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Cholinergic transmission underlies modulation of frustration by open field exposure

Mariana Psyrdellis [a], Ricardo Marcos Pautassi [b], Alba Mustaca [a,c], Nadia Justel [a,*]

[a] Laboratorio de Psicología Experimental y Aplicada (PSEA), Instituto de Investigaciones Médicas (IDIM), Consejo Nacional de Investigaciones Científicas y Técnicas (CONICET), Universidad de Buenos Aires (UBA), Argentina
[b] Instituto de Investigación Médica M. y M. Ferreyra (INIMEC), CONICET, Universidad Nacional de Córdoba (UNC), Argentina
[c] Universidad Abierta Interamericana (UAI), Argentina

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ABSTRACT

Frustration can be defined as an emotional state generated by the omission or devaluation in the quantity or quality of an expected appetitive reward. Thus, reactivity to a reward is affected by prior experience with the different reinforcer values of that reward. This phenomenon is known as incentive relativity, and can be studied by different paradigms. Although methodologically simple, the exploration of a novel open field (OF) is a complex situation that involves several behavioral processes, including stress induction and novelty detection. OF exposure can enhance or block the acquisition of associative and non-associative memories. These experiments evaluated the effect of OF exploration on frustration and the role played by the cholinergic system in this phenomenon. OF exploration before first or second trial of incentive downshift modulated the expression of frustration. This effect of OF was blocked by the administration of scopolamine either before or after OF exploration. These results indicate that the cholinergic system is involved in the acquisition and consolidation of OF information.

1. Introduction

Frustration is an emotional reaction found after a given expectation is violated (Amsel, 1962). This emotional state can be assessed in laboratory animals through the consummatory successive negative contrast paradigm (cSNC; Flaherty, 1996; Justel et al., 2012a,b; Papini et al., 2015; Ruetti et al., 2009). In a cSNC animals that have had extensive access to an appetitive, highly sweetened sucrose solution (e.g., 32%), are suddenly exposed to a devaluation of this expected reward (e.g. they are given a 4% sucrose solution). Animals that experience this switch exhibit a sudden drop in sucrose acceptance, suggesting they evaluate the value of the current reinforcer against the reactivated memory of the previously experienced reward. These animals show several neurobiological alterations, including enhanced corticosterone release (Flaherty et al., 1985) and alterations in opioid transmission (Pellegrini et al., 2005). Aggressive behavior is significantly enhanced after the shift (Papini et al., 2006), whereas sexual and social behaviors are severely affected (Freidin and Mustaca, 2004; Mustaca et al., 2000). Altogether, this evidence suggests that the cSNC is a reliable model for assessing frustration responses. It has been suggested that the experimental frustration resulting from cSNC induces emotional, cognitive behavioral, neuroendocrine, and physiological effects that are similar to those induced by the anticipation or presentation of exteroceptive nociceptive stimuli (Amsel, 1962; Daly, 1969; Gray, 1987; Konorsky, 1964; Papini et al., 2006; Ruetti et al., 2009).

The cSNC is modulated by several behavioral and pharmacological treatments, including neonatal stress (Ruetti et al., 2010), sexual contact (Freidin and Mustaca, 2004; Freidin et al., 2005), and by drugs that act on GABA (Becker and Flaherty, 1982; Kamenetzky et al., 2008; Justel et al., 2012a,b), opioid (Pellegrini et al., 2005; Wood et al., 2005) and cannabinoid receptors (Genn et al., 2004; for a review see Papini et al., 2015; Justel et al., 2014a).

Animals exposed to a novel environment, but not those accustomed to it, exhibit several behavioral reactions, including stress and novelty detection responses (Thiel et al., 1998). Novelty exposure, in turn, is a potent modulator of memory processes. For instance, Liu et al. (2015) found facilitated extinction of fear conditioning in animals that had been exposed to a novel environment 1 h before extinction (also see Menezes et al., 2015). An earlier study revealed greater appetitive learning in invertebrates when training sessions occurred in a novel environment (Kemenes and Benjamin, 1994).

