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Research article

Open field exposure facilitates recovery from an aversive emotional event: Involvement of adrenergic and cholinergic transmitter systems

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HIGHLIGHTS

- Exposure to an open field after frustration accelerated recovery from frustration.
- The open field effect was blocked by the cholinergic agonist scopolamine.
- The open field effect was blocked by the nonselective β blocker propranolol.
- Exposure to novelty is a valuable treatment for recovery from incentive loss.

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ABSTRACT

Successive negative contrast (SNC) is an incentive relativity procedure that has been widely used to model emotional reactivity in rodents. The reward downshift experienced during SNC is thought to result in frustration. The exploration of a novel open field (OF), a complex situation involving stress induction and novelty detection, can enhance or block the acquisition of associative and non-associative memories. Previous experiments found a modulatory effect of OF, applied before downshift trials, on SNC. This schedule, however, can affect retention performance by influencing attentional, motivational, motor or sensory-perceptual mechanisms at training or retention testing. The use of post-training OF exposure avoids these confounds. This work assessed the effect of OF exposure after the acquisition of the downshifted memory, with the goal of targeting the consolidation of this mnemonic trace. We also investigated the involvement of the cholinergic and adrenergic systems in this phenomenon. The results indicated that OF facilitates recovery from reward loss and that both transmitter systems, cholinergic and adrenergic, play a role in this effect of OF.

1. Introduction

Novelty exposure improves memory in human [1–3] and animals [4–7]. This effect, which in rats has been found throughout the lifespan [7–9] may be the result of novelty inducing long-term potentiation in the hippocampus, a marker of neural plasticity thought to contribute to memory formation [10–12]. The implications of these and other studies [i.e.,13] is that novelty may promote memory formation by acting upon the cascade of biochemical changes that are associated with long-term memory formation.

We have found that exploration of a novel environment (an open field, OF) modulates frustration responses [14–16]. Frustration can be defined as an emotional state generated by the omission or devaluation in the quantity or quality of an expected appetitive reward [17]. Many studies indicate that frustration exhibits emotional, behavioral, neuroendocrine and physiological correlates, which are analogous to those observed after the presentation or anticipation of aversive stimuli (e.g., exteroceptive nociceptive stimulation; 18–19). The adrenocorticotropic and corticosterone hormones are elevated in animals exposed to reward devaluation [20,21], and frustrated animals exhibit aggression, escape and sexual dysfunction [22–24], which can be inhibited by anxiolytics [25–27]. Frustration can be assessed with the successive negative contrast (cSNC) procedure. In this procedure, animals are

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repeatedly exposed to a highly concentrated sucrose solution (e.g., 32%) and, suddenly, they are exposed to a much less concentrated sucrose solution (e.g., 4%). These animals exhibit, when confronted with 4% sucrose, a lower consummatory response (i.e., lower intake of 4% sucrose) than animals always exposed to 4%, an effect taken as an index of frustration. Under this framework, the animals remember the 32% value of past sucrose, and the new reinforcer value pales in comparisons with that received earlier, thus resulting in avoidance and frustration [28–32]. In other words, the detection of a significant negative discrepancy between expected and actual rewards triggers a comparison between actual and anticipated (i.e., retrieved from memory) incentive values. This experimental model provides a window for the assessment of emotional memory [33–35].

In a previous study from our lab, OF exposure inhibited the expression of cSNC when timed 1 h, but not immediately before, the first downshift trial [14]. OF did not affect sucrose intake in control, un-frustrated animals. In other words, a violation in the expectation of reward was needed to observe the effect of novelty. The OF effect was blocked by the nonselective β blocker propranolol (PROP) or by the cholinergic antagonist scopolamine (SCOP), administered either before or after the OF [15,16]. The noradrenergic and cholinergic transmitters systems are heavily involved in learning and memory processes [36,37], and modulate novelty-induced arousal [38,39].

It is still unknown if OF exposure alters the consolidation of the downshifted memory. To this end, in the present study we applied the OF after the first encounter with the downshifted solution. The use of post-training OF exposure minimizes potentially confounding effects of this treatment, upon attentional, motivational, motor or sensory-perceptual mechanisms at training or at testing [40]. We also hypothesized that OF modulation of this memory would depend on the integrity of the noradrenergic and cholinergic transmission [41].

