# Mutual facilitation between activity-based anorexia and schedule-induced polydipsia in rats

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*Short title: Activity anorexia and schedule-induced polydipsia*

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## Abstract

The objective of this study was to evaluate the possible relationship between drinking (licks) in the schedule-induced polydipsia (SIP) phenomenon and running (turns in the wheel) in the activity-based anorexia (ABA) one. Within-subjects counterbalanced experiments were designed with male Wistar rats which underwent both behavioral procedures, half of them performed the ABA procedure first and the other half the SIP procedure first. In Experiment 1, the initial development of ABA facilitated the subsequent acquisition of SIP, however, the first acquisition of SIP retarded the subsequent development of ABA. Given that SIP exposure implied food restriction, it could be that adaptation to the food regime contributed to lowering ABA manifestation. Thus, Experiment 2 was carried out exactly in the same way as the first one with the exception that animals, which went first through SIP prior to undergoing the ABA procedure, had no food restriction. In this case, both ABA and SIP as first experiences facilitated the further development of SIP and ABA, respectively. It is suggested that running in ABA may be functionally similar to drinking in SIP, being therefore possible to think of both behaviors as induced by the schedule/regime of intermittent food availability.



## Keywords

Schedule-induced polydipsia, activity-based anorexia, licks, wheel turns, food-deprivation level, rats.

## Introduction

Epling and Pierce (1988) used the term “activity-based anorexia” (ABA) to refer to the animal model of human anorexia nervosa, a serious eating disorder characterized by a large body weight loss resulting from severe restriction of food intake that is usually accompanied by high levels of exercise (cf. the most recent versions of the International Classification of Mental and Behavioural Disorders – ICD-10 - and the Diagnostic and Statistical Manual of Mental Disorders – DSM 5th Edition -). Pierce and Epling (1994) indicated that most cases of anorexia nervosa are actually examples of activity anorexia, noting precisely that the disease combines self-imposed food restriction with an excessive increase in physical activity (de Paz et al., 2020).

The most common model of anorexia nervosa consists of exposing laboratory rats to a regime of food deprivation, allowing its availability for only one hour a day, and having free access to an activity wheel where rats can exercise all day except during mealtime (cf. Carrera et al., 2014). The combination of food diet and exercise causes animals to reduce their body weights quickly and eventually stop eating, reason why Routtenberg and Kuznesof (1967) first called this phenomenon "self-starvation".

Epling and Pierce (1992) advanced the idea that the excessive running normally obtained when exposing rats to the ABA procedure would be a behavior induced by the regime of intermittent food occurrence while having continuous access to a running wheel in the experimental situation.

Induction refers to the property of reinforcers to elicit behavior naturally related to its occurrence (Pellón et al., 2020). The first demonstration of such phenomenon was by

Falk (1961) after exposing hungry (but not thirsty) rats to an intermittent food reinforcement schedule with continuous access to a water bottle in the experimental chambers. Rats performed the operant response (lever pressing) that leaded to food reinforcers but also drunk large amounts of water in connection to food pellet delivery. This excessive drinking was on occasions labelled "psychogenic polydipsia" (Falk, 1969), but "schedule-induced polydipsia" (SIP) (Falk, 1966) was the term best accepted given its more descriptive nature. SIP is characterized by rats drinking little water immediately after the ingestion of each food pellet that appears intermittently, resulting in an excessive accumulation of liquid over the course of experimental sessions, which in case of Falk was of more than 3 hours.

SIP was considered the prototype of a category of behavior named "adjunctive" by Falk (1971), different from operant or other forms of learned behavior. This kind of distinction has been always in dispute (Wetherington, 1982), and nowadays the operant vs. adjunctive dichotomy is not so widely accepted, having been proposed same behavioral mechanisms for both behaviors (see Baum, 2012; Killeen & Pellón, 2013). For example, drinking and lever pressing occurring under intermittent food reinforcement schedules are altered similarly by response-outcome consequences or depend on the same on variables related to reinforcement occurrence (Pellón, 1992; Ruiz et al., 2016). Therefore, the many behaviors that had been studied under the label of adjunctive: polydipsia (Falk, 1961), running on an activity wheel (Levitsky & Collier, 1968), licking an air current (Mendelson & Chillag, 1970), or aggression (Azrin et al., 1966), seem to share common characteristics.

In the case of running, food-deprived rats submitted to intermittent food delivery will engage in high levels of wheel-turning if having it available during experimental sessions

(Gutiérrez-Ferre & Pellón, 2019; Riley et al., 1985; White, 1985). This wheel running has been found to interact with induced drinking (Penney & Schull, 1977; Roper, 1978; Staddon & Ayres, 1975; Wetherington & Riley, 1986). For example, Roper (1978) found a reduction in drinking rate when rats had the possibility to wheel run, which resumed when access to the wheel was blocked. This competition between drinking and wheel running indicates that both behaviors might be of the same nature. Furthermore, the temporal distributions of licks and turns along inter-food intervals seem to indicate some sort of cooperation among them (cf. Pellón & Killeen, 2015; Wetherington & Riley, 1986).

In an attempt to give support to the proposal that running in the ABA procedure is a behavior induced by intermittent food occurrence (such as drinking in SIP experiments), experimental studies were designed that exposed laboratory rats to ABA and SIP procedures balancing their order of presentation. This was done to evaluate the degree of facilitation in the development of one of these behavioral phenomena by prior exposure to the other one. This constitutes a follow up of previous data reported by Labajos and Pellón (2018) in which development of ABA was accelerated by previous SIP experience, based on the idea that both running and drinking share common functionalities.

## Experiment 1

In order to evaluate the possible interaction between drinking in SIP and running in ABA, laboratory rats were subjected to a fixed time (FT) 60 s schedule of administration of food pellets in the case of SIP and food availability of one hour a day in the case of ABA. The order of exposure to those procedures was counterbalanced across animals, in order to

test whether the development of one of the behaviors facilitates the subsequent development of the other. In the case of SIP, the choice of the FT 60 s schedule was due to the fact that, in our laboratory (e.g., Flores & Pellón, 1995), it has been systematically shown to be a schedule that induces an intermediate rate of drinking, which leaves room to observe possible facilitating or reducing effects of the previous ABA experience.

## Methods

### *Subjects*

Sixteen experimentally naïve male Wistar Han rats were the subjects of this study, being obtained from Charles River Laboratories (Lyon, France) with 60 days of age and having an approximate mean weight of 220 g (between 200 and 225 g) when they arrived at the animal facility in UNED. The animals were housed in groups of four subjects in plexiglass home cages (55 x 33 x 30 cm) in an environmentally controlled room at a temperature of 21°C and 60% relative humidity, with a light/dark cycle of 08:00h/20:00h. All the rats were acclimatized to the usual conditions of the laboratory from the first day of their arrival, with chow food (Envigo, Barcelona, Spain) and water available at all times. At 90 days of age, all rats were individually housed in plexiglass home cages (18 x 32.5 x 20.5 cm) covered by an aluminum grid surface with two concave spaces where food and a water bottle were arranged, all ad libitum. They were then randomly divided into two groups (n=8 in each group), becoming the SIP-ABA and the ABA-SIP groups, according to the time sequence of the procedures that they would undergo. All care and experimental procedures were in accordance with the Spanish Royal Decree 53/2013 regarding the protection of experimental animals and with the European Union Council Directive 2010/63. The UNED bioethics committee approved the experimental protocol.

*Apparatus*

The SIP procedure was carried out in eight Letica LI-836 conditioning chambers (customized by Cibertec SA, Madrid, Spain) of identical dimensions (29 x 24.5 x 35.5 cm) with an aluminum grid floor and plexiglass walls. Each chamber was equipped with a small fan that produced a noise of 60 dB, which in turn worked as background noise. A small window in the right outer wall allowed the investigator to see the inside of the chambers. The front and back panels were made of aluminum, while the side walls and ceiling were made of transparent acrylic. Behind the front panel, there was a dispenser that delivered 45 mg food pellets (Bio-Serv, Flemington, NJ, USA) into an aperture in the center of the front wall at 3.7 cm from the grid floor. Two 3 W DC bulbs, placed 27 cm from the grid floor, provided the lighting for the chambers. Calibrated water bottles whose nozzles were accessible to the animals through a hole 3.2 x 3.9 cm wide and high, respectively, were placed on the right wall of each chamber. The spouts of the bottles were placed 20 cm behind the hole, so that the rats could not maintain permanent contact with them. The generated data were recorded directly on a desktop computer located in the same room, equipped with Windows XP operating system and through the MED-PC IV software (Georgia, VT, USA).

The ABA procedure was performed in eight individual cages located in the vivarium that were made of transparent methacrylate with measures of 21 x 45 x 24 cm (Cibertec SA, Madrid, Spain). On the right side, each cage had an activity wheel 9 cm wide by 34 cm in diameter, and on the left side, on the aluminum grid that covered the upper part of the cage, two concave spaces where a bottle filled of water and food could be placed. Each activity wheel had a brake device controlled by a Pentium II 233 Mhz desktop computer, located in a separate laboratory room, equipped with Windows XP operating

system and MED-PC IV software that recorded the running and drinking of the rats continuously 23 hours a day.

*Procedures*

A research design was carried out where all the rats went through both procedures, SIP and ABA, in sequential order, which was counterbalanced between the subjects. All rats received in total 30 sessions of SIP and, at maximum, another 30 sessions of ABA, with a month of rest between both procedures. During this rest period, rats were kept housed individually and maintained at 100% of their estimated free-feeding body weight based on standardized growth curves calculated for each individual rat.

*Schedule-induced polydipsia.* Both groups, SIP-ABA and ABA-SIP, following the study's design and in two different time phases, depending on the group, were exposed to the SIP procedure, with all rats having been previously restricted their food availability until they reached 85% of their free-feeding body weight in line with their theoretical weight (standardized growth curve provided by Charles River Laboratories).

