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**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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**1 Abstract**

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

18

**19 Keywords**

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

## 1 Introduction

2

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

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

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

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

1 Falk (1961) after exposing hungry (but not thirsty) rats to an intermittent food  
2 reinforcement schedule with continuous access to a water bottle in the experimental  
3 chambers. Rats performed the operant response (lever pressing) that led to food  
4 reinforcers but also drank large amounts of water in connection to food pellet delivery.  
5 This excessive drinking was on occasions labelled “psychogenic polydipsia” (Falk,  
6 1969), but “schedule-induced polydipsia” (SIP) (Falk, 1966) was the term best accepted  
7 given its more descriptive nature. SIP is characterized by rats drinking little water  
8 immediately after the ingestion of each food pellet that appears intermittently, resulting  
9 in an excessive accumulation of liquid over the course of experimental sessions, which in  
10 case of Falk was of more than 3 hours.

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

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

1 (Gutiérrez-Ferre & Pellón, 2019; Riley et al., 1985; White, 1985). This wheel running has  
2 been found to interact with induced drinking (Penney & Schull, 1977; Roper, 1978;  
3 Staddon & Ayres, 1975; Wetherington & Riley, 1986). For example, Roper (1978) found  
4 a reduction in drinking rate when rats had the possibility to wheel run, which resumed  
5 when access to the wheel was blocked. This competition between drinking and wheel  
6 running indicates that both behaviors might be of the same nature. Furthermore, the  
7 temporal distributions of licks and turns along inter-food intervals seem to indicate some  
8 sort of cooperation among them (cf. Pellón & Killeen, 2015; Wetherington & Riley,  
9 1986).

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

18

## 19 **Experiment 1**

20

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

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

## 6 **Methods**

### 7 *Subjects*

8 Sixteen experimentally naïve male Wistar Han rats were the subjects of this study, being  
9 obtained from Charles River Laboratories (Lyon, France) with 60 days of age and having  
10 an approximate mean weight of 220 g (between 200 and 225 g) when they arrived at the  
11 animal facility in UNED. The animals were housed in groups of four subjects in plexiglass  
12 home cages (55 x 33 x 30 cm) in an environmentally controlled room at a temperature of  
13 21°C and 60% relative humidity, with a light/dark cycle of 08:00h/20:00h. All the rats  
14 were acclimatized to the usual conditions of the laboratory from the first day of their  
15 arrival, with chow food (Envigo, Barcelona, Spain) and water available at all times. At  
16 90 days of age, all rats were individually housed in plexiglass home cages (18 x 32.5 x  
17 20.5 cm) covered by an aluminum grid surface with two concave spaces where food and  
18 a water bottle were arranged, all ad libitum. They were then randomly divided into two  
19 groups (n=8 in each group), becoming the SIP-ABA and the ABA-SIP groups, according  
20 to the time sequence of the procedures that they would undergo. All care and experimental  
21 procedures were in accordance with the Spanish Royal Decree 53/2013 regarding the  
22 protection of experimental animals and with the European Union Council Directive  
23 2010/63. The UNED bioethics committee approved the experimental protocol.

1 *Apparatus*

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

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

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

### 3 *Procedures*

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

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

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



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

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

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

#### 6 *Data analysis*

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

$$12 \quad f(n) = a_0 + a_1n + a_2n^2 + a_3n^3 + a_4n^4 . \quad (1)$$

13 For each data set, we tried different fitting curves, for example, (1) as it is, or with  
 14  $a_3 = a_4 = 0$  (parabola), or with  $a_2 = a_3 = a_4 = 0$  (straight line), or other combinations  
 15 with at least one vanishing parameter. We also considered the generalized polynomial  
 16  $f(n) = a_0 + a_1n^{b_1} + a_2n^{b_2}$ , as it is or with  $a_2 = 0$ , as well as exponential or logarithmic  
 17 fits, which never gave better results than (1) except in one exponential case:

$$18 \quad f(n) = c_0 + c_1 \exp(c_2 n) . \quad (2)$$

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

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

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

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

## 11 **Results**

### 12 *Schedule-induced polydipsia*

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

23

*Insert Figure 1 about here*

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

#### 9 *Activity-based anorexia*

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

20 *Insert Figure 2 about here*

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

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

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

## 17 **Discussion**

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

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

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

19

## 20 **Experiment 2**

21

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

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

## 12 **Methods**

### 13 *Subjects*

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

1 protection of experimental animals and with the European Union Council Directive  
2 2010/63. The UNED bioethics committee approved the experimental protocol.

### 3 *Apparatus*

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

### 5 *Procedures*

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

### 12 *Data analysis*

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

## 16 **Results**

### 17 *Schedule-induced polydipsia*

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



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

5 *Insert Figure 3 about here*

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

### 13 *Activity-based anorexia*

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

21 *Insert Figure 4 about here*

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

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

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

## 11 Discussion

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

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

12

### 13 **General Discussion**

14

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

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

1 Levitsky & Collier, 1968). Gutiérrez-Ferre and Pellón (2019) have recently reaffirmed  
2 the induced nature of running in rats after intermittent exposure to food delivery when  
3 compared with massive food administration, and its modulation by the frequency of food  
4 reinforcement. If running can be induced by the reinforcement schedule similarly to  
5 drinking, and both show similar characteristics and functionality (cf. Killeen & Pellón,  
6 2013), then the results of the current study might show that running in the ABA  
7 phenomenon could (by analogy) be induced by the occurrence of food at regular intervals  
8 of time, albeit on the order of hours instead of seconds/minutes. This proposal was already  
9 advanced by Epling and Pierce (1992), although they did not provide much experimental  
10 evidence to support it.