2. Materials and methods

2.1. Experimental subjects

One hundred and twenty two male Wistar rats, born and reared at the vivarium of Instituto de Investigaciones Médicas Alfredo Lanari (IDIM-CONICET, Buenos Aires, Argentina) were used (Exp. 1:42 animals; Exp. 2:39 animals; Exp. 3:41 animals). The vivarium is kept at constant temperature (around 22 °C) and humidity (around 60–70%), and has a light-dark cycle of 12 h (lights on at 07:00 h).

The animals, which were approximately 100 days old at the start of the experiment, were individually housed and had ad libitum access to water. They were weighed daily and the average ad libitum weight was 380 g (range: 280–516 g). The amount of food was gradually reduced over 7 days until animals reached 85% of its ad libitum weight. This level of deprivation was maintained throughout the experiment by administering the appropriate amount of food at least 20 min after the end of the daily trial. Animals were kept under food deprivation for a total of 15 days.

2.2. Apparatus

The rats were given access to sucrose in five boxes (24 × 29 × 21 cm; MED Associates, St. Albans, VT, USA). The floor consisted of aluminum bars (0.4 cm diameter, 1.1 cm apart from center to center). In the center of a lateral wall was a 5 cm hole, 3.5 cm deep and 1 cm above the floor, through which a sipper tube could be manually introduced from the outside. When fully inserted, the sipper tube protruded 2 cm into the box. A photocell was located in front of the tip of the sipper tube inside this hole. Time in contact with the sipper (measured in 0.01 s increments) was automatically recorded by a computer that measured the cumulative amount of time that the photocell was activated during the trial. Previous studies that employed the sucrose concentrations used in the present experiments indicated that contact with the sipper exhibits a significant correlation with fluid intake [41]. Moreover, several studies have concurrently used contact with the sipper and fluid intake and yielded comparable results with either dependent variable [42–44]. Each box was enclosed in a sound and light attenuating cubicle that featured white noise and diffused light. Sucrose solutions (w/v) were prepared by mixing 320 or 40 g of commercial sugar in 1 l of tap water to obtain the final 32% and 4% sucrose solutions, respectively.

Four OF were used as means of exposure to novelty. They were made of grey acrylic (50 × 50 × 50 cm), and divided in 9 equal squares. They were located in the floor of the room. Animals were exposed to the regular ambient noise of the experimental room. The control animals that remained in the homecage were also exposed to environmental noises (i.e., white noise was only applied in the MED chambers). A light bulb (100 W) was suspended on top of the OF.

2.3. Behavioral procedures

After 7 days of food deprivation, the animals were exposed to the assigned sucrose concentration in their home cage. A habituation day was first conducted to attenuate taste neophobia. The water bottle was filled with 20 ml of the corresponding sucrose solution and made available for 40 min. The next day the cSNC, which was composed of two phases, began. (1) Pre-shift phase: The animals were exposed to the 32% or 4% sucrose solution 5 min each day for 5 days/trials. (2) Post-shift phase: Twenty-four hours after the last pre-shift trial, all rats had access to a 4% sucrose solution for 5 min each day for 3 days/trials. Responses to sucrose were tested in daily 5-min trials. Each trial began the first time the photocell was activated. After 5 min, the animal was taken to the housing cage, and the conditioning box was cleaned with a damp towel. A schematic design of each experiment can be found on top of each Figure.

OF exposure (duration: 5 min) was performed immediately after the first downshift trial (i.e., post-training exposure to novelty). Control (CTRL) and experimental animals were given similar handling and transportation from the housing to the experimental room. The only difference between the groups was that experimental, but not control, animals were exposed to the OF. Animals in the experimental group were gently placed in the center of the OF and allowed free exploration for 5 min; whereas controls remained in the homecage.

2.4. Drug administration

SCOP and PROP were administered immediately after OF or CTRL condition (according to the experimental condition) at a dose of 0.5 mg/kg or 4.5 mg/kg, respectively. The doses were selected from previous experiments [14–16]. Both drugs were purchased from Sigma Aldrich Laboratories (Buenos Aires, Argentina) and given intraperitoneally (i.p.) at a volume of 1.0 ml/kg (vehicle: physiological saline, 0.09, v/v).