Given this background, it should not be a surprise that the exploration of a novel open field (OF) can enhance or block memory acquisition

* Corresponding author at: Laboratorio de Psicología Experimental y Aplicada (PSEA), Instituto de Investigaciones Médicas (IDIM), CONICET, Universidad de Buenos Aires, Combatientes de Malvinas 3150, PB, 2do cuerpo, Buenos Aires, CABA, Argentina.
E-mail addresses: nadiajustel@gmail.com, nadiajustel@conicet.gov.ar (N. Justel).

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(Justel and Psyrdellis, 2014; Myskiw et al., 2014), depending on factors such as timing of treatment (e.g., before or after learning acquisition or testing; Blake et al., 2011; Boccia et al., 2005; Izquierdo and McGaugh, 1985, 1987; Netto et al., 1985; Yang and Tang, 2011). Altogether, it seems that novelty exposure – as delivered via application of OF – can be used as a useful tool for the analysis of memory acquisition, consolidation, and retrieval (Izquierdo et al., 2003).

It has been recently found that exposure to an OF 1 h, but not immediately before the first downshift trial (from 32% to 4% sucrose solution), inhibited the expression of cSNC (Justel et al., 2014b). On the other hand, exposure to the OF prior to the second downshift trial enhanced the frustration effect (Justel et al., 2014c). OF did not affect sucrose intake when the frustration effect was absent, i.e. a violation in the expectation of reward was needed to observe the effect of novelty. Both effects were blocked by the nonselective beta blocker propranolol, administered either before or after the OF (Justel et al., 2014c). The first and second post-shift trials of cSNC are functionally different and seemed to reflect primary or unconditional frustration and conditioned frustration, respectively (Amsel, 1992). Several studies indicate that pharmacological or behavioral treatments affect behavior differently when given during each trial (Becker, 1986; Becker and Flaherty, 1982, 1983; Flaherty, 1990; Flaherty et al., 1997; Pellegrini et al., 2005; Wood et al., 2005; for a review Ruetti and Justel, 2010).

Our previous work (Justel et al., 2014b, 2014c) indicated that the exploration of an OF prior to the first or second encounter with the devaluated solution modulates the expression of cSNC, and pinpointed the role played by the noradrenergic system in the phenomenon. The aim of the present study was to evaluate the role of the cholinergic system in the OF effect on frustration, during the first and second encounter with the downshifted sucrose solution. The effect of administering scopolamine hydrochloride (SCOP), a muscarinic cholinergic antagonist, immediately *before* OF exposure was analyzed in Experiments 1 and 3. Experiments 2 and 4, in turn, examined the effect of SCOP administered *after* the OF experience. These manipulations were meant to affect the acquisition and consolidation of the OF-related memory, respectively.

The central cholinergic system has been implicated in learning and memory processes (Klinkenberg and Blokland, 2010; McGaugh and Roozendaal, 2002, 2009; Robinson et al., 2011) and particularly in the facilitating effects of novelty exposure on memory acquisition. 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 (Aloisi et al., 1997; Giovannini et al., 1998; Thiel et al., 1998; Popovic et al., 2015). While the vast majority of the research has reported SCOP-induced memory impairments (Klinkenberg and Blokland, 2010), some have indicated a facilitation of memory after SCOP administration (Roldan et al., 2001). Popovic et al. (2015) administered SCOP immediately after the acquisition of a step-through passive avoidance task. A SCOP-induced memory impairment was found when animals were tested 24 h after the training (i.e. rats given SCOP exhibited shorter latencies than controls to step-through to the compartment associated with the electric shock). SCOP treated animals, however, exhibited significantly higher latency to step-through to the compartment when the test was performed 48 h after the training trial. In other words, under these circumstances SCOP administration resulted in better memory retention. Another study exposed animals to a novel, nose-poking task during consolidation of an avoidance task. SCOP administration in-between tasks impaired acquisition of the nose-poke task but spared the consolidation of the avoidance learning (Blake et al., 2011).