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

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

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

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

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

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

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

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

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

10

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12

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16

## 17 **Open Practices Statement**

18

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

21

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23



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1 **Appendix.**

2

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

4

5

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

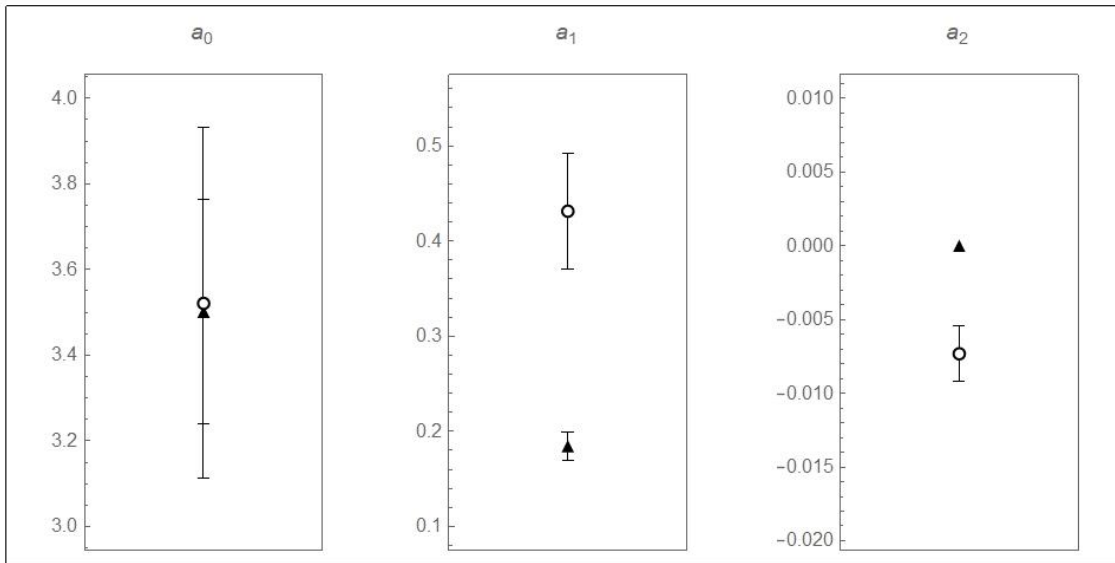
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7 Table A1. Best-fit parameters  $\pm$  standard error for schedule-induced drinking of SIP-

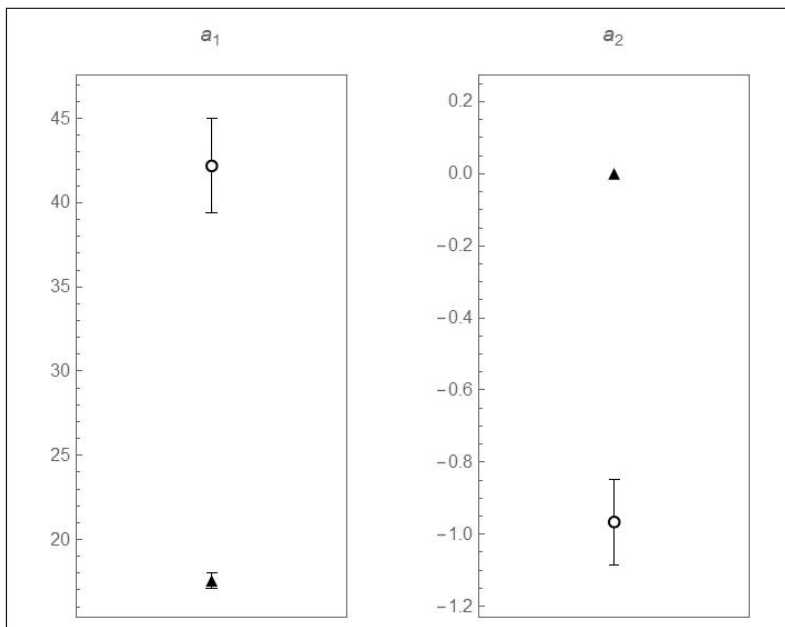
8 ABA and ABA-SIP groups in Experiment 1. Reported are only the parameters of the

9 curve (1) which are nonzero for at least one of the groups. An increasing number of

10 digits for the parameter values is shown.



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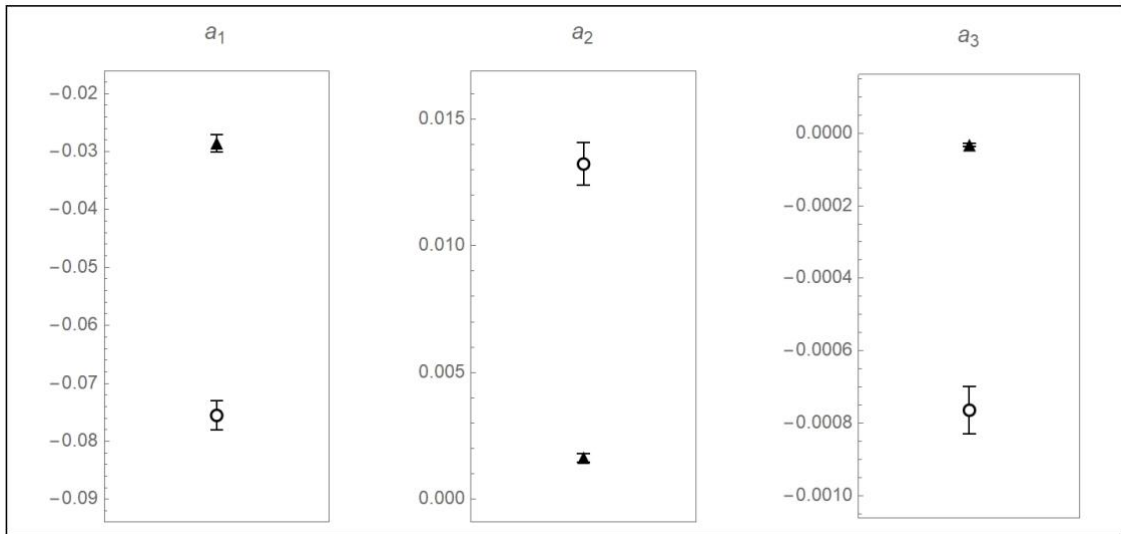
4 Figure A1. Comparison of the best-fit parameters for schedule-induced drinking of the  
 5 SIP-ABA group (black triangles) and the ABA-SIP group (white circles) in Experiment  
 6 1. Top panel: water consumption. Bottom panel: licks. Error bars are the SE calculated  
 7 for the best fit.