2.5. Experimental designs

Across experiments, a between-subjects experimental design was used. The first Experiment employed a 2 (sucrose solution given during the pre-shift phase: 32% or 4%) × 2 (Treatment: exposure or not to the open field after the first shift trial; OF and CTRL

groups respectively) factorial design. Four groups were formed: 32-4/OF (group given 32% sucrose solution during pre-shift phase and exposed to OF immediately after the first shift trial); 32-4/CTRL (group given 32% sucrose solution during pre-shift phase and not exposed to OF); 4-4/OF (group given 4% sucrose solution during pre-shift phase and exposed to OF immediately after the first shift trial); and 4-4/CTRL (group given 4% sucrose solution during pre-shift phase and not exposed to OF).

Experiment 1, and previous work [14–16], indicated that sucrose acceptance was not affected in unshifted groups (i.e., those exposed to 4% sucrose in both phases), regardless OF exposure or drug (i.e., SCOP or PROP) treatment. As mentioned before, these groups were therefore discarded in Experiments 2 and 3, which evaluated the effect of SCOP and PROP administration on the OF effect. In these Experiments all animals were given 32% sucrose during pre-shift trials and 4% sucrose during post-shift trials.

Experiment 2 employed a 2 (Treatment: OF or CTRL) × 2 (Drug administration: Scopolamine, SCOP or Vehicle, VEH) factorial design. Four groups were formed: OF/SCOP, OF/VEH, CTRL/SCOP, CTRL/VEH.

Experiment 3 employed a 2 (Treatment: OF or CTRL) × 2 (Drug: Propranolol, PROP or Vehicle, VEH) factorial design. Four groups were formed: OF/PROP, OF/VEH, CTRL/PROP, CTRL/VEH.

In Experiments 2 and 3, the OF exposure took place after the first encounter with the downshifted solution and the drug administration was conducted immediately after the OF exposure.

2.6. Data analysis

Shapiro-Wilk and Levene's tests indicated that, across datasets, the assumptions of homogeneity of variance and normality were maintained. In each experiment time in contact with the sipper during the pre-shift and post-shift phases were independently analyzed via repeated measures (RM) Analysis of Variance (ANOVA). In Experiment 1 Sucrose Solution given during the post-shift (32 and 4%) and Treatment (OF and CTRL) were the between factors, whereas Trial (i.e., 1 to 5 in the pre shift, 6 to 8 in the post shift) was the RM. In Exp. 2 and 3 Treatment (OF and CTRL) and Drug (SCOP or PROP, depending on the Experiment, and VEH) were the between factors, whereas Trial (i.e., 1 to 5 in the pre shift, 6 to 8 in the post shift) was the RM.

OF exposure was videotaped for later scoring by 2 experimenters who were blind to the conditions of the subjects. These observers were provided with a written description of the behaviors to be quantified. A training meeting, which included practice with pre-recorded videos, was conducted before the actual measurement of the Experiment's records. The OF was divided into 9 squares. Frequency of entries into the peripheral and central squares and time spent in these areas were recorded. The goal was to assess potential alterations in anxiety response or in overall locomotor activity, after the downshift. Inter observer reliability was substantial and significant, $r(20) = 0.89$, $p < 0.0001$.

Post-hoc least-significant difference (LSD) pairwise comparisons were conducted to analyze significant main effects and significant interactions. The partial Eta square ($\eta 2p$) was utilized to estimate effect size. The alpha value was set at 0.05 and the SPSS software package was used to compute descriptive and inferential statistics.