Based on previous results, the hypotheses were that the OF applied before the first or second downshift trial would exert opposite effects on frustration (inhibition and facilitation, respectively). It was relatively uncertain whether SCOP would facilitate or block these effects (Blake et al., 2012; Izquierdo and McGaugh, 1985; Popovic et al., 2015; Roldan et al., 2001).

2. Materials and methods

2.1. Experimental subjects

Two hundred and twenty male Wistar rats, born and reared at the vivarium of Instituto de Investigaciones Médicas Alfredo Lanari (IDIM-CONICET, Buenos Aires, Argentina) were used. The animals, which were approximately 120 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 361 g (range: 274–496 g). The amount of food was gradually reduced over 7 days until animals reached 85% of its ad libitum weight. All animals reached the target weight by day 7. 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. Thus, animals were kept under food deprivation for a total of 15 days. Animals were maintained in a light–dark cycle of 12 h (lights on at 07:00 h). The housing and testing rooms were maintained at a constant temperature (around 22 °C) and humidity (around 60–70%).

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 (Mustaca et al., 2002). Moreover, several studies have concurrently used contact with the sipper and fluid intake and yielded comparable results with either dependent variable (Papini et al., 1988; Papini and Pellegrini, 2006; Riley and Dunlap, 1979). 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 open fields were used as means of exposure to novelty. They were made of gray 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 (i.e., no white noise was employed). A light bulb (100 W) was suspended on top of the apparatus to provide illumination.

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. The water bottle was filled with 20 mL of the corresponding sucrose solution and made available for 40 min. This procedure was intended to attenuate taste neophobia. 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. This phase was meant to facilitate the encoding of an appetitive memory. (2) Post-shift phase: 24 h 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. After the post-shift phase

the experiment was considered completed. The specific groups and schematic design of each experiment are described on top of each Figure.

OF exposure (duration: 5 min) was performed 1 h before the first or second downshift trial (depending on the experiment). Control (CTRL) and experimental animals were given similar handling and transportation. 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 apparatus and allowed free exploration for 5 min; whereas controls remained in the homecage.

2.4. Drug administration

SCOP (CAS Number 6533–68-2; Sigma Aldrich, Buenos Aires, Argentina) was diluted in physiological saline (0.09, v/v) and administered intraperitoneally (dose: 0.0, 0.1, 0.5 or 1.0 mg/kg; volume: 1.0 mL/kg; vehicle: physiological saline), immediately after or 20 min before OF or CTRL condition (according to the experiment and to the experimental condition).

2.5. Experimental designs

In Experiments 1 to 4 all animals were given 32% sucrose during pre-shift trials and 4% sucrose during post-shift trials. The first Experiment employed a 2 (treatment: exposure or not to the open field; OF and CTRL groups respectively) × 4 (drug: 0.0, 0.1, 0.5 or 1.0 mg/kg SCOP) factorial design. Eight groups were formed: OF/VEH; OF/0.1; OF/0.5; OF/1.0, CTRL/VEH; CTRL/0.1, CTRL/0.5 and CTRL/1.0.

Experiment 1 allowed the selection of the most effective SCOP dose, in terms of affecting cSNC (i.e., 0.5 mg/kg).Thus, Experiments 2 to 4 employed a 2 (treatment: OF or CTRL) × 2 (drug: 0.5 or 0.0 mg/kg SCOP) factorial design. Four groups were formed: OF/SCOP, OF/VEH, CTRL/SCOP, CTRL/VEH.

In Experiments 1 and 2 animals were exposed to the OF in the first trial with the downshifted solution and SCOP was given 20 min before (Exp. 1) or immediately after (Exp. 2) OF exposure. In Experiments 3 and 4 animals were exposed to the OF in the second post shift trial and SCOP was given 20 min before (Exp. 3) or immediately after (Exp. 4) OF exposure. In each Experiment groups were composed by a minimum of 7 and a maximum of 10 animals.