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

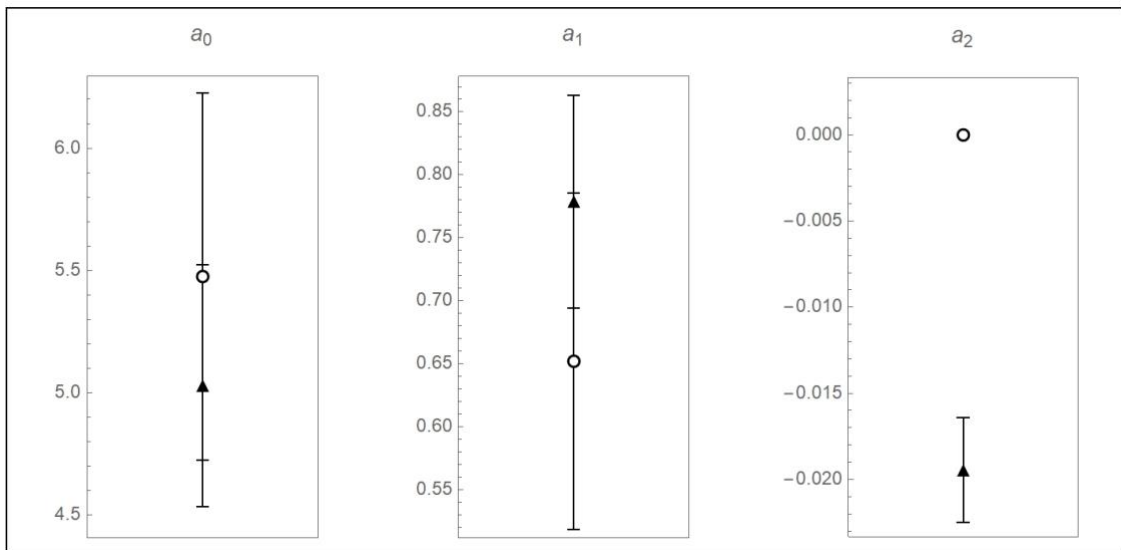
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2 Table A2. Best-fit parameters  $\pm$  standard error for activity-based anorexia of SIP-ABA  
3 and ABA-SIP groups in Experiment 1. Reported are only the parameters of the curve  
4 (1) which are nonzero for at least one of the groups. An increasing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

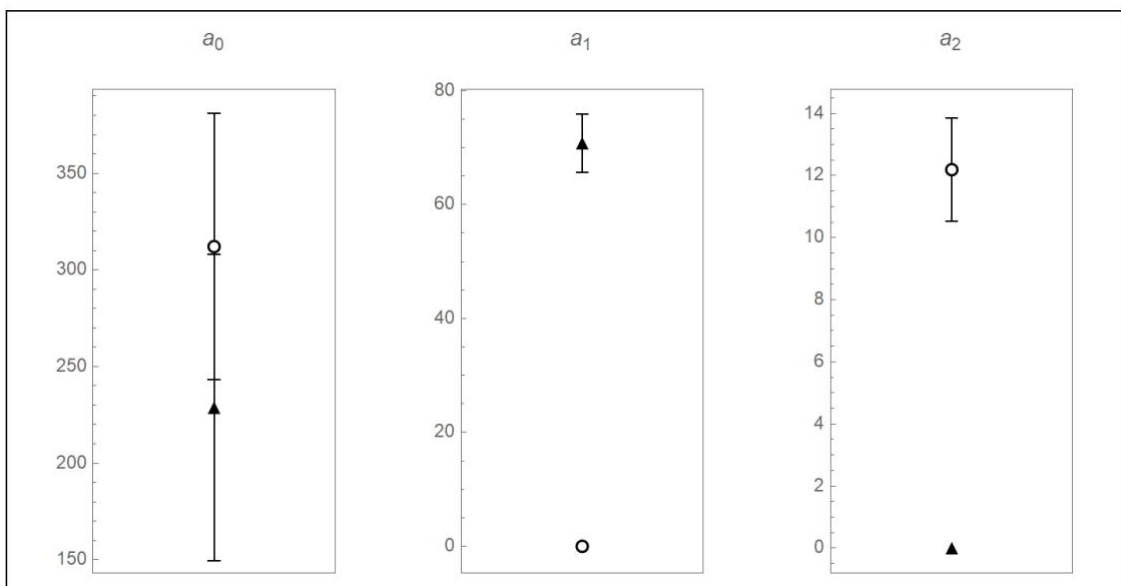
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2 Figure A2. Comparison of the best-fit parameters for activity-based anorexia of the SIP-