The day before the start of the SIP procedure (day 0), a 30-minute adaptation session to the experimental chambers was carried out, which consisted in depositing 20 food pellets in the feeders, keeping the light and fan on, but without installing the water bottles. The SIP procedure began a day later (day 1) and continued daily at the same time of the day, also for 30 minutes, from 5:45 p.m. to 6:15 p.m., for 30 sessions in total. Before placing the rats in their conditioning chambers and starting each experimental session, their weights were recorded daily on the laboratory weighing scales in order to control the amount of food to be given to the rats after each experimental session, at about 20 minutes after finishing the session, so that the animals were maintained at the criterion

weight reduction. Once the rats were weighed, the conditioning chambers were prepared by coupling the bottles with 100 ml fresh tap water to the experimental chambers, then each rat was introduced into its chamber and the FT 60 s schedule was initiated by releasing a food pellet at said time intervals until the total administration of 30 pellets over a period of 30 minutes. The termination of the experimental session was indicated by switching off the lights and disconnecting the fan in the chambers. During the experimental sessions, the licks given by each rat to the spout of the bottle were recorded, accumulating as total licks.

*Activity-based anorexia.* Following the design of the experiment, both groups went through this procedure at two different time phases. The ABA-SIP group first went through ABA, and the SIP-ABA group went through ABA in a second phase, after having passed the 30 SIP sessions and after the one-month rest period had elapsed. For all rats in both groups, their weight at the beginning of the ABA procedure was 100% with respect to their own theoretical weight. On day 0 of the experiment, at 7:00 p.m., the ABA procedure began by introducing each of the eight rats into their eight experimental cages and attaching a bottle with 100 ml of water to each cage with the activity wheel free to run. The next day, at 6:00 p.m., day 1 of the ABA experiment began, with 23 hours having passed since the rats were first introduced into the activity cages. The rats were weighed individually and then introduced back to their cages, where food (100 g of food chow) and water (100 ml refilled bottles) were placed in the cages. A one-hour food intake period during which the brakes were activated then commenced. When the intake period was over, the bottles were removed to measure the water consumed by the rats in the food period and were refilled to 100 ml before the start of the next period of 23 hours of access to running. The remaining food was also withdrawn to be weighed in order to record the

daily food consumption of each rat. The ABA procedure was in operation for each rat until it reached a loss of more than 25% of its initial body weight for two consecutive days, at which time the animal was removed from the experiment. If this criterion of body weight was not reached, the animals were removed from the procedure at the 30th ABA session.

*Data analysis*

We performed a best-fit analysis of the experimental data followed by a Bayesian model selection procedure. Each data set is represented with the points $\big(n, f(n)\big)$, where *n* is the session number (horizontal axis in the plots) and $f(n)$ is the value of the datum (vertical axis: ml of water, licks, weight percentage, g of food, or turns). Consider the fourth-order polynomial

$$f(n) = a_0 + a_1 n + a_2 n^2 + a_3 n^3 + a_4 n^4 \ . \qquad (1)$$

For each data set, we tried different fitting curves, for example, (1) as it is, or with $a_3 = a_4 = 0$ (parabola), or with $a_2 = a_3 = a_4 = 0$ (straight line), or other combinations with at least one vanishing parameter. We also considered the generalized polynomial $f(n) = a_0 + a_1 n^{b_1} + a_2 n^{b_2}$, as it is or with $a_2 = 0$, as well as exponential or logarithmic fits, which never gave better results than (1) except in one exponential case:

$$f(\mathrm{n}) = c_0 + c_1 \exp(c_2\, n) \ . \qquad (2)$$

After carrying out the best fit with each curve, we discarded fits where: (a) one or more parameters were zero within one standard deviation, or (b) fits where the *p*-value was > 0.05. Instead of the discarded fit, in case (a) we considered the corresponding fit where the parameter or parameters were set to zero as a prior. In case (b), we set to zero

first $a_4$ and, if the resulting fit had other parameters with a high $p$-value, also $a_3 = 0$, and so on. In this sense, all the best fits presented in this paper are statistically significant. Finally, Bayes and Akaike Information Criteria (IC) of the surviving curves were compared, and we selected as *the* best fit the curve with the lowest IC.

For each data set, we compared the value of the best-fit parameters in the SIP-ABA and ABA-SIP groups to check whether the two groups showed a significantly different trend. Trends where all the parameters overlapped within one standard deviation were considered as equal.

All analyses were performed with Wolfram Mathematica v.12.1.1. Data used for analyses are available from the corresponding author upon request.

## Results

### *Schedule-induced polydipsia*

Figure 1 (upper panel) shows the mean (± standard error) of the amount of water consumed in milliliters during the 30 sessions of the SIP procedure for both groups of the experiment. A progressive increase in water consumption can be observed throughout the sessions and generally a higher level of intake for the ABA-SIP group, showing a more rapid reach of the final levels of drinking in comparison to the SIP-ABA group. The best-fit curves are significantly different in the parameters $a_1$ and $a_2$ (see the Appendix). The most important difference is in $a_2$, which is zero in the SIP-ABA case (straight line) and nonzero in the ABA-SIP case (quadratic curve). The ABA-SIP curve reaches a behavioral maximum earlier than the SIP-ABA line, flattening to the end to show a level similar to the SIP-ABA line.

*Insert Figure 1 about here*

The lower panel of Figure 1 shows the mean (± standard error) of the records of licks to the water bottles made by the rats of both groups during the 30 sessions of SIP. As with water consumption, a progressive increase of the licks can be seen as the experimental sessions progressed and a generally higher level of behavior in the ABA-SIP group, especially in the early 15 sessions. As with water intake, the best-fit curves differ both in $a_1$ and $a_2$, but here the nonlinear curve goes under the straight line before the end of the procedure. Again, there was a more rapid acquisition of final licking in the ABA-SIP group (nonlinear curve) in comparison with the SIP-ABA group (straight line).

*Activity-based anorexia*

The upper panel of Figure 2 shows the mean (± standard error) of the proportion of daily body weight loss of the rats of both groups while the ABA procedure was in place until the first rat of each group reached the withdrawal criterion. For the ABA-SIP group on the ninth day the first rat had to be withdrawn, however for the SIP-ABA group, which passed in a second phase through ABA, the first rats were not removed until session 26. In this case, the best fit of both groups followed the same cubic function but with different parameters (see the Appendix). The ABA-SIP curve shows a steeper weight loss and, in general, a faster rate of change, the saddle in the ABA-SIP curve being compress in just a handful of sessions compared with the more extended and milder decrease in the SIP-ABA curve.

*Insert Figure 2 about here*

The middle panel of Figure 2 shows the mean (± standard error) of the amount of food ingested by rats throughout the daily experimental sessions. In general, a progressive increase in the grams of food ingested can be observed as the ABA procedure progressed,

with no apparent differences between the two groups in the experiment for the sessions where they can be compared. More precisely, two of the three parameters of the best fit are the same within one standard deviation, while the third, responsible for the convexity of the SIP-ABA curve, has been determined as nonvanishing for the SIP-ABA case from a greater number of points with respect to the ABA-SIP case. Therefore, we cannot conclude that the two curves are different.

The bottom panel of Figure 2 shows the mean (± standard error) of the level of running exerted on the activity wheel during the 9 sessions that the whole ABA-SIP group and the 26 sessions that the whole SIP-ABA group were in the experimental cages submitted to the ABA procedure. A progressive increase in running can be observed as the experimental sessions progressed, with a running level that in general was somewhat higher for the ABA-SIP group. The parameters of the best-fit curves of the data are different except $a_0$ which, just like the other cases, it only reflects the fact that the two groups started with the same initial conditions, i.e., that they were equally prepared before the procedure begun. While the SIP-ABA curve follows a linear trend, the ABA-SIP one increases more steeply in a nonlinear way.

## Discussion

The objective of the study was to investigate the possible relationship between drinking in the SIP phenomenon and running in the ABA phenomenon. For this purpose, we hypothesized that previous experience in any of these behavioral manifestations should facilitate the subsequent acquisition of the other phenomenon, following the logic of the interchangeability of behaviors induced by reinforcement schedules (Staddon, 1977). Schedule-induced behavior was initially referred to as adjunctive behavior (Falk, 1971), as it is generated by scheduling intermittent reinforcement without explicit contingency

arranged between the behavior and the reinforcer, such as drinking in SIP and running in ABA seem to follow, being as well not determined by a biological need of water or activity, respectively. In accordance with this theoretical approach, pre-exposure to ABA facilitated the initial development of SIP, but pre-exposure to SIP, however, retarded the development of ABA, this result being in principle contrary to the previous one and the theoretical starting approach.

The non-facilitation of SIP on the development of ABA in the corresponding group of the anorexia procedure is still to be clarified. We hypothesize that these contradictory results regarding the effect of SIP on ABA could be due to the previous experience of animals with a food restriction regime to keep them at 85% during the SIP procedure, since it has been shown that prior adaptation to food regime retards or prevents the further development of ABA (Cano et al., 2006; Dwyer & Boakes, 1997; Lett et al, 2001; Ratnovsky & Neuman, 2011). Therefore, Experiment 2 repeated the previous experiment but keeping the animals at 100% of their body weight during the SIP procedure, just as when the ABA procedure is started, even at the risk of rats drinking too little during exposure to the intermittent schedule of food administration due to the need for a certain degree of hunger to facilitate induction (cf. Falk, 1971; Pellón, 1992; see however Todd et al., 1997).

## Experiment 2

Experiment 1 showed that ABA experienced first facilitated the subsequent acquisition (but not maintenance) of SIP, but this facilitation did not occur in the opposite situation of prior development of SIP over subsequent development in ABA. This apparent

discrepancy in the results may be due to the fact that previous experience with food restriction (such as during exposure to the SIP procedure) normally retards the development of ABA (e.g., Dwyer & Boakes, 1997; Lett et al., 2001), result which however has not been documented regarding the acquisition of SIP. Discarding this influence was the purpose for which Experiment 2 was designed, which was exactly the same as the first one, with the only caveat that the rats of the SIP-ABA group were maintained at 100% of their body weight during the sessions that the SIP procedure lasted so that rats had no experience in food restriction before being exposed to ABA. To match the condition of food deprivation in the SIP procedure, the rats of the ABA-SIP group were also maintained at 100% of their body weight when they were exposed to the SIP experience in the second phase of the experiment.