3. Results

3.1. Analysis of time in contact with the sipper tube during phase 1 (Exp. 1 to 3)

The animals were exposed to the 32% (Exp. 1 to 3) or 4% (Exp. 1) sucrose solution 5 min each day for 5 days/trials. This pre-shift phase (i.e., "phase 1") was devoid of OF or pharmacological treatment, and was meant to facilitate the encoding of an appetitive memory. The statistical analyses yielded very similar results across Experiments. The ANOVAs yielded significant main effect of Trials [Experiment 1: $F_{4,152} = 176.62$, $p < 0.000$, ($\eta 2p = 0.823$), Experiment 2: $F_{4,140} = 155.47$, $p < 0.000$, ($\eta 2p = 0.816$); Experiment 3: $F_{4,148} = 192.12$, $p < 0.000$, ($\eta 2p = 0.839$)]. In Exp. 1 the Trials x Solution interaction also achieved significance [$F_{4,152} = 7.24$, $p < 0.000$, ($\eta 2p = 0.16$)]. Subsequent Post hoc comparisons indicated that the groups that had access to the 32% sucrose solution had a greater consummatory behavior in the first three trials than those that received the 4% sucrose solution [Trial 1 $F_{1,38} = 8.12$, $p < 0.007$; Trial 2 $F_{1,38} = 8.69$, $p < 0.005$; Trial 3 $F_{1,38} = 12.16$, $p < 0.001$]. The ANOVAs for Experiment 2 and 3 indicated the lack of significant main effects or significant interactions [Exp. 2: Treatment $p = 0.861$; Drug $p = 0.808$; Treatment x Drug $p = 0.650$; Trials x Drug $p = 0.983$; Trials x Treatment $p = 0.71$; Trials x Treatment x Drug $p = 0.19$; Experiment 3: Treatment $p = 0.508$; Drug $p = 0.976$; Treatment x Drug $p = 0.495$; Trials x Drug $p = 0.279$; Trials x Treatment $p = 0.715$; Trials x Treatment x Drug $p = 0.17$]. The subsequent sections describe the analyses only for the post shift phase of each Experiment.

3.2. Experiment 1. Open field attenuates frustration

The aim was to investigate the effect of OF exposure in the consolidation of an aversive memory induced by incentive downshift. Twenty-four hours after the last pre-shift trial, all rats had access to a 4% sucrose solution for 5 min each day, for 3 days (i.e., trials 6, 7 and 8). Half of the animals explored the open field (duration: 5 min) immediately after the end of the trial, while the other half remained untreated.

As shown in Fig. 1, the animals exposed to the downshift (i.e., groups 32-4) exhibited, when compared with controls always exposed to the 4% sucrose solution, an abrupt decrease in their consummatory behavior. The recovery from frustration, however, seemed to be much faster in those animals that explored the OF after the downshift than in those that remained untreated. The statistical analysis corroborated these impressions. The RM ANOVA yielded significant main effects of Solution [$F_{1,38} = 305.56$, $p < 0.000$ ($\eta 2p = 0.89$)], Treatment [$F_{1,38} = 18.51$ $p < 0.000$ ($\eta 2p = 0.328$)] and Trials [$F_{2,76} = 71.79$, $p < 0.0001$ ($\eta 2p = 0.654$)]. The following interactions were also significant: Solution x Treatment [$F_{1,38} = 13.01$, $p = 0.001$ ($\eta 2p = 0.255$)], Trials x Solution [$F_{2,76} = 89.35$, $p < 0.000$, ($\eta 2p = 0.702$)], Trials x Treatment [$F_{2,76} = 30.37$, $p < 0.000$ ($\eta 2p = 0.44$)], and Trials x Solution x Treatment [$F_{2,76} = 23.84$, $p < 0.0001$ ($\eta 2p = 0.386$)].

The Post hoc analyses indicated similar level of time in contact with the sipper tube (s) during trial 6 (post-shift) in 32-4/CTRL and 32-4/OF groups ($p > 0.05$). Across trials, time in contact with the sipper in these groups was significantly lower than that observed in un-shifted (i.e., 4-4/CTRL and 4-4/OF) groups, a result indicative of cSNC [Trial 6 $F_{1,38} = 375.87$, $p < 0.000$; Trial 7: $F_{1,38} = 202.38$, $p < 0.000$; Trial 8: $F_{1,38} = 156.95$, $p < 0.000$]. The Post hoc analyses also indicated significantly greater time in contact with the tube (s) in the 32-4/OF than in the 32-4/CTRL group, during trials 7 and 8 of post-shift [Trial 7: $F_{1,38} = 42.41$, $p < 0.000$; Trial 8: $F_{1,38} = 112.89$, $p < 0.000$]. It has been suggested that, during the trials after the first encounter with the downshifted sucrose solution (i.e., trials 7 and 8 of post-shift in the present study), the animals progressively recovery from frustration [34]. Under this theoretical framework, the animals exposed to OF in Experiment 1 had a faster recovery from frustration than control counterparts given the downshift but devoid of OF exposure.