3 ABA group (black triangles) and the ABA-SIP group (white circles) in Experiment 1.

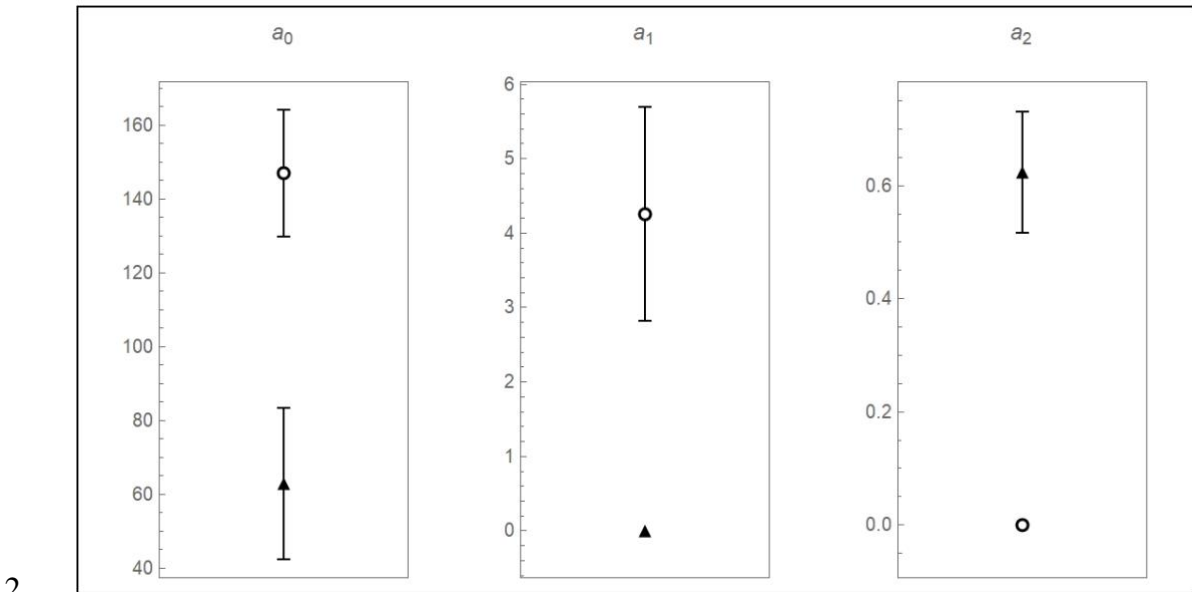
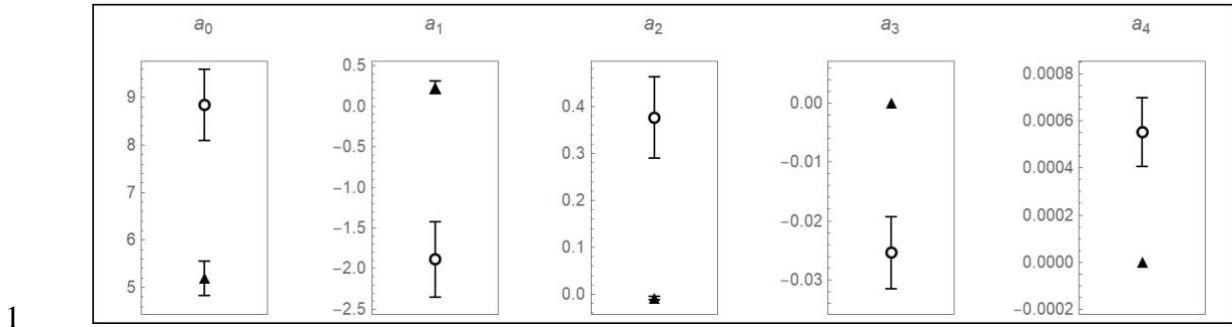
4 Top panel: relative body weight loss. Middle panel: food intake. Bottom panel: wheel

5 turns. Error bars are the SE calculated for the best fit.

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

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



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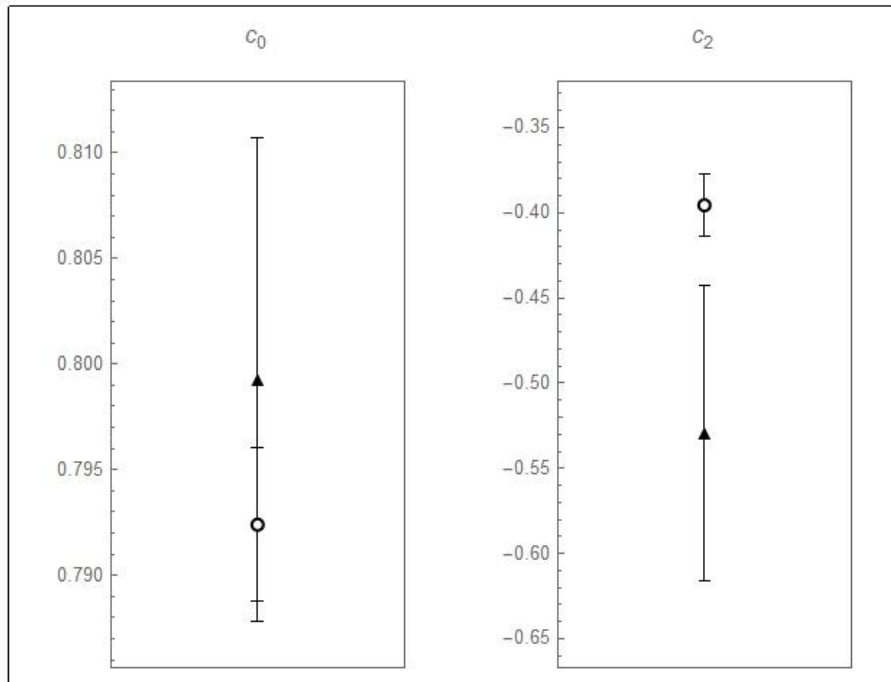
4 Figure A3. Comparison of the best-fit parameters for schedule-induced drinking of the  
 5 SIP-ABA group (black triangles) and the ABA-SIP group (white circles) in Experiment  
 6 2. Top panel: water consumption. Bottom panel: licks. Error bars are the SE calculated  
 7 for the best fit.