In Experiment 5 the animals had access to 4% sucrose, in every trial. In the 6th trial the animals received SCOP or vehicle and 20 min after they explored the OF (duration: 5 min) or remained in their homecages. Animals were only exposed to 4% sucrose in trials 7 and 8 (i.e., no OF exposure or SCOP administration occurred in these trials). Four groups were thus created: OF/SCOP, OF/VEH, CTRL/SCOP, CTRL/VEH. This experiment analyzed the possibility that SCOP exerted unspecific enhancing or decreasing effects in sucrose intake behavior. Prior studies have shown that SCOP can alter consumption of a 4% sucrose solution (Flaherty and Meinrath, 1979). Moreover, in Experiments 1–4 OF exposure occurred 1 h before the downshift trials and SCOP was given immediately before or immediately after OF. It was, therefore, conceivable that SCOP could have had an independent effect in sucrose acceptance.

2.6. Data analysis

The data sets were tested for normality and homogeneity of variance through Shapiro-Wilk and Levene's tests, respectively. The results indicated that the assumptions of homogeneity 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). Treatment (OF and CTRL) and Drug were the between factors, whereas Trial (1 to 5 in the pre shift, 6 to 8 in the post shift) was the RM.

In the first experiment, OF exposure was videotaped for later scoring by 2 experimenters who were blind to the conditions of the subjects. Inter observer reliability was substantial and significant, as revealed by Pearson product moment correlation coefficient, $r(11) = 0.95$, $p < .01$. Entries into any of the squares (total entries) and entries into the central square (central entries) were recorded. The goal was to assess potential unspecific effects of SCOP. A one way ANOVA was used to analyze these measures.

Post-hoc least-significant difference (LSD) pairwise comparisons were conducted to analyze significant main effects and significant interactions. The partial Eta square (η^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 during phase 1 (Experiments 1 to 5)

The analyses yielded very similar results across Experiments. The ANOVAs yielded significant main effect of Trials, which indicated that all groups gradually increased their time in contact with the sipper (s) throughout this phase, Experiment 1: $F(4, 248) = 90.49$, $p < 0.0001$, (η^2p = 0.59); Experiment 2: $F(4, 140) = 56.58$, $p < 0.0001$, (η^2p = 0.62); Experiment 3: $F(4, 140) = 84.5$, $p < 0.0001$, (η^2p = 0.71); Experiment 4: $F(4, 112) = 81.59$, $p < 0.0001$, (η^2p = 0.74); Experiment 5: $F(4, 148) = 36.57$, $p < 0.0001$, (η^2p = 0.49). Across experiments there was no main effect of treatment, drug or significant interactions (Table 1). The subsequent sections, therefore, describe the analyses only for post shift phase of each Experiment. Means and standard errors for time in contact with the sipper (s) in each Experiment are depicted in Figs. 1 to 5.

3.2. Experiment 1: scopolamine's effect on OF acquisition in the first trial of incentive downshift

In this Experiment SCOP was given 20 min before OF exposure, during the first downshift trial. The aim was to assess SCOP effects during the acquisition of the OF-related memory during the first downshift trial.

OF exposure inhibited the expression of devaluation. This effect, which replicates earlier findings by Justel et al. (2014b, 2014c), was blocked by the administration of SCOP prior to OF exposure. The magnitude of this effect was fairly similar across the different doses employed (Fig. 1). These impressions were corroborated by the statistical analysis. The ANOVA for post-shift scores yielded a significant main effect of Drug $F(1, 61) = 9.67$, $p < 0.0001$ (η^2p = 0.32), Trials $F(2, 122) = 55.36$, $p < 0.0001$ (η^2p = 0.48), a significant Trials x Treatment interaction $F(2, 122) = 3.73$, $p < 0.03$ (η^2p = 0.027) and Treatment x Drug interaction $F(1, 61) = 6.84$, $p < 0.0001$ (η^2p = 0.25). *Post hoc* tests were used to analyze the Treatment x Drug interaction. These analyses indicated that, throughout the post-shift phase, scopolamine treatment did not affect the behavior of the groups not exposed to the open field ($p > 0.05$). On the other hand, time in contact with the sipper among subjects exposed to the OF was significantly higher in vehicle treated rats (i.e., OF/VEH group) than in counterparts given any dose of SCOP (i.e., groups OF/0.1, OF/0.5 and OF/1.0). The difference between group OF/1.0 and group OF/0.5 was also significant ($p < 0.05$). The *post hoc* employed to analyze the Trials x Treatment interaction indicated a significant difference between OF and CTRL groups in trial 6 ($p > 0.05$).

