschek et al. (2014) described a remarkable interference effect (an increase in RT) for negative compared to positive or neutral words in fibromyalgia. In this line, several studies using dot-probe tasks in chronic pain patients have reported slower RTs

towards pain-related faces (Khatibi et al., 2009) and sensory pain words (Liossi et al., 2009, 2011) for incongruent as compared to congruent trials. Accordingly, this attentional bias towards pain-related information in fibromyalgia have been explained as a specific difficulty for disengaging attention away from threat (Haggman et al., 2010; Schoth and Liossi, 2010, 2013; Cardoso et al., 2021). Thus, it could be proposed that patients with fibromyalgia would be unable to efficiently build on information derived from facial expressions (i.e., attentional capture to pain-related information) to then regulate (i.e., cognitive control) and subsequently assign attention resources to spatial target processing (i.e., disengage attention from pain-related information).

How do these data fit into the current perspectives on the attentional biases in fibromyalgia? According to neurocognitive and experimental models, two functional brain mechanisms might be underlying the selective attentional bias here represented by the altered neural pattern in patients with fibromyalgia involving not only an increase of the automatic allocation of attention to pain-related stimulation but also a deficit for efficiently distributing cognitive control resources (Bishop, 2008; Cisler and Koster, 2010; Heeren et al., 2013; Fu et al., 2017). In this vein, further findings have suggested that exogenous or automatic attention effects on negative emotional expressions are related to amplitude modulations of the P2 ERP component, which seems to be generated in cortical parietal regions belonging to the dorsal attention network. This attentional network is involved in the reorientation of processing resources toward emotional stimuli according to their priority (Gottlieb, 2007; Bisley and Goldberg, 2010). On the order hand, diminished amplitudes of N2a have been associated with a decrease in neural activity within the anterior cingulate cortex (ACC), as one of the main cortical areas linked to the cognitive control network (Van Veen and Carter, 2002; Hauser et al., 2014). Accordingly, the altered functioning of this network may contribute to the presence of difficulties in disengaging attention from threat (Eysenck et al., 2007; Cisler and Koster, 2010; Price et al., 2014; Fu et al., 2017). However, it has been argued that attentional disengagement impairments seem to be a consequence of both automatic and controlled cognitive mechanisms (Cisler and Koster, 2010). Therefore, it could be hypothesized that the attentional bias to threat in fibromyalgia may be sustained by these two networks underlying not only the early detection of negative events (encompassing bottom-up processes) but also the purposeful efforts for monitoring, handling and regulating threat-related information (Cisler and Koster, 2010) linked to a top-down control (Fu et al., 2017). These results are in agreement with the current models of attention to pain arguing that the processing of pain-related events and attentional mechanisms devoted to them would be sharing similar neural networks (Moriarty et al., 2011; Wu et al., 2018), establishing that attention to pain-related information depends on both bottom-up and top-down neural mechanisms (Legrain et al., 2009).

The present study includes some aspects that deserve mention for a better understanding of the current findings. Despite dot-probe has become the most widely experimental task used to explore attentional biases in different pathologies (Bar-Haim et al., 2007; Peckham et al., 2010; Schoth et al., 2012; Todd et al., 2018), some methodological aspects related to its reliability are still under debate (Clarke et al., 2013; Van Rooijen et al., 2017; Chapman et al., 2019). It seems that the stimulus display time, target presentation time, delay SOA, among other details involved in the task design may be important to explain differences in the results obtained by some investigations (see an exhaustive review in Torrence and Troup, 2018). In contrast with previous studies, the inclusion of neutral baseline condition (i.e., neutral-neutral right-left pair of faces) in the present research has allowed exploring in a deep extent attentional biases in fibromyalgia giving the chance to unravel