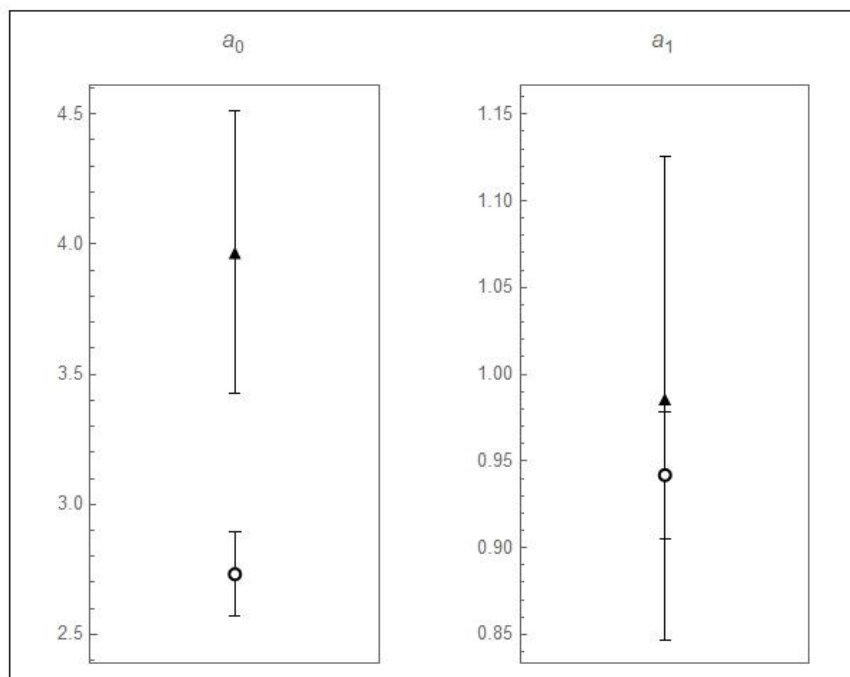
	Weight SIP-ABA	Weight ABA-SIP
$c_0$	$0.799 \pm 0.011$ ( $p = 10^{-7}$ )	$0.792 \pm 0.004$ ( $p = 10^{-11}$ )
$c_1$	$1 - c_0$	$1 - c_0$
$c_2$	$-0.529 \pm 0.087$ ( $p = 0.004$ )	$-0.395 \pm 0.018$ ( $p = 10^{-6}$ )
	Food intake SIP-ABA	Food intake ABA-SIP
$a_0$	$3.97 \pm 0.54$ ( $p = 0.002$ )	$2.73 \pm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

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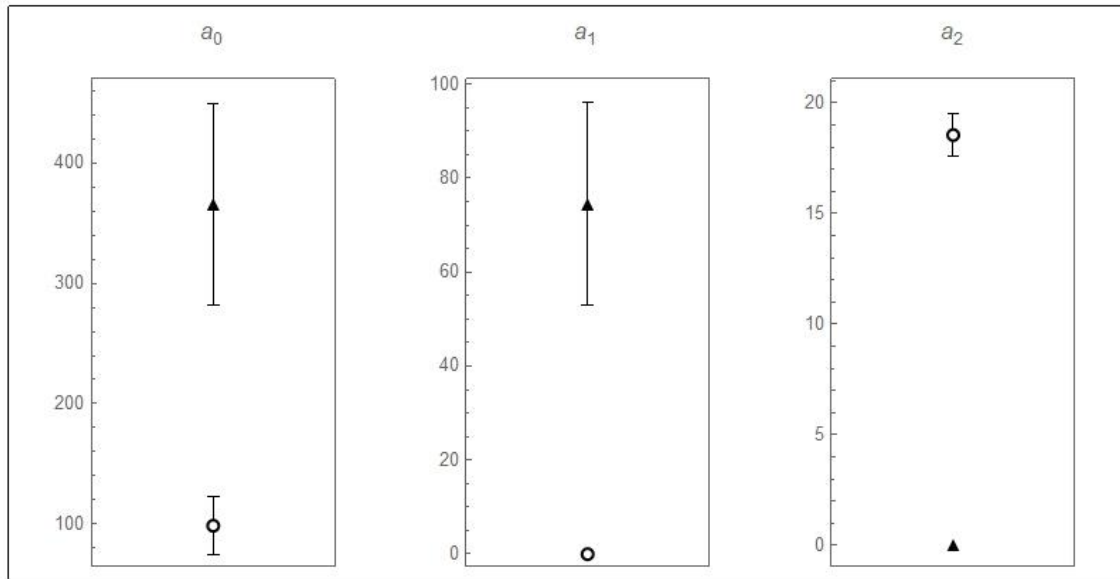
2 Table A4. Best-fit parameters  $\pm$  standard error for activity-based anorexia of SIP-ABA  
3 and ABA-SIP groups in Experiment 2. We report only the parameters of the curves (1)  
4 and (2) which are nonzero for at least one of the groups. An increasing number of digits  
5 for the parameter values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



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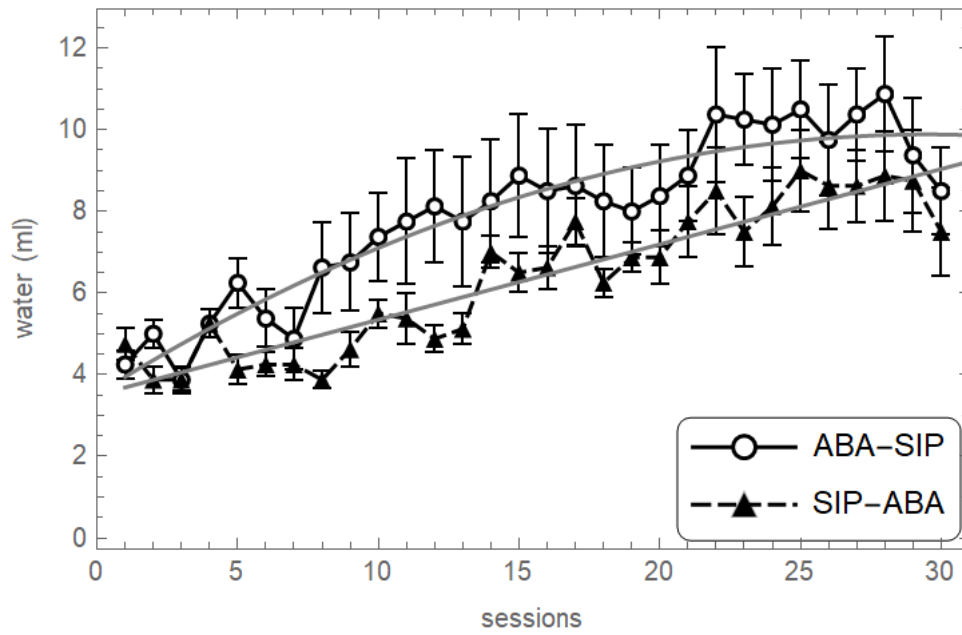
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3 Figure A4. Comparison of the best-fit parameters for activity-based anorexia of the SIP-