## Methods

### *Subjects*

The experimental subjects were sixteen male Wistar Han rats, which, as in Experiment 1, were obtained from Charles River Laboratories (Lyon, France) with 60 days of age and with an average body weight of 218 g (between 196 and 240 g) at arrival at the animal facility in UNED. All procedures for receiving, caging, and caring for rats were identical to those described in the previous experiment, being maintained under the same environmental conditions of temperature, humidity, and light-dark cycle. The rats were randomly distributed into the two SIP-ABA and ABA-SIP groups (n=8 in each group). In order to control weight, a growth curve estimate based on the information provided by Charles River was used as a reference. As in Experiment 1, all care and experimental procedures were in accordance with the Spanish Royal Decree 53/2013 regarding the

protection of experimental animals and with the European Union Council Directive 2010/63. The UNED bioethics committee approved the experimental protocol.

*Apparatus*

The apparatus were the same as those described for Experiment 1.

*Procedures*

The same research design was performed as in Experiment 1, so that all rats went through both procedures (SIP and ABA) in sequential orders counterbalanced between subjects with 20 days of rest between both procedures. They received a total of 20 sessions of SIP and for ABA, whatever sessions that were necessary for each rat to reach 75% decrease in weight for two consecutive days. The only difference with the previous experiment was that the animals were kept at 100% of their weight during the SIP procedure.

*Data analysis*

As in Experiment 1, we implemented a model selection based on a nonlinear best-fit analysis. Calculations were performed with Wolfram Mathematica v.12.1.1. Data used for analyses are available from the corresponding author upon request.

## Results

*Schedule-induced polydipsia*

Figure 3 (upper panel) shows the mean (± standard error) of water consumption in milliliters during the 20 SIP sessions for both groups of the experiment. A slight increase in water consumption is observed as the experimental sessions progressed and a certain higher level of fluid intake can be observed for the ABA-SIP group. The best fit is described by 5 parameters, all different across the groups (see the Appendix). The form

of the curves reflects that SIP was hardly acquired in any of the groups as a consequence of animals not being food deprived. Overall, the ABA-SIP curve shows a more erratic form compared to the SIP-ABA one, which reaches a maximum monotonically and then starts to decrease.

*Insert Figure 3 about here*

In the lower panel of Figure 3, the mean (± standard error) of the number of licks given to water bottle spouts by both groups of rats during the 20 sessions of SIP is shown. As with water consumption, a slight progressive increase in licks can be seen as the experimental sessions progressed, more pronounced in the ABA-SIP group (straight line) with also a generally higher level of licking, but only during the first 15 sessions (as in Experiment 1). After that point, the nonlinear trend of the SIP-ABA group takes over and the number of licks in the last 5 sessions is larger in the latter group.

*Activity-based anorexia*

The upper panel of Figure 4 shows the mean (± standard error) of the proportion of daily body weight loss of the rats of both groups while the ABA procedure was in course. It is observed that the decrease in body weight, although drastic for both groups, was somewhat more pronounced in SIP-ABA rats that reached the withdrawal criterion one session before the ABA-SIP rats. The best fit is an exponential curve for both groups, with statistically different coefficient in the exponent, reflecting the steeper rate of change registered for the SIP-ABA group.

*Insert Figure 4 about here*

The middle panel of Figure 4 shows the mean (± standard error) of the amount of food ingested by rats throughout the daily experimental sessions. In general, a progressive

increase in the grams of food ingested can be seen as the ABA procedure progressed, with a slightly higher consumption in the SIP-ABA group. The best-fit curves are straight parallel lines (same slope), the SIP-ABA line being above the ABA-SIP one.

The lower panel of Figure 4 shows the mean (± standard error) of the level of running exerted on the activity wheel during the sessions that the whole ABA-SIP and SIP-ABA groups were in the experimental cages undergoing the ABA procedure. A progressive increase in running can be observed as the experimental sessions progressed, a level of running that was, in general, somewhat higher for the SIP-ABA group during the first 4 sessions. As in Experiment 1, the SIP-ABA curve is a straight line while the ABA-SIP curve is a parabola with no linear term, $a_1 = 0$ (see the Appendix).

## Discussion

The purpose of this second experiment was, like the first one, to try to experimentally test the hypothesis of mutual facilitation between SIP and ABA that could not be fully demonstrated in the previous experiment by the possible interference of food restriction exposure in SIP prior to ABA experience, since it is known that adaptation to the meal regime (in this case 1 hour of food at the same time every day) can retard or prevent the subsequent development of ABA (e.g., Dwyer & Boakes, 1997; Lett et al., 2001). Therefore, an experiment identical to Experiment 1 was implemented but keeping the rats at 100% of their body weight during exposure to SIP, now obtaining a slight facilitation of the development of ABA by previous exposure to SIP (just the opposite of what had been obtained in Experiment 1) coupled with the higher level of running shown by the animals in the SIP-ABA group versus those in the ABA-SIP group. The facilitating effect on the development of SIP due to previous experience in ABA was replicated as in Experiment 1, although perhaps at a somewhat lower level due to the lower development

of SIP because the animals were not deprived of food. In this regard, the present results coincide with those reported by Todd et al. (1997) by demonstrating that food deprivation is not a necessary condition for the development of SIP, although it strongly modulates it. In this regard, it is important to note that the SIP procedure lasted 20 sessions in Experiment 2 in comparison to the 30 sessions that lasted in Experiment 1. This was due to the longer time that took drinking (water consumption and licking) to stabilize when animals were food deprived (Experiment 1) as opposed to satiated (Experiment 2), who hardly developed SIP. As it can be seen in Figure 1, by session 20 behavior was not fully established. Likewise, the interpolated time between ABA / SIP experiences was shortened in Experiment 2 in comparison with Experiment 1, in concordance with the number of SIP sessions.

## General Discussion

The main reason for this investigation was to address the possible functional similarity of the behaviors of licking in the SIP phenomenon and wheel-running in the ABA one. By making a cross-comparison between the facilitative interactions of both behaviors, the idea was to demonstrate (or refute) that the level of running exerted by rats during ABA can resemble the licks given by those same rats during their exposure to a SIP procedure. By doing so, therefore, our knowledge about schedule-induced behaviors could be transferred to the explanation of the phenomenon of ABA.

After the first investigations by Falk in the 60s of the past century, SIP is considered as the best experimental example of schedule induction (Pellón, 1990, 1992; Roper, 1983; Staddon, 1977; Wetherington, 1982), a finding also extended to induced running (e.g.,

Levitsky & Collier, 1968). Gutiérrez-Ferre and Pellón (2019) have recently reaffirmed the induced nature of running in rats after intermittent exposure to food delivery when compared with massive food administration, and its modulation by the frequency of food reinforcement. If running can be induced by the reinforcement schedule similarly to drinking, and both show similar characteristics and functionality (cf. Killeen & Pellón, 2013), then the results of the current study might show that running in the ABA phenomenon could (by analogy) be induced by the occurrence of food at regular intervals of time, albeit on the order of hours instead of seconds/minutes. This proposal was already advanced by Epling and Pierce (1992), although they did not provide much experimental evidence to support it.

Briefly, the animals in the ABA procedure have food restriction and the food is administered intermittently, thus having the two conditions necessary for the food to function as a behavior-inducing event. Moreover, as in other studies on schedule-induced behavior, animals are not deprived of the behavior to be induced, and such behavior is related to the inducing event. In the case of ABA, given that animals are hungry, and that food is scarce, it is highly likely that running will be induced, which would be the manifestation in the laboratory of the movement that animals would make in search of food. The initiation of running through an induction mechanism can later be reinforced by the occurrence of the food itself (Álvarez et al., 2016), which would result in an increase in running to the point of being dysfunctional, a characteristic which has been attributed to excessive behaviors generated by reinforcement induction (e.g., Moreno & Flores, 2012). The entry into this cycle of excessive activity and weight loss would eventually lead to loss of intake, possibly because the reinforcement value of food is reduced (see, however, de Paz et al., 2019), but usually, after stopping the procedure when

a reduction to 75% of body weight is reached, such deterioration does not occur. In the current experiments, even though there were differences in the development of ABA across groups of animals, they did not differ in the level of food intake (but on the level of wheel turns) in Experiment 1 (see Figure 2), or interestingly was even higher for the rats that run more and showed a greater vulnerability to ABA in Experiment 2 (see Figure 4). This higher food consumption reflects the best adaptation to the feeding schedule of the SIP-ABA group given its prior experience with the SIP procedure (something lacking the ABA-SIP group), and thus contradicts the idea that ABA results from a failure to adapt to the food schedule (Dwyer & Boakes, 1997). The ABA phenomenon would therefore reproduce in the laboratory the initial stages of development of the disorder, which, if prolonged in time, would lead to gastrointestinal lesions and death, as was the case in the first experimental approaches to the phenomenon (e.g., Paré & Houser, 1973; Routtenberg & Kuznesof, 1967).

An additional fact that would be in line with the control exercised by the food over the activity would be that the running moments in the course of ABA shift from the night period to the moments before and after the occurrence of mealtime (e.g., Labajos & Pellón, 2018; Pérez-Padilla et al., 2010), in line with what is observed for schedule-induced behaviors (Staddon, 1977). Contrary to induction, however, Beneke et al. (1995) gave greater importance to the cyclic rhythms of environmental control (*zeitgebers*), such as the light / dark cycle, as an explanatory factor of the activity rather than the food regime per se. A test on this would require running experiments similar to the ones presented here with feeding periods located either during the day period of the cycle (as in here) or during the night (as in Dwyer & Boakes, 1997, or Paré, 1975), which so far have resulted in contradictory results as on to the effect of having feeding episodes during natural dark

periods on the speed of development of ABA. If circadian entrainment plays a facilitatory role in the development of ABA, it should develop faster if food episodes were programmed during the night part of the day cycle as rats will not have to displace their natural occurring moments of activity.