The corresponding ANOVA indicated that central or total entries into the OF were not affected by SCOP treatment ($p > 0.05$, data not shown), thus indicating that SCOP did not affect exploration of the OF.

In this experiment there was an interfering effect of OF upon incentive downshift. This replicates previous findings from Justel et al. (2014b, 2014c). New and important information is that this effect was completely blocked by SCOP administration 20 min before OF

Table 1
Contact with the sipper (s) during the pre-shift phase as a function of trial (pre-shift trial 1 to 5) and Experiment (1 to 4), in each experimental group. Values are expressed as means ± SEM.

Exp	Group	Trial 1	Trial 2	Trial 3	Trial 4	Trial 5
1	CTRL/0.1	119.57 ± 14.14	137.89 ± 12.25	156.29 ± 16.45	157.39 ± 12.84	182.83 ± 13.36
	CTRL/0.5	78.01 ± 12.75	124.95 ± 15.38	153.86 ± 11.36	161.10 ± 10.12	183.38 ± 8.77
	CTRL/1.0	93.09 ± 15.16	120.05 ± 9.80	139.86 ± 13.08	156.47 ± 14.05	191.51 ± 9.76
	CTRL/VEH	109.39 ± 9.75	135.09 ± 16.63	149.29 ± 16.34	169.09 ± 9.37	179.79 ± 9.76
	OF/0.1	82.99 ± 11.73	129.52 ± 12.67	131.92 ± 15.15	146.89 ± 16.71	170.12 ± 17.39
	OF/0.5	96.74 ± 10.33	131.59 ± 19.88	145.64 ± 19.28	173.46 ± 16.42	184.50 ± 13.05
	OF/1.0	108.28 ± 7.07	153.65 ± 11.16	158.17 ± 16.84	176.42 ± 11.86	185.43 ± 12.39
	OF/VEH	122.64 ± 9.44	146.60 ± 9.36	153.36 ± 8.37	153.28 ± 9.78	165.82 ± 12.47
2	CTRL/SCOP	94.93 ± 14.12	121.96 ± 12.31	149.83 ± 11.68	161.37 ± 8.06	179.55 ± 10.63
	CTRL/VEH	100.47 ± 19.29	125.78 ± 18.57	141.77 ± 18.19	146.10 ± 18.53	170.43 ± 21.97
	OF/SCOP	87.04 ± 13.99	126.56 ± 14.59	161.64 ± 15.88	176.52 ± 9.49	178.45 ± 11.37
	OF/VEH	92.29 ± 12.68	118.04 ± 10.44	141 ± 9.12	162.83 ± 9.16	172.98 ± 10.88
3	CTRL/SCOP	113.50 ± 14.04	137.82 ± 8.23	160.33 ± 12.01	180.16 ± 11.11	191.62 ± 12.46
	CTRL/VEH	96.64 ± 6.68	121.91 ± 11.61	153.52 ± 11.54	179.52 ± 13.88	187.90 ± 13.27
	OF/SCOP	106.63 ± 10.08	130.32 ± 10.54	165.84 ± 12.99	173.71 ± 12.79	195.25 ± 13.48
	OF/VEH	102.97 ± 8.89	122.57 ± 10.69	139.38 ± 9.37	170.89 ± 12.46	184.29 ± 14.47
4	CTRL/SCOP	48.63 ± 9.11	97.59 ± 12.12	125.08 ± 10.79	146.15 ± 6.57	142.72 ± 9.34
	CTRL/VEH	55.30 ± 11.68	88.34 ± 15.79	130.65 ± 13.27	144.69 ± 9.51	145.02 ± 14.45
	OF/SCOP	50.07 ± 9.71	100.43 ± 12.01	112.86 ± 6.01	159.89 ± 12.71	167.76 ± 9.24
	OF/VEH	53.39 ± 10.92	101.31 ± 9.09	129.53 ± 6.31	125.84 ± 6.38	153.36 ± 14.55
5	CTRL/SCOP	45.59 ± 11.37	82.16 ± 16.56	90.87 ± 11.88	90.31 ± 11.19	90.91 ± 10.91
	CTRL/VEH	40.54 ± 7.54	57.59 ± 9.7	98.49 ± 11.51	97.87 ± 12.88	100.14 ± 13.56
	OF/SCOP	34.59 ± 6.49	75.63 ± 9.23	95.92 ± 12.28	90.53 ± 10.96	91.73 ± 8.24
	OF/VEH	44.23 ± 3.14	65.15 ± 3.07	74.76 ± 2.48	90.97 ± 2.78	100.54 ± 2.17