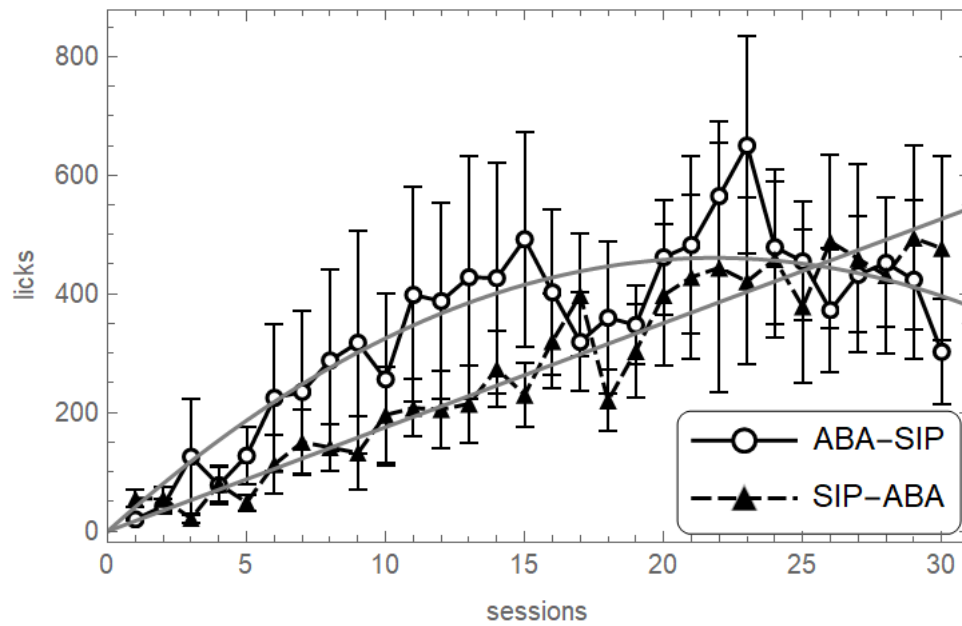
4 ABA group (black triangles) and the ABA-SIP group (white circles) in Experiment 2.

5 Top panel: relative body weight loss. Middle panel: food intake. Bottom panel: wheel

6 turns. Error bars are the SE calculated for the best fit.



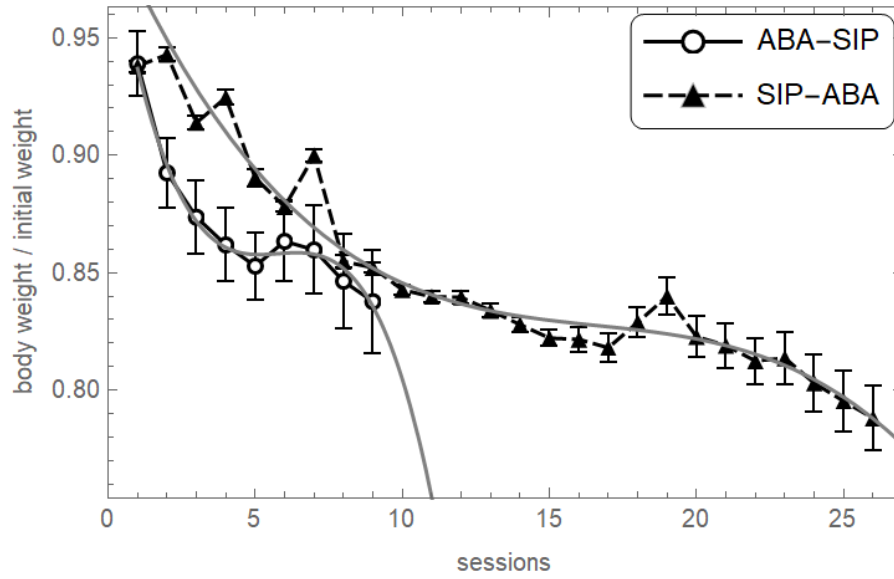
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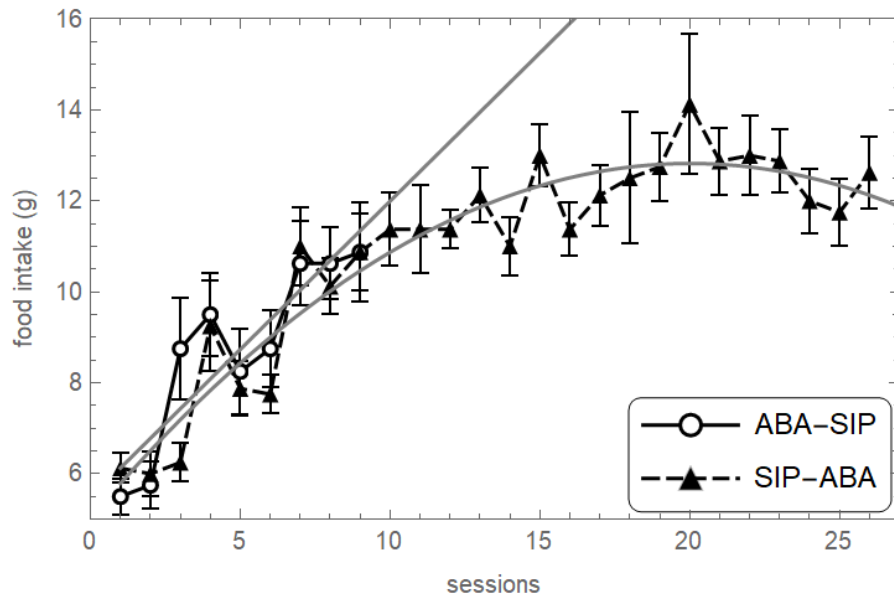
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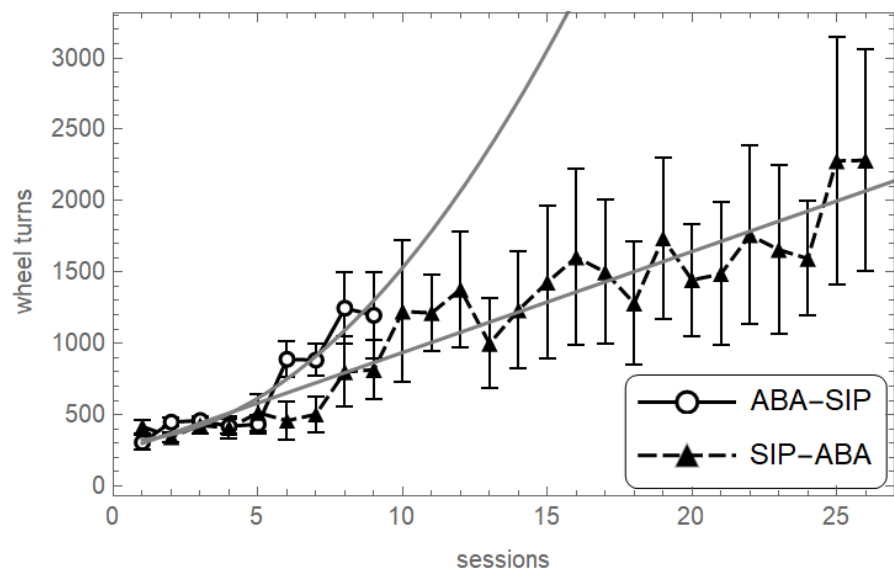
4 Figure 1. Water consumption and licks given to the bottle spout (mean  $\pm$  SE) throughout  
 5 all sessions of Experiment 1 in both groups of rats that went directly through schedule-  
 6 induced polydipsia (SIP-ABA) or who did so after a previous experience of activity-based  
 7 anorexia (ABA-SIP).