Before concluding, it is important to discuss the possible need of incorporating additional controls before taking final firm conclusions about the facilitatory role on ABA of SIP and vice versa. The common effect of food intermittency claimed here was possibly not fully controlled because of the lack of incorporating groups of animals exposed to the water bottle or the running wheel on a first experimental phase but without such intermittency in food occurrence. In the case of the facilitatory effect on ABA this would imply a control group of animals being previously exposed to the conditioning chambers with water available and the same amount of food delivered in massed, not intermittently, as now the control had no previous experience at all. The underlying idea of the present proposal predicts that such control group should not result in a facilitation of ABA development because of the lack of pre-experience with intermittent food, but of course, this needs to be tested. However, the objective of this control condition may be difficult to achieve because, as seen from Experiment 2, animals must not be food deprived during the SIP experience; thus little drinking is expected to occur both in the intermittent and the massed groups so as to detect differences in ABA afterwards. In line with this, we have collected data that show a positive relationship between level of licking in SIP and level of running in ABA (Labajos, 2019), which may be a more promising approach to explore. In the case of the facilitation of SIP, it is not clear how such an additional control should be run on the previous ABA experience. One possibility is to have animals maintained with constant access to food and running wheel throughout the

day. Under those circumstances it is known that animals gain weight, albeit less than if they did not have access to the wheel (e.g., Pinos et al, 2023). However, different weights influence the development of ABA (Boakes & Dwyer, 1997). The other possibility is to give such controls access to the similar amount of food than the experimental ABA animals but without time restriction to eat it (a way to control for intermittency keeping the overall amount of food constant across groups of animals: Brooks et al., 1990). Under these circumstances, rats develop anorexia similarly than under the standard ABA procedure.

The claim that running in ABA is induced in nature seems contradicted by the work of Kanarek and Collier (1983) which showed that four regularly spaced 15-minute meals per day, or two 30-minute meal periods a day, produced less wheel running activity than did one 60-minute meal. The different spacing of meals had an effect on running that appeared to be opposite in trend than if it had been induced by food delivery, and therefore had an effect on the development of ABA contrary to what would be expected based on running being induced by food occurring at regular spacing times. Two limitations should be considered before concluding that Kanarek and Collier's results contradict the position defended here. First, in order to analyze the induced nature of running, the way in which we manipulate the data seems to be critical, as linear decreasing functions of running with increases in inter-food interval length are only obtained when data are transformed in terms of rate (Pellón, 2012), something that was not the case in the report of Kanarek and Collier. Second, in order to analyze the degree of weight loss that the various food regimes have on the development of ABA, proper control groups with the same feeding schedules but without possibility of running should be incorporated, as it is likely that the more

severe food regimes will lead by themselves to more severe weight losses (apart from the contribution of exercising).

Keeping the previous caveats present, the analysis of our results, and the apparent mutual facilitation between drinking and running shown here, may support the idea that activity can be induced by the intermittent occurrence of biologically relevant events, such as food for an animal with a certain level of hunger, and in this way use our knowledge on the controlling variables of reinforcement schedules (such as reinforcer magnitude, frequency or delay) to influence activity levels, with the potential to manipulate them as a therapeutic tool to be explored.

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## Open Practices Statement

The data and materials for all experiments are available upon request to the corresponding author.

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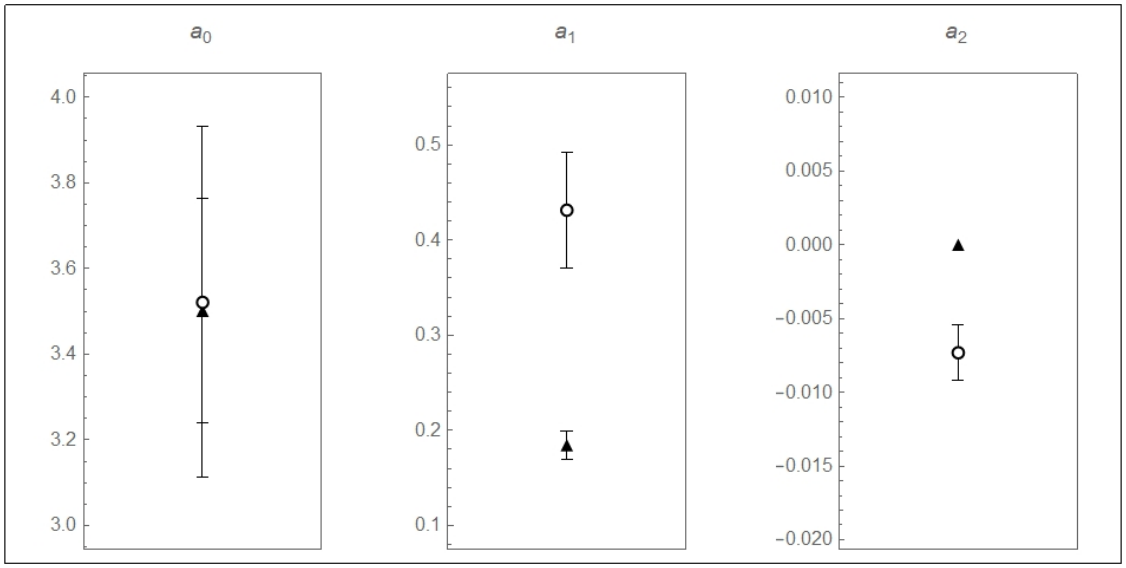
**Appendix.**

Values of the best-fit parameters of Figures 1-4 as well as their comparison.

| | Water SIP-ABA | Water ABA-SIP |
|---|---|---|
| $a_0$ | 3.50 ± 0.26 ($p = 10^{-13}$) | 3.52 ± 0.41 ($p = 10^{-9}$) |
| $a_1$ | 0.185 ± 0.015 ($p = 10^{-12}$) | 0.431 ± 0.061 ($p = 10^{-7}$) |
| $a_2$ | 0 | –0.0073 ± 0.0019 ($p = 0.0007$) |
| | **Licks SIP-ABA** | **Licks ABA-SIP** |
| $a_1$ | 17.55 ± 0.45 ($p = 10^{-25}$) | 42.19 ± 2.79 ($p = 10^{-14}$) |
| $a_2$ | 0 | –0.966 ± 0.118 ($p = 10^{-8}$) |

Table A1. Best-fit parameters ± standard error for schedule-induced drinking of SIP-ABA and ABA-SIP groups in Experiment 1. Reported are only the parameters of the curve (1) which are nonzero for at least one of the groups. An increasing number of digits for the parameter values is shown.



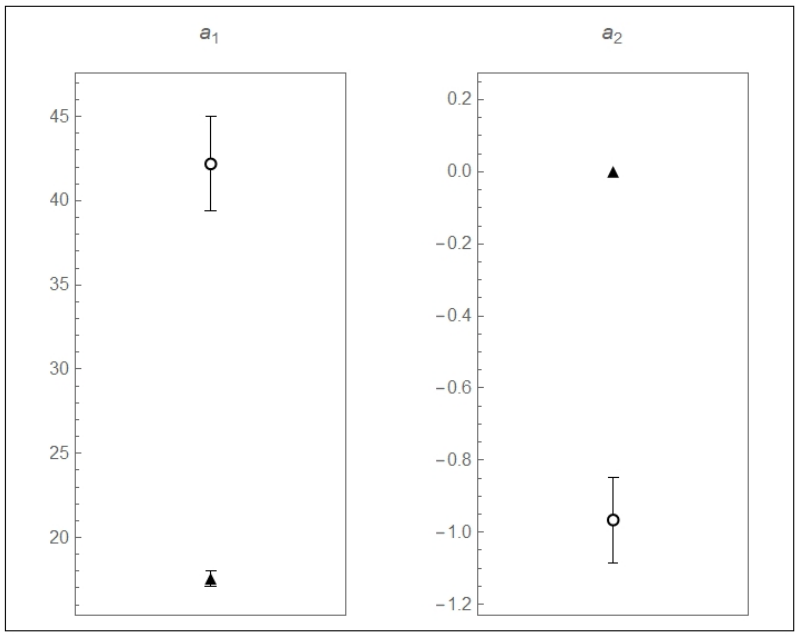
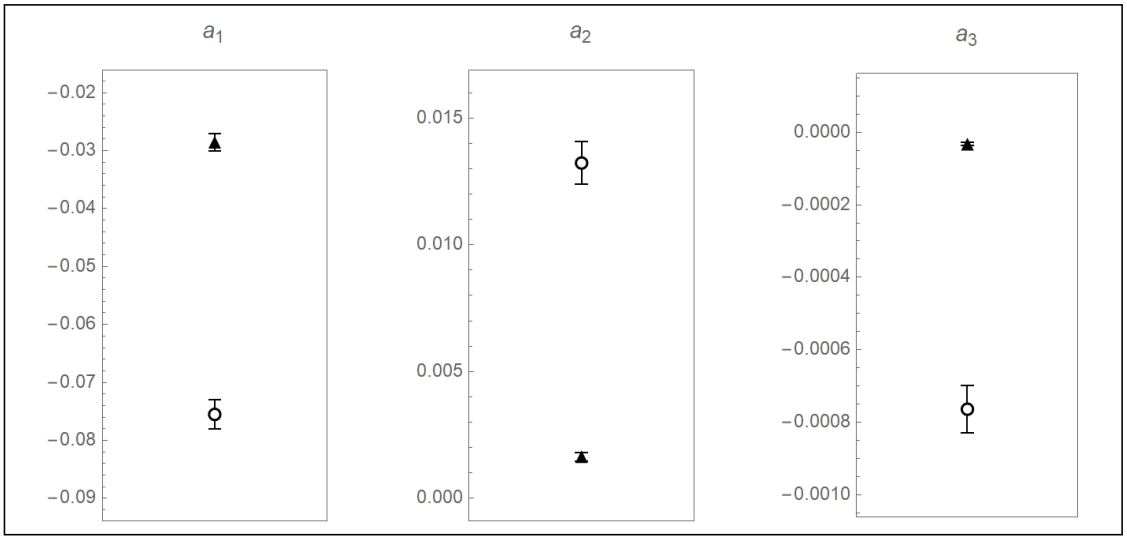