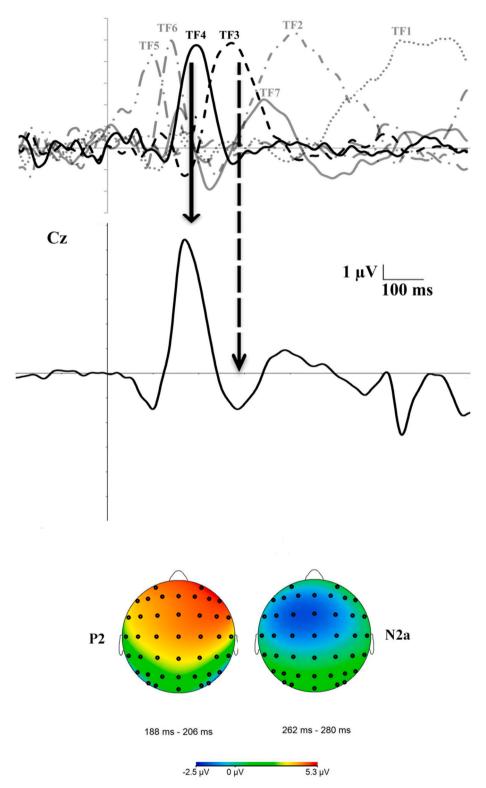


Fig. 3. tPCA: Factor loadings after Promax rotation. TF4 (P2) is highlighted by the black continuous line and TF3 (N2a) is represented by the black discontinuous line. Scalp maps show the topographical distribution of the P2 and N2a components.

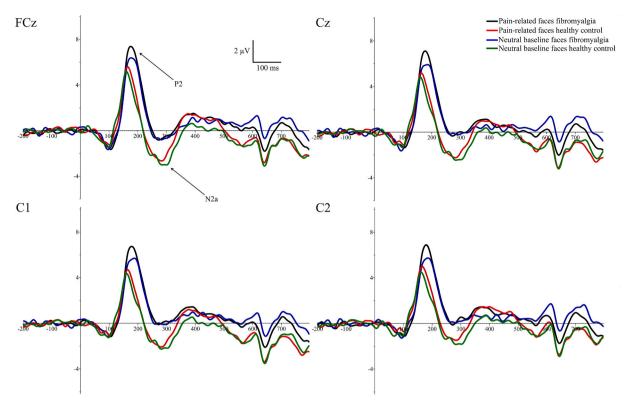


Fig. 4. Grand averages in the range of selected electrodes (FCz, Cz, C1, C2). Two components related to attentional processing to faces (P2 and N2a) can be more clearly observed. Black line represents fibromyalgia patients in pain-related faces condition and blue line represents neutral baseline faces condition. Red line represents HC subjects in pain-related faces condition and green line represents neutral baseline condition. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

the distinct mechanisms involved in it (Koster et al., 2004). However, some authors have suggested that negative finding engagement effects (i.e., faster responses when the target replace the location of a threat-related stimulus compared to neutral) may be due indeed to an attentional capture effect to threat signals that would be preventing for a quick motor response. It has been suggested that the inclusion of a threatening baseline condition (i.e., pain-pain right-left pair of faces) would allow us to improve paradigm features. Moreover, although these modifications of dot-probe tasks (i.e., the inclusion of neutral baseline condition) were developed to solve the problem of non-attentional behavioural effects (i.e., general slowing or freezing), longer response latencies for incongruent conditions have been described as not necessarily a reflection of difficulties in disengaging attention from threat-related information (Clarke et al., 2013). In line with Clarke et al. (2013), future experimental designs for exploring attentional biases should control non-attentional behavioural freezing effects, either including control trials where threat and neutral stimuli were presented within an attended locus and therefore non-spatial movement of attention was required (this effect can then be statistically removed from effects observed when attention is required to move; see Mogg et al., 2008). Alternatively, a simultaneous presentation of both threat-related and neutral stimuli on every trial can be also used (this removes the need for separate control trials as threat stimuli are always present). Future investigations should be designed systematizing these methodological properties or checking for the use of other alternative tasks and/or techniques to explore the attentional bias (e.g., spatial cueing task or eye-gaze measures).