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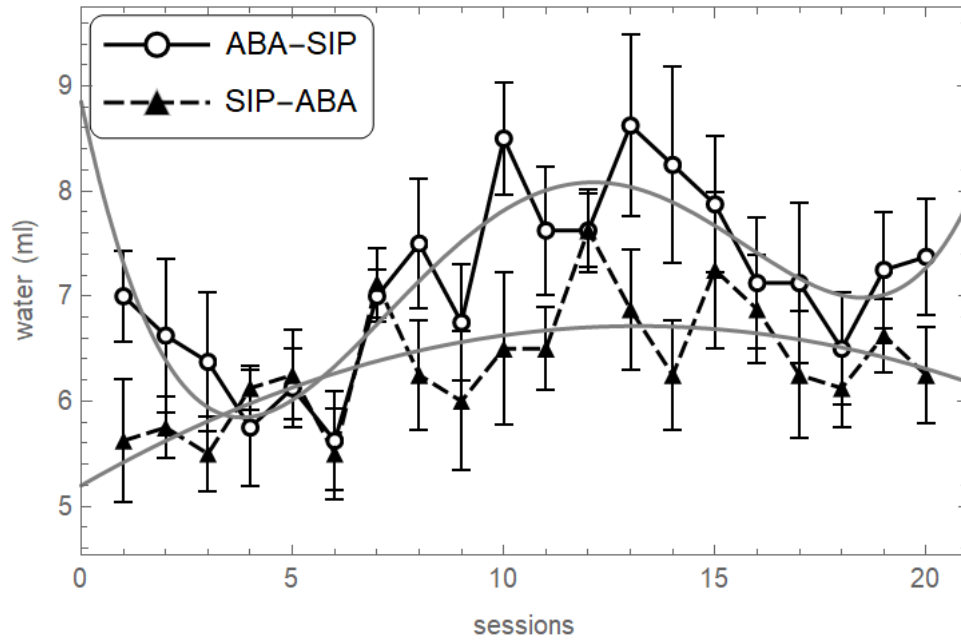
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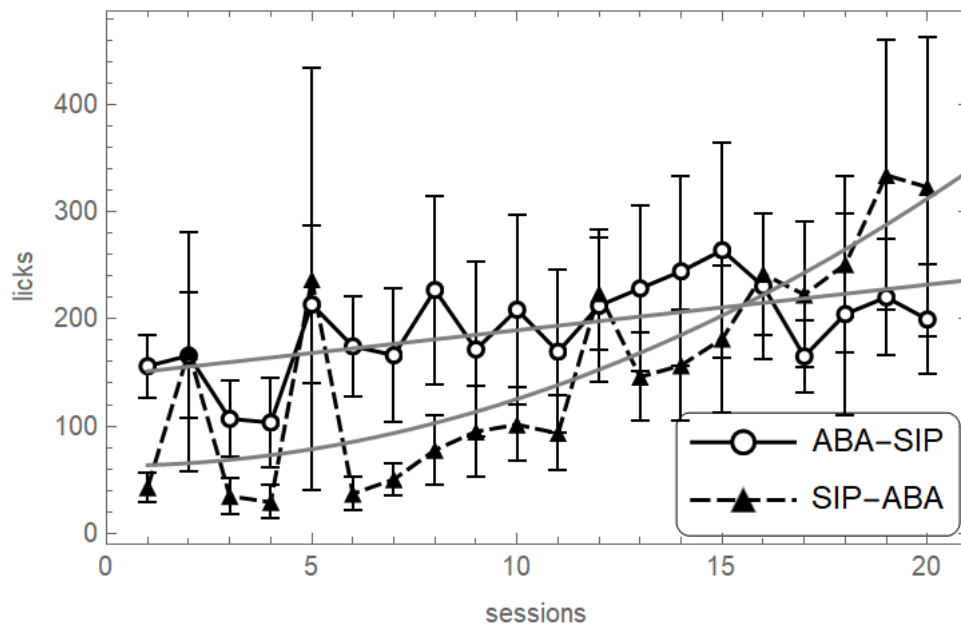
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2 Figure 2. Relative reduction of body weight, food consumption in grams, and turns on the  
3 activity wheel (mean  $\pm$  SE), throughout the sessions of Experiment 1 and for the two  
4 groups of rats that went through ABA directly (ABA-SIP) or who underwent it after a  
5 schedule-induced drinking experience (SIP-ABA). For ABA-SIP rats, the first animal  
6 eliminated was in session 9, for SIP-ABA rats, the first animal eliminated was in session  
7 26.