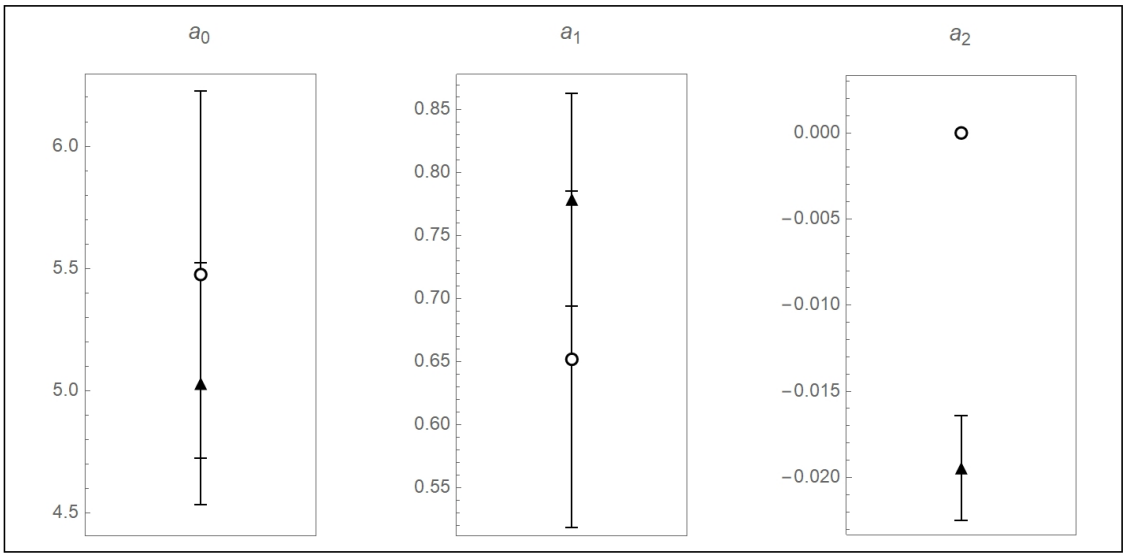

Figure A1. Comparison of the best-fit parameters for schedule-induced drinking of the SIP-ABA group (black triangles) and the ABA-SIP group (white circles) in Experiment 1. Top panel: water consumption. Bottom panel: licks. Error bars are the SE calculated for the best fit.

| | Weight SIP-ABA | Weight ABA-SIP |
|---|---|---|
| $a_0$ | 1 | 1 |
| $a_1$ | –0.029 ± 0.001 ($p = 10^{-15}$) | –0.076 ± 0.002 ($p = 10^{-7}$) |
| $a_2$ | 0.0016 ± 0.0002 ($p = 10^{-9}$) | 0.0132 ± 0.0008 ($p = 10^{-6}$) |
| $a_3$ | –0.000033 ± 0.000005 ($p = 10^{-6}$) | –0.000763 ± 0.000066 ($p = 0.00002$) |
| | Food intake SIP-ABA | Food intake ABA-SIP |
| $a_0$ | 5.03 ± 0.49 ($p = 10^{-9}$) | 5.48 ± 0.75 ($p = 0.0003$) |
| $a_1$ | 0.779 ± 0.084 ($p = 10^{-9}$) | 0.652 ± 0.133 ($p = 0.003$) |
| $a_2$ | –0.0195 ± 0.0030 ($p = 10^{-6}$) | 0 |
| | Wheel turns SIP-ABA | Wheel turns ABA-SIP |
| $a_0$ | 228.75 ± 79.24 ($p = 0.008$) | 312.11 ± 68.72 ($p = 0.004$) |
| $a_1$ | 70.770 ± 5.131 ($p = 10^{-12}$) | 0 |
| $a_2$ | 0 | 12.1896 ± 1.6650 ($p = 0.0003$) |

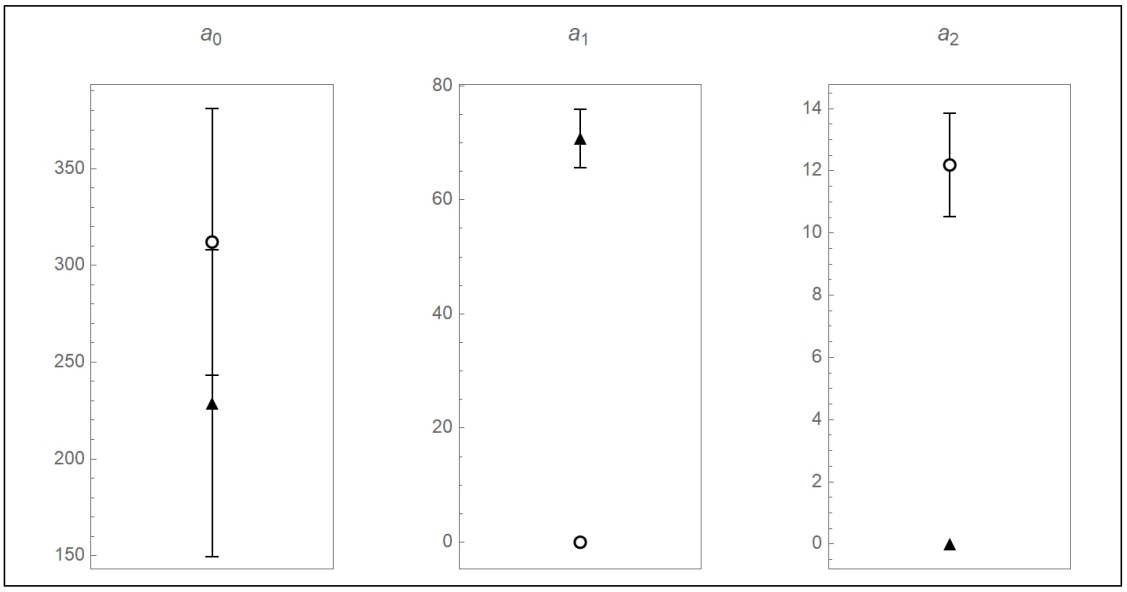
Table A2. Best-fit parameters ± standard error for activity-based anorexia of SIP-ABA and ABA-SIP groups in Experiment 1. Reported are only the parameters of the curve (1) which are nonzero for at least one of the groups. An increasing number of digits for the parameter values is shown. By definition, $a_0$=1 for the weight fit (100% body weight before the first session).


$a_1$
−0.02
−0.03
−0.04
−0.05
−0.06
−0.07
−0.08
−0.09
$a_2$
0.015
0.010
0.005
0.000
$a_3$
0.0000
−0.0002
−0.0004
−0.0006
−0.0008
−0.0010

1


$a_0$
6.0
5.5
5.0
4.5
$a_1$
0.85
0.80
0.75
0.70
0.65
0.60
0.55
$a_2$
0.000
−0.005
−0.010
−0.015
−0.020

2

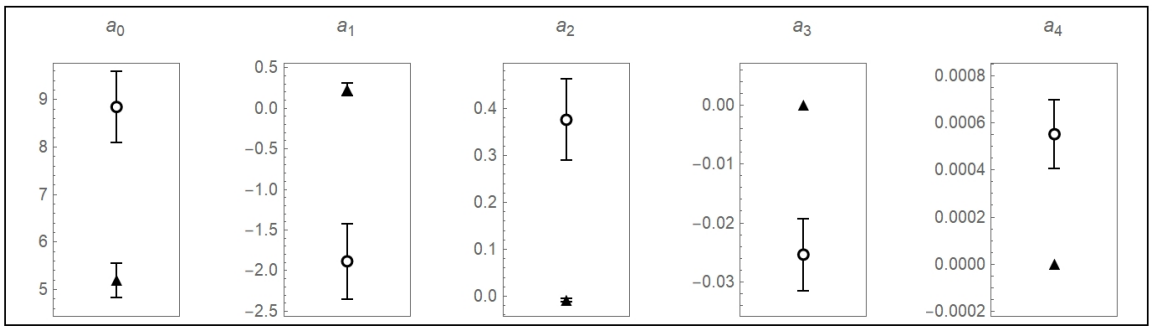

$a_0$
350
300
250
200
150
$a_1$
80
60
40
20
0
$a_2$
14
12
10
8
6
4
2
0

3

Figure A2. Comparison of the best-fit parameters for activity-based anorexia of the SIP-ABA group (black triangles) and the ABA-SIP group (white circles) in Experiment 1. Top panel: relative body weight loss. Middle panel: food intake. Bottom panel: wheel turns. Error bars are the SE calculated for the best fit.

| | Water SIP-ABA | Water ABA-SIP |
|---|---|---|
| $a_0$ | 5.20 ± 0.36 ($p = 10^{-10}$) | 8.84 ± 0.74 ($p = 10^{-9}$) |
| $a_1$ | 0.230 ± 0.079 ($p = 0.01$) | –1.883 ± 0.464 ($p = 0.001$) |
| $a_2$ | –0.0087 ± 0.0037 ($p = 0.03$) | 0.3763 ± 0.0868 ($p = 0.0006$) |
| $a_3$ | 0 | –0.02535 ± 0.00614 ($p = 0.0009$) |
| $a_4$ | 0 | 0.000552 ± 0.000145 ($p = 0.002$) |
| | Licks SIP-ABA | Licks ABA-SIP |
| $a_0$ | 62.89 ± 20.42 ($p = 0.007$) | 147.00 ± 17.19 ($p = 10^{-7}$) |
| $a_1$ | 0 | 4.256 ± 1.435 ($p = 0.009$) |
| $a_2$ | 0.6240 ± 0.1074 ($p = 0.00002$) | 0 |

Table A3. Best-fit parameters ± standard error for schedule-induced drinking of SIP-ABA and ABA-SIP groups in Experiment 2. Reported are only the parameters of the curve (1) which are nonzero for at least one of the groups. An increasing number of digits for the parameter values is shown.