On the other hand, as it was already mentioned, patients with fibromyalgia who were under pharmacological treatment (antidepressants or benzodiazepines) were asked to stop it 48 h before starting the study. Despite drug consumption has been statistically controlled to neutralise its influence on the experimental manipulations involving attentional processes, future research only including patients who are free of medication is recommended to be done. Otherwise, potential effects linked to maintain or discontinue the usage of drugs affecting cognition should be strictly considered. Finally, is should be mentioned that only female patients participated in the present study. Although prevalence of this syndrome has been reported as significantly higher in females than males (Mas et al., 2008; Katz et al., 2010; Wolfe et al., 2018), future studies should include patient's samples composed of both males and females for exploring clinical symptoms of this chronic pain syndrome to improve the generalization of results.

Despite extensive efforts to unravel the nature of attentional biases in chronic pain patients it still remains unclear up to date (Van Ryckeghem et al., 2019). In this sense, several conclusions might be derived from the present findings. Our data showed the presence of a selective attentional bias to pain-related information characterizing patients with fibromyalgia at both neural and behavioural levels during the performance on a dot-probe task. Extending prior findings, neural results describe a two-stage neural pattern underlying attentional deficits in fibromyalgia.

Table 5Description and statistical results for the ERP components detected by the tPCA in response to facial expressions.

Temporal Factor	Peak	Scalp Distribution	ANOVAs Facial expressions (d.f. $= 1$, 44)	ANOVAs Group (d.f. $= 1$, 44)	ANOVAs Facial expressions by Group (d.f. $=$ 1, 44)
TF5 (P1/N1)	100	SF1(frontal)	F = 0.098, p = 0.755	F = 0.216, p = 0.644	F = 0.067, p = 0.796
	ms	SF2 (left parieto-occipital)	F = 0.192, p = 0.664	F = 0.489, p = 0.488	F = 0.271, p = 0.605
		SF3(centro-parietal)	F = 1.168, p = 0.286	F = 0.833, p = 0.366	F = 0.107, p = 0.745
		SF4(centro-parietal)	F = 0.019, p = 0.892	F = 0.158, p = 0.693	F = 0.708, p = 0.405
TF6 (N170)	150	SF1 (frontal)	F = 0.353, p = 0.555	F = 0.725, p = 0.399	F = 1.693, p = 0.200
	ms	SF2 (occipital)	F = 1.485, p = 0.229	F = 0.828, p = 0.368	F = 0.175, p = 0.678
		SF3 (right parieto-	F = 0.083, p = 0.775	F = 0.280, p = 0.599	F = 0.088, p = 0.769
		occipital)	F = 0.001, p = 0.972	F = 0.295, p = 0.590	F = 0.293, p = 0.591
		SF4(centro-parietal)	F = 0.009, p = 0.924	F = 0.217, p = 0.644	F = 1.037, p = 0.314
		SF5 (fronto-central)			
TF4 (P2)	196	SF1 (frontal)	F = 4.629, p = 0.037*	F = .963, p = 0.332	F = 0.963, p = 0.332
	ms	SF2 (parieto-occipital)	F = 2.800, p = 0.101	F = 0.032, p = 0.860	F = 1.279, p = 0.264
		SF3 (right centro-parietal)	F = 0.379, p = 0.541	F = 0.308, p = 0.582	F = 0.990, p = 0.325
		SF4 (fronto-central)	F = 3.239, p = 0.079	F = 3.566, p = 0.066	F = 6.841, p = 0.012*
TF3 (N2)	274	SF1 (frontal)	F = 0.188, p = 0.733	F = 1.955, p = 0.169	F = 0.087, p = 0.770
	ms	SF2 (fronto-central)	F = 1.535, p = 0.222	F = 8.833, p = 0.005*	F = 0.142, p = 0.708
		SF3 (parieto-occipital)	F = 0.782, p = 0.381	F = 0.499, p = 0.484	F = 0.000, p = 0.983
		SF4 (centro-parietal)	F = 0.318, p = 0.576	F = 1.297, p = 0.261	F = 1.862, p = 0.179
TF7 (P3)	350	SF1 (frontal)	F = 1.560, p = 0.218	F = 0.173, p = 0.679	F = 0.556, p = 0.460
	ms	SF2 (right centro-parietal)	F = 0.128, p = 0.722	F = 0.993, p = 0.324	F = 0.132, p = 0.718
		SF3 (parieto-occipital)	F = 0.259, p = 0.614	F = 0.100, p = 0.753	F = 0.163, p = 0.688

Table 6Factor scores and standard deviations (in parenthesis) of P2 and N2a components of Pain-related and Neutral baseline faces. Factor scores are divided in fibromyalgia patients and healthy control group.