The ANOVAs for behavioral activity during OF exposure (frequency of entries and time spent in the peripheral and central areas of the OF) indicated the lack of significant main effects (entries

Groups	Trials 1-5	Trial 6	Trials 7-8
4-4/CTRL	4%	4% → CTRL	4%
4-4/OF	4%	4% → OF	4%
32-4/CTRL	32%	4% → CTRL	4%
32-4/OF	32%	4% → OF	4%

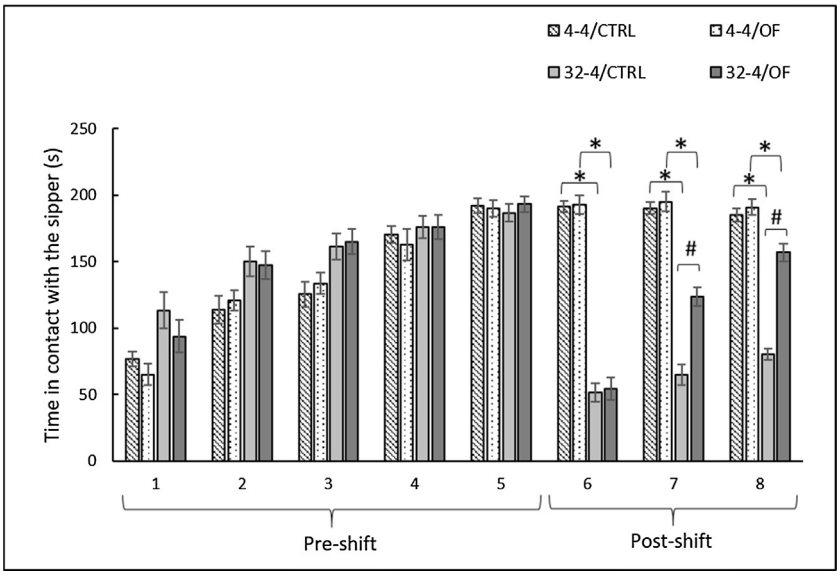

Fig. 1. Time in contact with the sipper tube (s) in animals exposed to consummatory successive negative contrast, in Experiment 1. During the pre-shift, animals were given 5 daily, 5-min trials of access to 4 or 32% sucrose. During the post-shift, the animals received three 3 daily, 5-min trials (i.e., trials 6, 7 and 8) of access to a 4% sucrose solution. Animals were given a single exposure to an open field (OF) immediately after the first downshift trial (OF Groups) or were left in their homecages after the downshift (CTRL group). Four experimental groups were thus defined according to the pre-shift solution consumed and the open field exposure: 32-4/OF (n = 12), 32-4/CTRL (n = 12), 4-4/OF (n = 8), 4-4/CTRL (n = 10). The asterisk indicates significant differences between 4 and 4/OF vs. 32-4/OF groups, or between 4 and 4/CTRL vs. 32-4/CTRL groups ($p < 0.0001$). The pound indicates significant differences between 32 and 4/OF and 32-4/CTRL groups ($p < 0.0001$). Vertical lines represent SEM.

Table 1
Frequency of entries into the peripheral and central squares of the open field and time spent in each of these areas, in the 4-4/OF and 32-4/OF groups. *r* = Inter observer reliability.

Behavior	4-4/OF group	32-4/OF group	*r*
Peripheral squares entries (frequency)	57 ± 4.14	58 ± 2.48	0.97
Time spent in peripheral squares (s)	285.48 ± 2.46	283.64 ± 2.63	0.89
Central squares entries (frequency)	3.5 ± 0.5	3.25 ± 0.75	0.90
Time spent in central squares (s)	6.67 ± 2.14	8.33 ± 2.36	0.89

into peripheral squares $p = 0.832$, time spent in peripheral squares $p = 0.626$, entries into central squares $p = 0.798$, time spent in central squares $p = 0.62$; see descriptive data at Table 1). It seems that the downshift did not affect the exploration of the OF.

3.3. Experiment 2. Scopolamine antagonizes the OF effect on frustration

After establishing that OF exposure modulates the consolidation of frustration, Experiment 2 assessed if this effect of novelty could be inhibited by the cholinergic receptor antagonist SCOP. The drug was given after OF exposure, during the first downshift trial.

Experiment 2 replicated the main finding of Experiment 1; i.e., OF exposure facilitated recovery from frustration. Perhaps more important, SCOP administration blocked this effect of OF [see Fig. 2]. These impressions were corroborated by the ANOVA, which yielded a significant main effect of Trial [$F_{2,70} = 208.78$, $p < 0.0001$, ($\eta 2p = 0.856$)]; and significant Trial x Treatment [$F_{2,70} = 12.17$, $p < 0.0001$, ($\eta 2p = 0.258$)]; Trial x Drug [$F_{2,70} = 16.41$, $p < 0.0001$, ($\eta 2p = 0.319$)]; Treatment x Drug [$F_{1,35} = 7.61$, $p < 0.009$, ($\eta 2p = 0.179$)] and Trial x Drug x Treatment [$F_{2,70} = 12.41$, $p < 0.0001$, ($\eta 2p = 0.262$)] interactions.