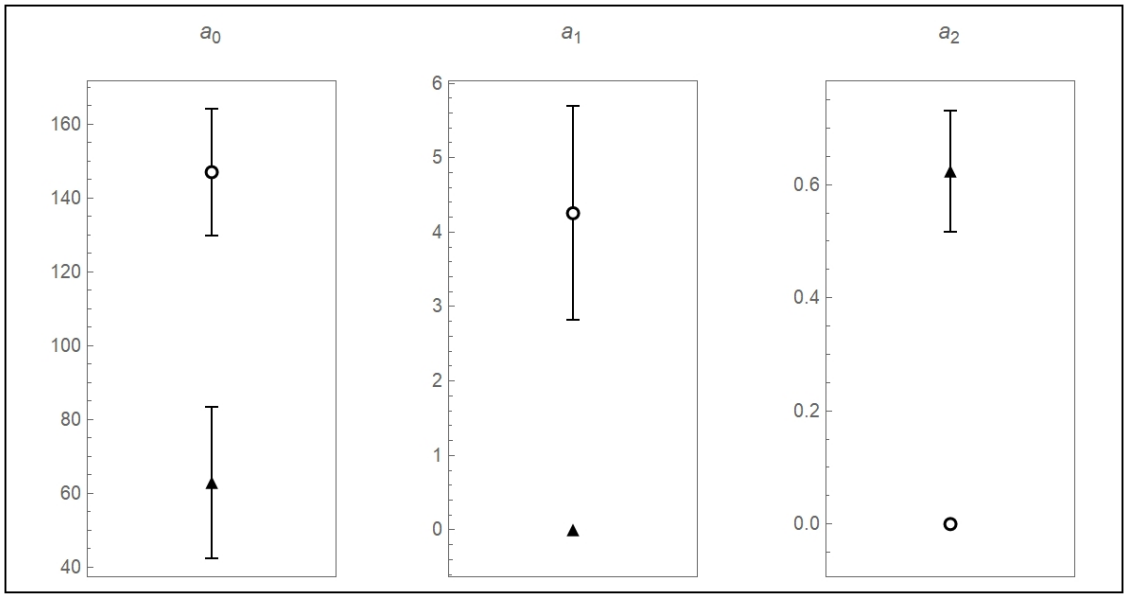
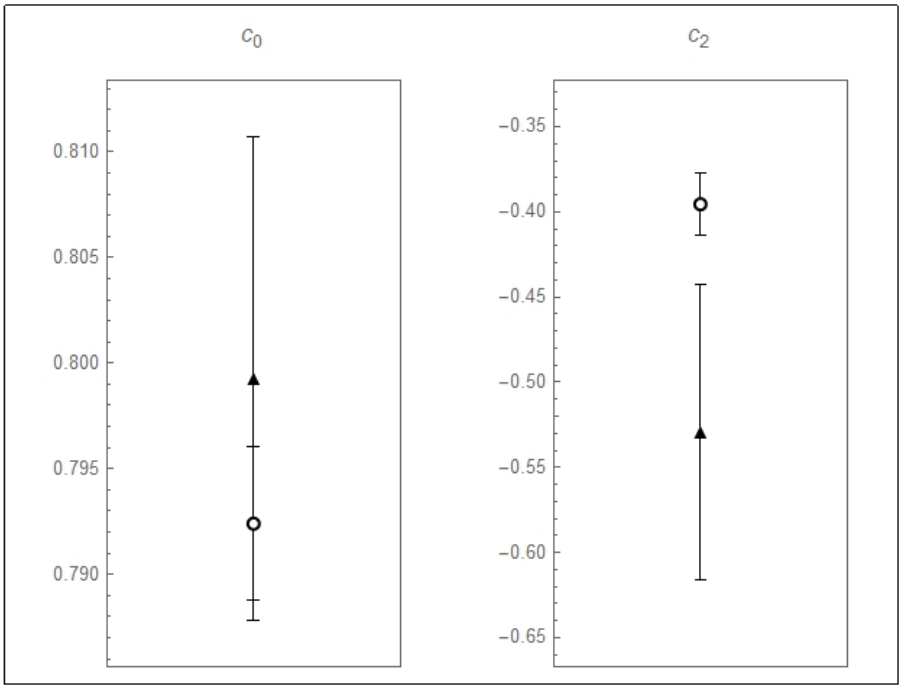



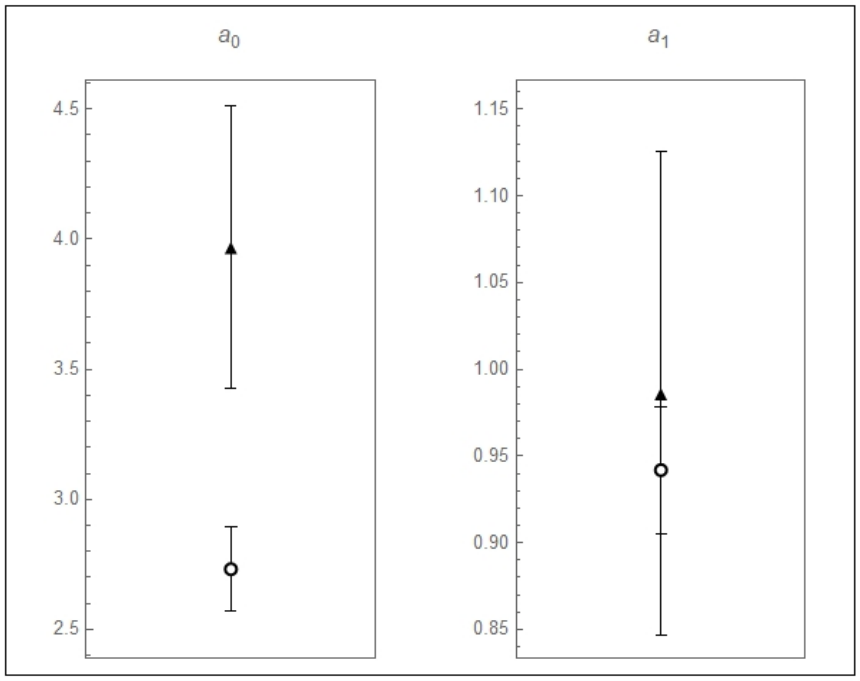

Figure A3. Comparison of the best-fit parameters for schedule-induced drinking of the SIP-ABA group (black triangles) and the ABA-SIP group (white circles) in Experiment 2. Top panel: water consumption. Bottom panel: licks. Error bars are the SE calculated for the best fit.

| | Weight SIP-ABA | Weight ABA-SIP |
|---|---|---|
| $c_0$ | 0.799 ± 0.011 ($p = 10^{-7}$) | 0.792 ± 0.004 ($p = 10^{-11}$) |
| $c_1$ | $1 - c_0$ | $1 - c_0$ |
| $c_2$ | –0.529 ± 0.087 ($p = 0.004$) | –0.395 ± 0.018 ($p = 10^{-6}$) |
| | Food intake SIP-ABA | Food intake ABA-SIP |
| $a_0$ | 3.97 ± 0.54 ($p = 0.002$) | 2.73 ± 0.16 ($p = 0.00001$) |
| $a_1$ | 0.986 ± 0.139 ($p = 0.002$) | 0.942 ± 0.037 ($p = 10^{-6}$) |
| | Wheel turns SIP-ABA | Wheel turns ABA-SIP |
| $a_0$ | 365.89 ± 83.95 ($p = 0.02$) | 98.50 ± 24.11 ($p = 0.02$) |
| $a_1$ | 74.471 ± 21.555 ($p = 0.04$) | 0 |
| $a_2$ | 0 | 18.559 ± 0.933 ($p = 0.00004$) |

Table A4. Best-fit parameters ± standard error for activity-based anorexia of SIP-ABA and ABA-SIP groups in Experiment 2. We report only the parameters of the curves (1) and (2) which are nonzero for at least one of the groups. An increasing number of digits for the parameter values is shown. By definition, $c_0$+$c_1$= 1 for the weight fit (100% body weight before the first session).


$c_0$
0.810
0.805
0.800
0.795
0.790
$c_2$
−0.35
−0.40
−0.45
−0.50
−0.55
−0.60
−0.65

1


$a_0$
4.5
4.0
3.5
3.0
2.5
$a_1$
1.15
1.10
1.05
1.00
0.95
0.90
0.85

2

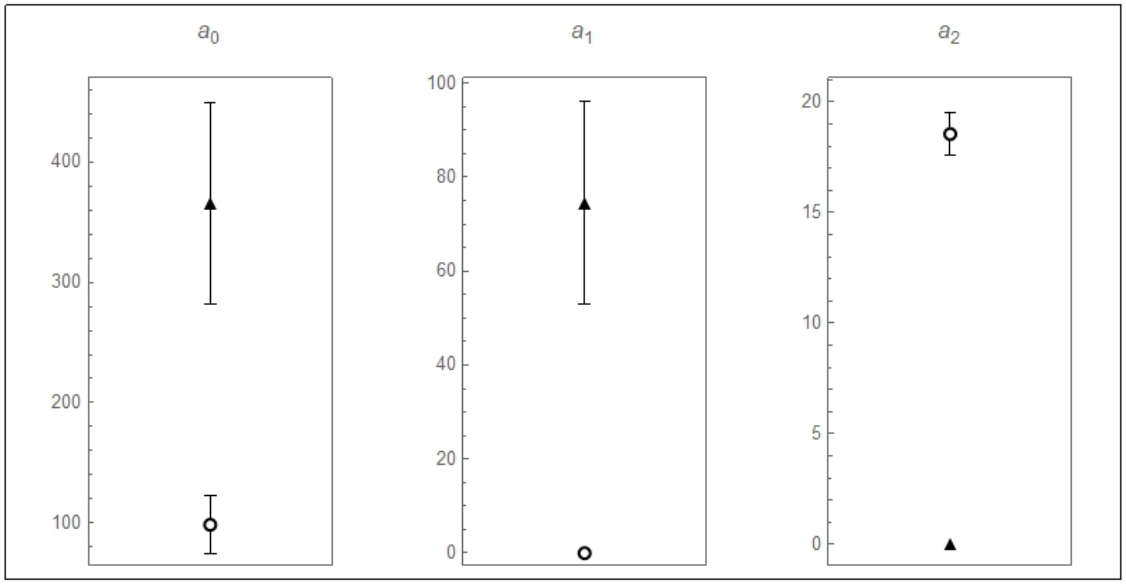
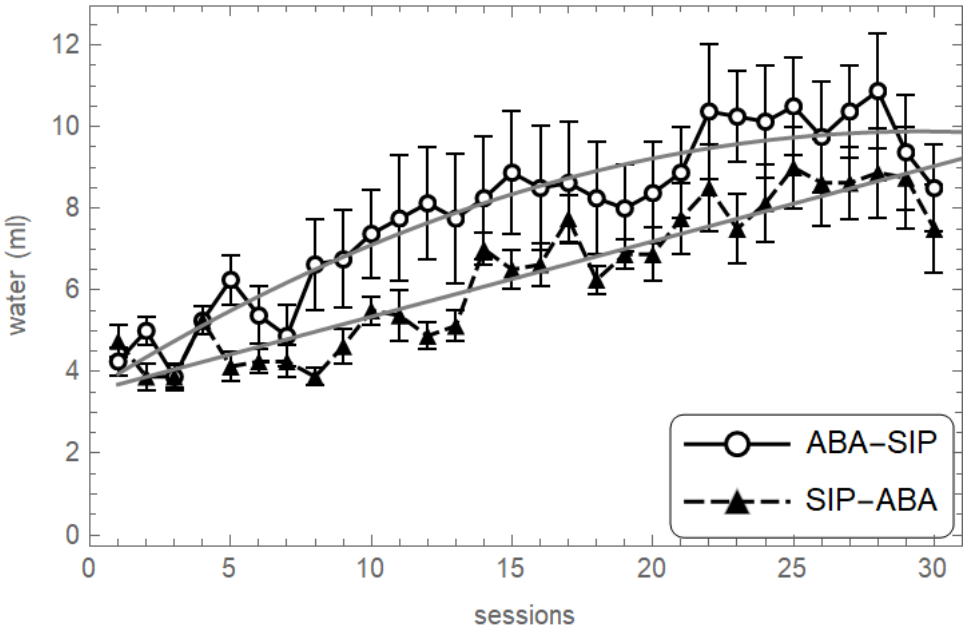