	FM Patients		HC	
	Pain- related	Neutral baseline	Pain- related	Neutral baseline
P2a factor scores	0.43 (1.04)	-0.28 (.87)	0.11 (1.01)	-0.22 (.96)
N2a factor scores	0.47 (.77)	0.33 (.78)	-0.33 (1.03)	-0.40 (1.07)
P2 latency (ms)	183.27 (5.58)	194.00 (6.07)	180.35 (5.34)	179.13 (5.81)

Pain-related facial expressions were able to rapidly engage the allocation of automatic attentional resources at early stages of the processing (bottom-up mechanisms), as reflected by amplitude modulations in P2 component. Subsequently, the decreases of N2a amplitude would suggest that the patients exhibited a significant deficit in attentional control at more strategic processing stages involving top-down processes. Such alteration in the distribution of attentional control resources made it also evident at the behavioural level where patients with fibromyalgia might have difficulties disengaging their attention from pain-related information. It should be noted that despite the fact that the main interactions results data showed a medium to high statistical powers (1- β > 0.70) future studies should consider increasing the sample size. Taken together, current findings provide evidence of the presence of an

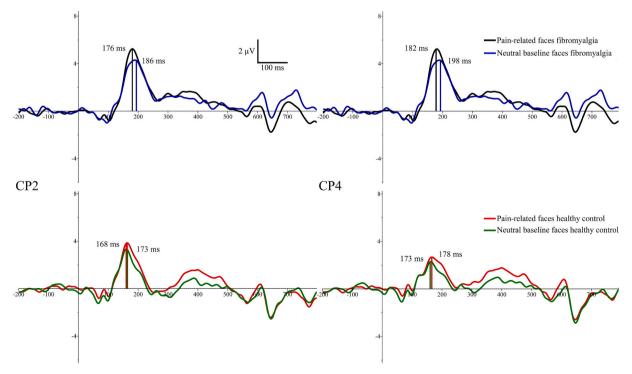


Fig. 5. Grand averages in the range of selected electrodes (CP2 and CP4). P2 latency deviations can be observed. The above pictures represent P2 latencies for patients with fibromyalgia. The below pictures represent this P2 latencies for HC participants. Vertical lines point the moment where P2 amplitude is peaking.

Table 7Statistical results after controlling the use of psychotropic drugs in the fibromyalgia group. ANOVAs were computed for electrophysiological activity (fronto-centro-parietal P2 and frontal N2a) and behavioral data (reaction times).

	Antidepressant ANOVAs	Benzodiazepines ANOVAs
Electrophysiological data P2		
Frontal (SF1)	$\begin{array}{l} F_{(1,20)} = 0.526; p = \\ 0.477 \end{array}$	$F_{(1,20)} = 3.804; p = 0.065$
Frontocentral (SF4)	$F_{(1,20)} = 2.537; p = 0.127$	$F_{(1,20)} = 0.195; p = 0.664$
Centroparietal	$F_{(1.20)} = 0.098; p =$	F _(1,20) = 0.661; p =
(latency)	0.758	0.426
N2		
Frontal (SF2)	$F_{(1,20)} = 0.913; p = 0.378$	$F_{(1,20)} = 3.401; p = 0.080$
Behavioural data		
Reaction times	$F_{(1,44)} = 0.360, p = 0.612$	$F_{(1,44)} = 0.388, p = 0.598$

attentional bias in fibromyalgia towards pain-related information along with a deficit in the allocation of cognitive resources reflected in a clear difficulty in attention disengagement from these pain-related signals. Both brain and behavioural results would allow us to clarify the attentional dysfunction in patients with fibromyalgia. The present results may contribute to a better understanding of attentional processing in fibromyalgia, and therefore to facilitate a rehabilitation pathway of the attentional bias modification treatments (Carleton et al., 2011, 2020).

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Credit author statement

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Declaration of competing interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.neuropsychologia.2021.108141.

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