The Post hoc tests indicated that all groups exhibited similar level of time in contact with the sipper during trial 6 of the post-shift. During trials 7 and 8 of post shift phase the OF/VEH group had greater sucrose acceptance than the CTRL/VEH group [Trial 7: $F_{1,35} = 19.56$, $p < 0.0001$; Trial 8: $F_{1,35} = 9.85$, $p < 0.003$], and effect that was antagonized by SCOP [OF/VEH vs OF/SCOP; Trial 7: $F_{1,35} = 27.62$, $p < 0.0001$; Trial 8: $F_{1,35} = 9.88$, $p < 0.003$].

3.4. Experiment 3. Propranolol antagonizes the OF effect on frustration

We hypothesized that the OF effect on frustration would depend on secretion of epinephrine. This was examined by administering PROP after the rats were exposed to the OF on the first downshift trial. PROP is a drug that impedes epinephrine binding to peripheral β-adrenergic receptors.

As can been seen in Fig. 3, all groups exhibited similar level of time in contact with the sipper (s) in trial 6 (post-shift). Twenty-four hours later, in trial 7 (post-shift), those animals that explored the OF after the first-downshift exhibited greater consummatory behavior than untreated counterparts. This effect of OF seemed to be absent in animals given OF followed by PROP. The ANOVA yielded main effects of Treatment [$F_{1,37} = 7.81$, $p < 0.008$, ($\eta 2p = 0.174$)] and Trials [$F_{2,74} = 75.91$, $p < 0.0001$, ($\eta 2p = 0.672$)]. The two-way interaction between Trial and Drug [$F_{2,74} = 5.91$, $p < 0.004$, ($\eta 2p = 0.138$)]; and Treatment and Drug [$F_{1,37} = 4.43$, $p < 0.04$, ($\eta 2p = 0.107$)] also

Groups	Trials 1-5	Trial 6	Trials 7-8
CTRL/VEH	32%	4% → CTRL → VEH	4%
CTRL/SCOP	32%	4% → CTRL → SCOP	4%
OF/VEH	32%	4% → OF → VEH	4%
OF/SCOP	32%	4% → OF → SCOP	4%