Figure A4. Comparison of the best-fit parameters for activity-based anorexia of the SIP-ABA group (black triangles) and the ABA-SIP group (white circles) in Experiment 2. Top panel: relative body weight loss. Middle panel: food intake. Bottom panel: wheel turns. Error bars are the SE calculated for the best fit.



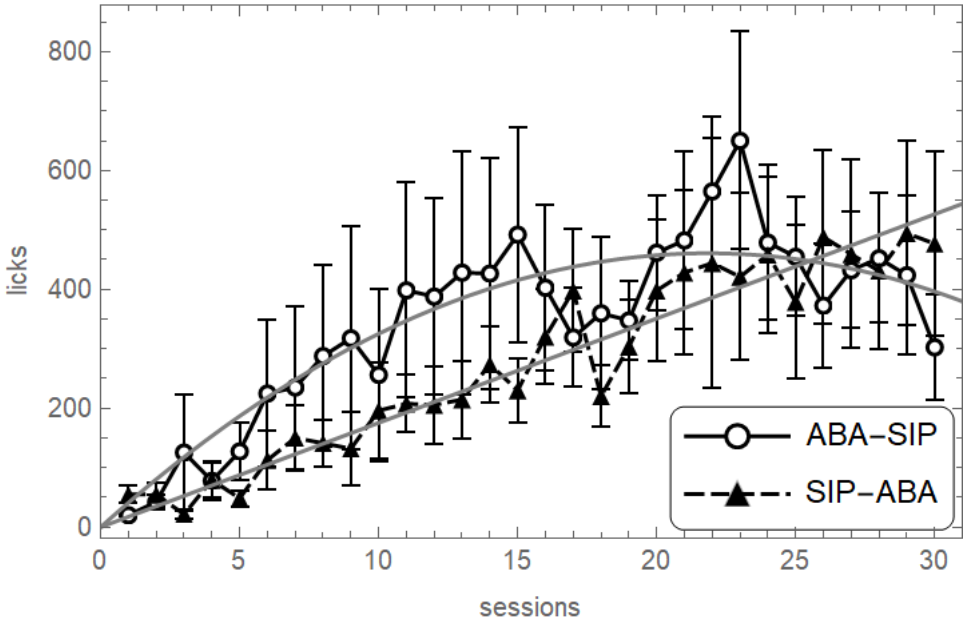
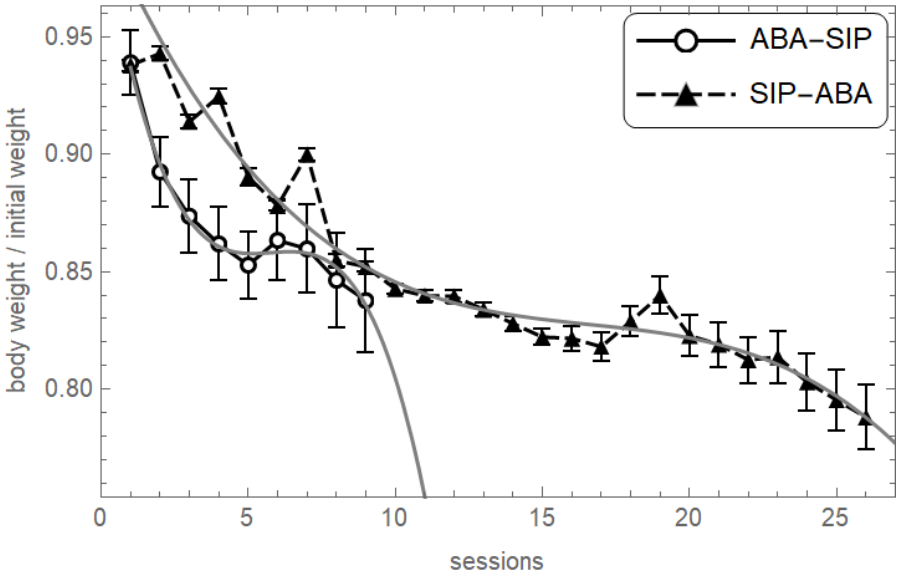
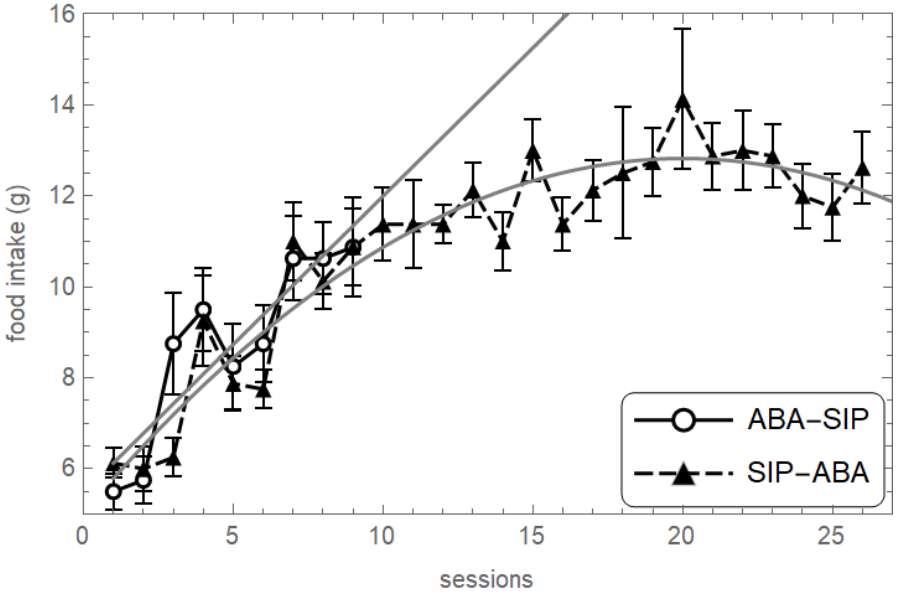



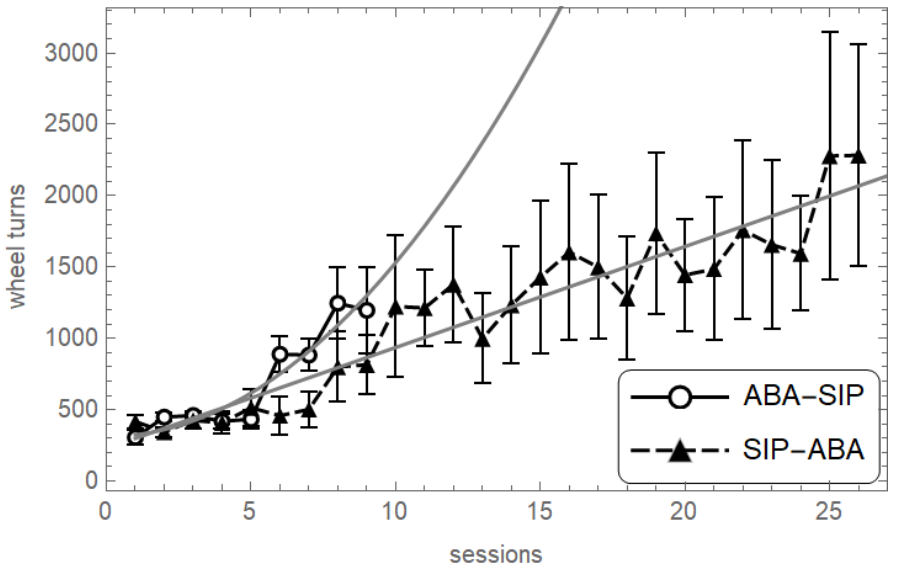

Figure 1. Water consumption and licks given to the bottle spout (mean ± SE) throughout all sessions of Experiment 1 in both groups of rats that went directly through schedule-induced polydipsia (SIP-ABA) or who did so after a previous experience of activity-based anorexia (ABA-SIP).


body weight / initial weight
0.95
0.90
0.85
0.80
0
5
10
15
20
25
sessions
ABA–SIP
SIP–ABA