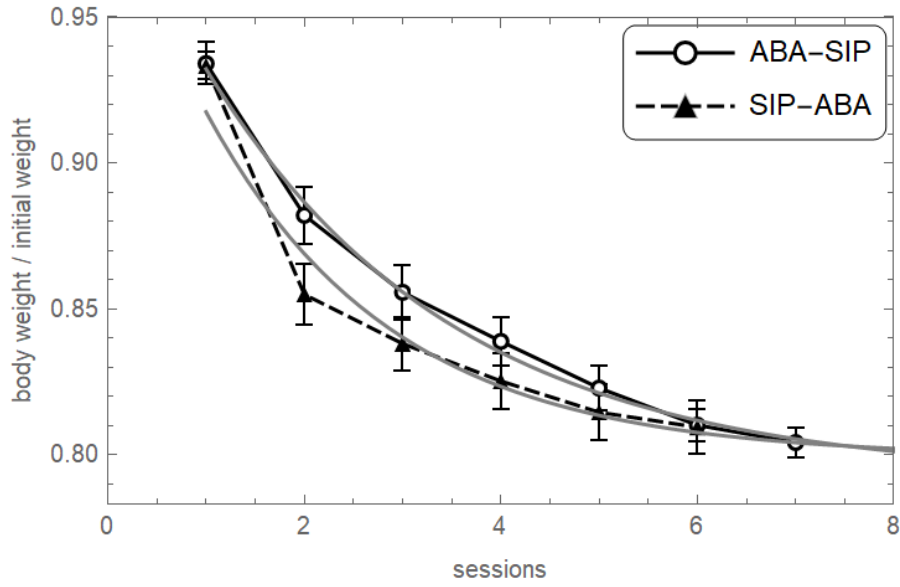
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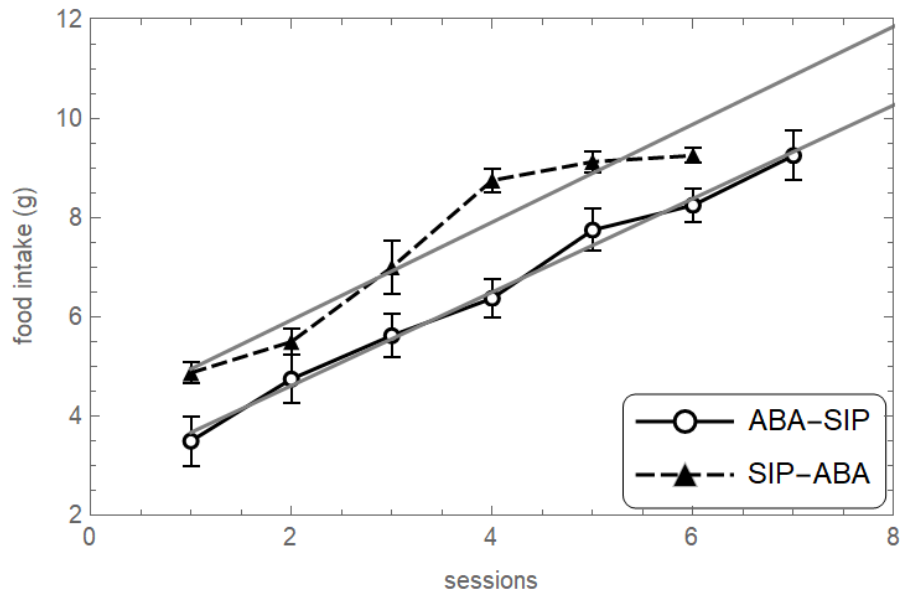
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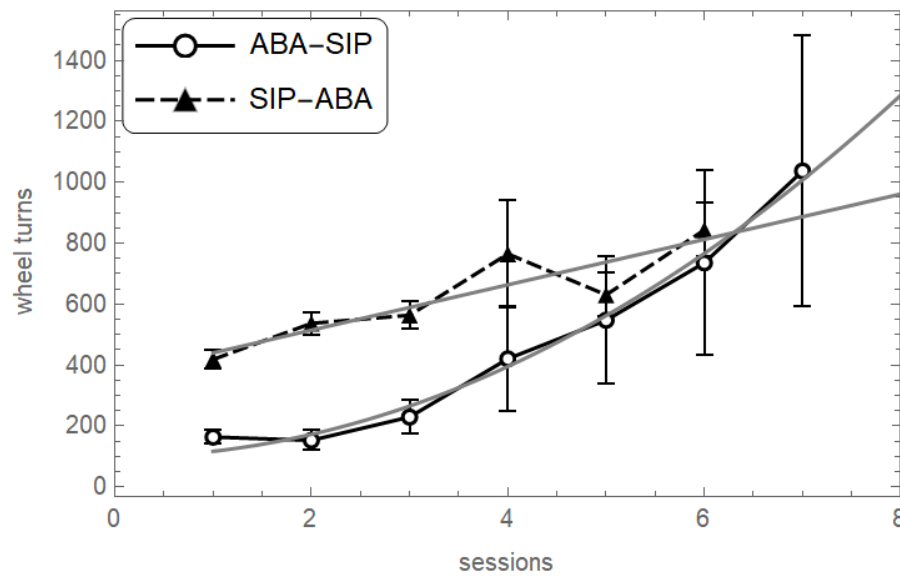
4 Figure 3. Water consumption and licks given to the bottle spout (mean  $\pm$  SE) throughout  
 5 the sessions of Experiment 2 in the two groups of rats that went directly through schedule-  
 6 induced polydipsia (SIP-ABA) or who underwent it after a previous experience in  
 7 activity-based anorexia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



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