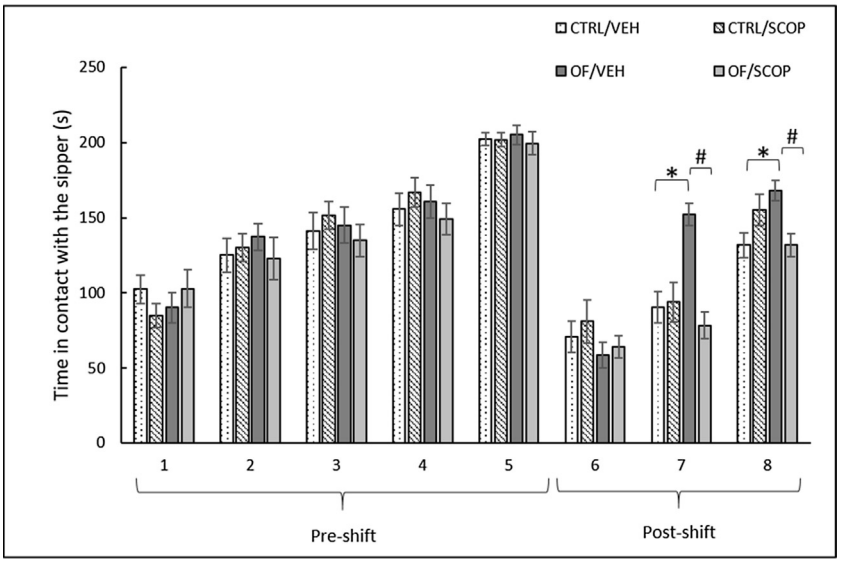

Fig. 2. Time in contact with the sipper tube (s) in animals exposed to incentive downshift, in Experiment 2. During the pre-shift animals were given 5 daily, 5-min trials of access to 32% sucrose. During the post-shift animals received three 3 daily, 5-min trials of access to a 4% sucrose solution. Animals were given a single exposure to an open field immediately after the first downshift trial (OF Groups) or were left in their homecages before the downshift (CTRL group). Immediately after OF exposure the subjects were administered scopolamine (0.5 mg/kg, SCOP) or vehicle (VEH). Four experimental groups were thus defined according to the open field exposure and drug administration: CTRL/VEH (n = 10), CTRL/SCOP (n = 9), OF/VEH (n = 10), OF/SCOP (n = 10). The asterisk indicates significant differences between CTRL/VEH and OF/VEH groups ($p < 0.0001$). The pound indicates significant differences between OF/VEH and OF/SCOP groups ($p < 0.003$). Vertical lines represent SEM.

achieved significance. The Trial x Drug x Treatment three-way interaction [$F_{2,74} = 4.89$, $p < 0.01$, ($\eta 2p = 0.117$)] was significant as well.

The Post hoc tests corroborated that, during trial 7 of post-shift, the animals in the OF/VEH group exhibited greater sucrose acceptance than counterparts in groups OF/PROP [$F_{1,37} = 17.22$, $p < 0.0001$] or CTRL/VEH [$F_{1,37} = 15.1$, $p < 0.0001$]. The difference between OF/VEH and CTRL/VEH also achieved significance in trial 8 of post-shift [$F_{1,37} = 10.42$, $p < 0.003$]. These results confirm, yet again, that animals that explore the OF recover faster from frustration. Novel information is that PROP blocked the facilitating effect of OF, underscoring the involvement of the adrenergic system in this effect.

4. Discussion

The present set of experiments assessed the effect of OF exploration on consolidation of an emotional, hedonically aversive, event (i.e. frustration). The results indicated that exposure to the novel OF facilitates recovery from the aversive situation. Findings from Experiment 2 and 3 indicate that epinephrine and acetylcholine are involved in this effect of OF exposure.

An influential theory of frustration postulates that, in downshift trials, animals acquire two different memories: an egocentric memory of the negative emotional event (the emotional memory of the aversive internal state formed during and after the first downshift trial) and an allocentric memory that updates the new, less preferred incentive [the incentive memory from environmental events external to organism; see 45–46]. Treatments that are administered after the downshift trial could enhance the egocentric memory or interfere with the allocentric memory, in either case a suppression of consummatory behavior would be expected. Whereas treatments that interfere with the egocentric memory and enhance allocentric memory should facilitate the recovery from frustration and enhances consummatory behavior [45,46]. According to this theory, the OF employed in the present study falls under the umbrella of treatments that interfere with the egocentric memory and enhance the allocentric memory. The fast recovery from incentive downshift may depend, at least partially, on a memory update that encodes the 4% sucrose solution in place of the 32% received during the pre-shift phase [47]. An alternative explanation takes into account that incentive disengagement and redirection of behavior to other sources of reward have been described as some of the strategies used by mammals in a situation of frustration [35]. Under this framework, exploration of the open field just after the devaluation event could have stimulated either of these behaviors and therefore facilitated the recovery from the aversive situation. The effect of OF could also be classified as a retroactive interference: post-training presentation of the OF altered the effects of the downshift. According to this, OF modulated memory consolidation, a process by which labile memories become persistent [48].

It has been proposed that novel stimuli elicit a learning signal, triggering exploration and facilitating neuroplasticity [49,50]. More in detail, these and other authors suggested that unpredicted stimuli (such as the OF environment used in the present study) trigger exploration likely to facilitate access to new resources (i.e., food, mates). Therefore, these stimuli hold adaptive significance and may thus gain preferential status for memory encoding [51].