1

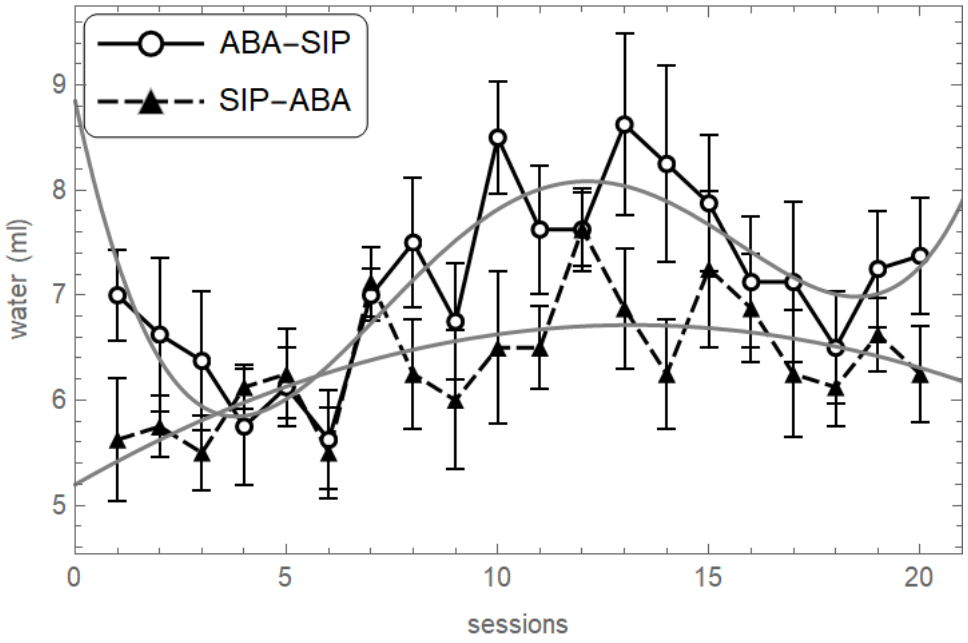

food intake (g)
16
14
12
10
8
6
0
5
10
15
20
25
sessions
ABA–SIP
SIP–ABA

2


wheel turns
3000
2500
2000
1500
1000
500
0
0
5
10
15
20
25
sessions
ABA–SIP
SIP–ABA

3

Figure 2. Relative reduction of body weight, food consumption in grams, and turns on the activity wheel (mean ± SE), throughout the sessions of Experiment 1 and for the two groups of rats that went through ABA directly (ABA-SIP) or who underwent it after a schedule-induced drinking experience (SIP-ABA). For ABA-SIP rats, the first animal eliminated was in session 9, for SIP-ABA rats, the first animal eliminated was in session 26.



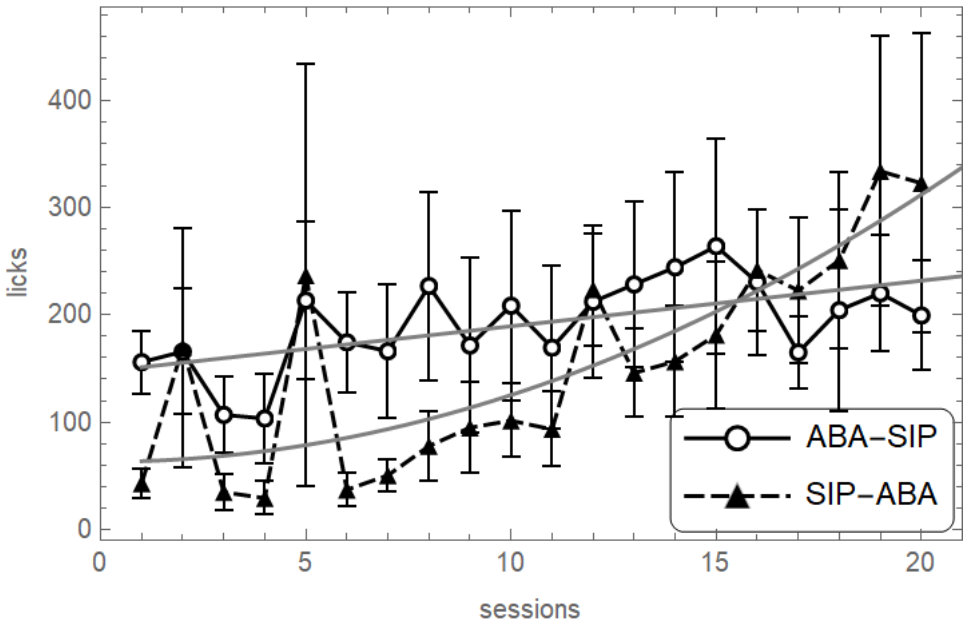
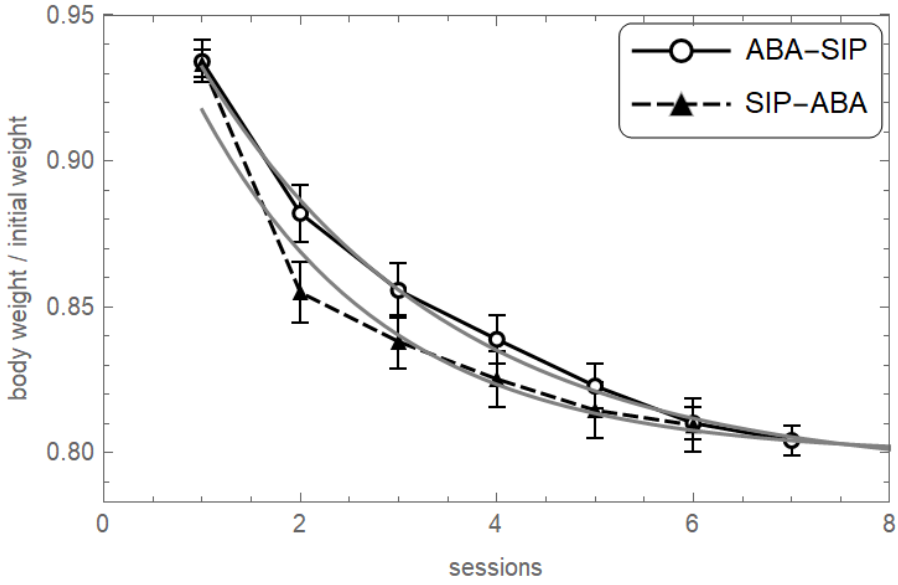
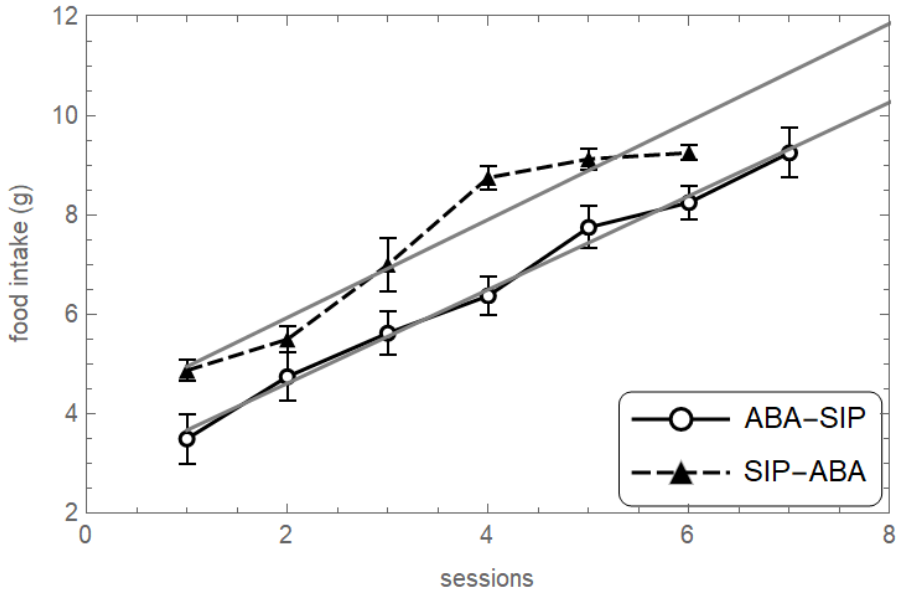



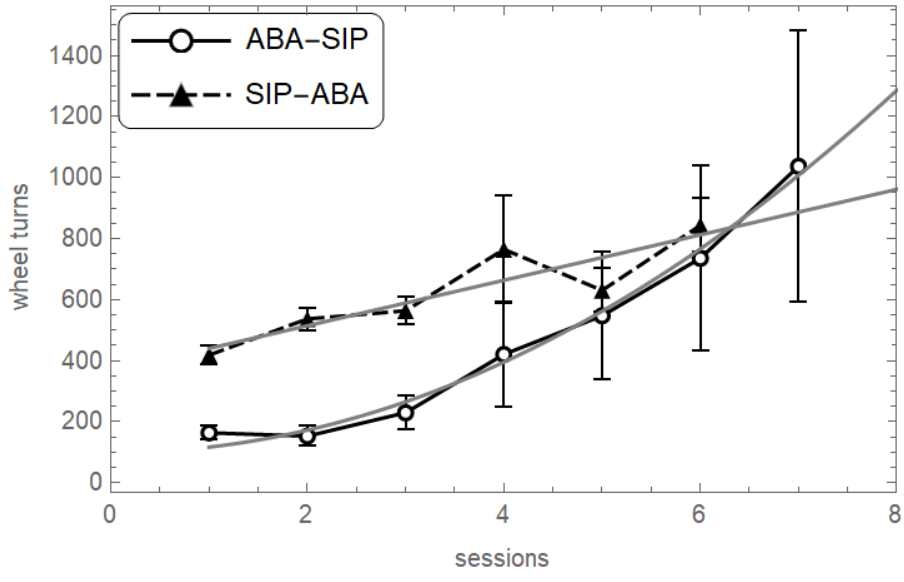

Figure 3. Water consumption and licks given to the bottle spout (mean ± SE) throughout the sessions of Experiment 2 in the two groups of rats that went directly through schedule-induced polydipsia (SIP-ABA) or who underwent it after a previous experience in activity-based anorexia (ABA-SIP).


0.95
0.90
0.85
0.80
body weight / initial weight
0
2
4
6
8
sessions
ABA–SIP
SIP–ABA

1


12
10
8
6
4
2
food intake (g)
0
2
4
6
8
sessions
ABA–SIP
SIP–ABA

2


1400
1200
1000
800
600
400
200
0
wheel turns
0
2
4
6
8
sessions
ABA–SIP
SIP–ABA

3

Figure 4. Relative body weight reduction, food consumption in grams, and turns on the activity wheel (mean ± SE), throughout the sessions of Experiment 2 and for the two groups of rats that went through ABA directly (ABA-SIP) or who underwent it after a schedule-induced drinking experience (SIP-ABA). For ABA-SIP rats, the first animal eliminated was in session 7, for SIP-ABA rats, the first animal eliminated was in session 6. Data first reported in Labajos and Pellón (2018).