Groups	Trials 1-5	Trial 6	Trials 7-8
CTRL/VEH	32%	4% → CTRL → VEH	4%
CTRL/PROP	32%	4% → CTRL → PROP	4%
OF/VEH	32%	4% → OF → VEH	4%
OF/PROP	32%	4% → OF → PROP	4%

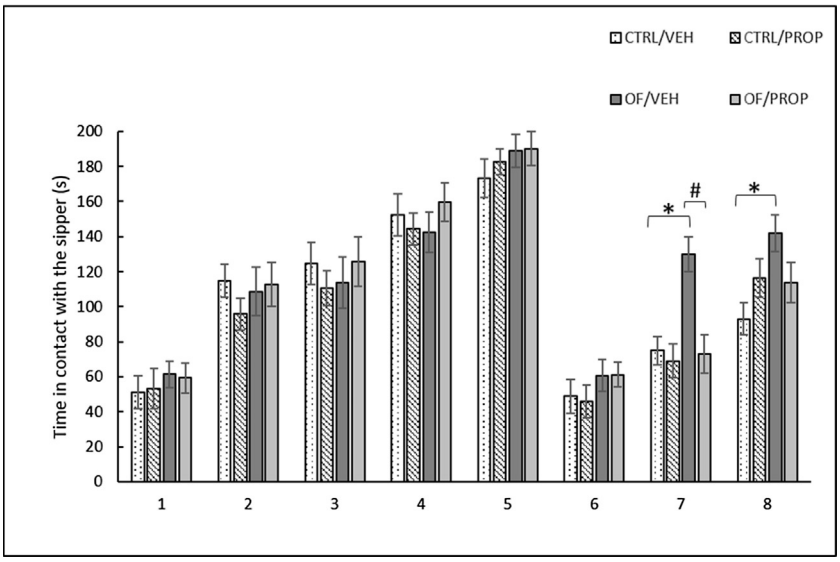

Fig. 3. Time in contact with the sipper tube (s) in animals exposed to incentive downshift, in Experiment 3. During pre-shift animals were given 5 daily, 5-min trials of access to 32% sucrose. During the post-shift animals received three 3 daily, 5-min trials of access to a 4% sucrose solution. Animals were given a single exposure to an open field immediately after the first downshift trial (OF Groups) or were left in their homecages before the downshift (CTRL group). Immediately after OF exposure the subjects were administered propranolol (4.5 mg/kg, PROP) or vehicle (VEH). Four experimental groups were thus defined according to the open field exposure and drug administration: CTRL/VEH (n = 10), CTRL/PROP (n = 10), OF/VEH (n = 10), OF/PROP (n = 11). The asterisk indicates significant differences between CTRL/VEH and OF/VEH groups ($p < 0.003$). The pound indicates significant differences between OF/VEH and OF/PROP groups ($p < 0.0001$). Vertical lines represent SEM.

This is consistent with the finding that novelty facilitates LTP in the hippocampus, thus favoring the storage of information [51]. It could be hypothesized that, in the present experiments, the OF triggers exploration and helps encode the allocentric memory with the new, updated value, of sucrose [45,46].

Also related to our last point, it should be noted that the transient increase in arousal or attention, usually observed after novelty exposure, exerts a range of positive effects on ongoing tasks [2,52]. Novelty exposure increases neural plasticity and reward processing, facilitates the encoding of visual memory, enhances perception and motivation and decreases the latency of several behavioral responses [2]. In the present experiments, the temporal event near to exploration is the downshift situation, and the increase in arousal due to OF could potentiate the memory of the 4% sucrose solution, achieving that this memory fixated strongly and therefore accelerated recovery.

The explanations put forward for the present findings attribute an important role to the arousal and behavioral activation induced by OF exposure. These effects are likely mediated by increased noradrenergic activity in medial prefrontal cortex, medial striatum, basolateral amygdala and hippocampus [39,53–55]. The cholinergic system has also been associated to novelty's effect on learning [49,50]. Specifically, acetylcholine levels in the cortex and hippocampus have been observed to be greater in rats exposed to a novel open field than in control counterparts [56–59]. The results of the present study are congruent with these previous research. Administration of PROP or SCOP blocked OF effects on frustration recovery, without exerting significant effects on their own.

Many of life's stressful life events involve reward loss, such us death or separation from loved ones, retirement, jail, or losing a job, among others [35,46,60]. It is important, therefore, to develop treatments that facilitate recovery from incentive loss. The complexity of incentive relativity phenomena, however, is a major challenge for research. The present study represent progress towards developing an animal model suitable for testing the putative role of novelty, and its underlying neural machinery, as a treatment for these conditions.

5. Conclusions

Rats that explored an OF after the induction of frustration exhibited a faster recovery from this situation. This effect was block by the administration of antagonists of the cholinergic and adrenergic system. The present results consolidate the notion that exposure to novelty represents a simple, yet valuable behavioral treatment for recovery from incentive loss.

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