exploration, a result suggesting the involvement of the cholinergic system in the OF effect on frustration.

3.3. Experiment 2. Scopolamine's effect on OF consolidation in the first trial of incentive devaluation

In this Experiment SCOP (0.0 or 0.5 mg/kg) was given during the first downshift trial, immediately after OF exposure. The aim was to modulate the consolidation of the OF related-memory.

As depicted in Fig. 2, OF exploration inhibited the contrast effect found in control animals. This blocking effect was reversed by the administration of the cholinergic antagonist. Specifically, animals in the OF/SCOP show a similar downshift in their consummatory behavior as the control groups not exposed to the apparatus. The ANOVA for the post-shift phase indicated significant main effects of Treatment [$F(1, 35) = 4.94$, $p < 0.03$ ($\eta^2p = 0.124$)], Drug [$F(1, 35) = 12.87$, $p < 0.001$ ($\eta^2p = 0.269$)], and Trials [$F(2, 70) = 66.46$, $p < 0.0001$ ($\eta^2p = 0.655$)]. The interactions between Treatment and Drug [$F(1, 35) = 13.55$, $p < 0.001$ ($\eta^2p = 0.279$)], between Trials and Treatment [$F(2, 70) = 8.07$, $p < 0.0001$ ($\eta^2p = 0.187$)], as well as the Trials x Treatment x Drug interaction [$F(2, 70) = 8.78$, $p < 0.0001$ ($\eta^2p = 0.20$)], also yielded a statistically significant effect. *Post Hoc* tests indicated similar level of contact with the sipper behavior across trials in both control groups (CTRL/SCOP and CTRL/VEH) ($p > 0.05$). These analyses also indicated significantly less time in contact with the sipper in CTRL/VEH subjects than in OF/VEH counterparts, in trials 6 and 7 ($p < 0.05$). Also, the differences between the OF/SCOP and the OF/VEH group achieved significance in trials 6, 7 and 8 ($p < 0.05$).

This experiment indicated that SCOP treatment, given immediately after OF exposure, blocked the interfering effect of OF exposure upon incentive downshift.

3.4. Experiment 3. Scopolamine's effect on OF acquisition in the second trial of incentive devaluation

In this Experiment SCOP was administered before OF exposure in the second downshift trial. As depicted in Fig. 3, the basic control condition (i.e., group CTRL/VEH) exhibited an abrupt decrement in its consummatory behavior in the first downshift session, but quickly recuperated and significantly increased its time in contact with the sipper (s) during the second post-shift session. This was not the case for the OF/VEH group, which kept exhibiting a contrast effect during the second trial with the downshifted solution, which replicates previous findings (Justel et al., 2014b, 2014c). Perhaps more important, this promoting effect of open field exposure upon negative contrast was antagonized by scopolamine. The analyses corroborated these impressions. The ANOVA indicated a significant main effect of Trials [$F(2, 68) = 89.43$, $p < 0.0001$, $\eta^2p = 0.72$], and significant Trials x Treatment [$F(2, 68) = 3.45$, $p < 0.04$, $\eta^2p = 0.092$], and Trials × Treatment × Drug [$F(2, 68) = 5.18$, $p < 0.009$, $\eta^2p = 0.132$] interactions. *Post hoc* tests indicated that all groups behaved similarly during the first post-shift session. Yet the CTRL/VEH group exhibited significantly greater sucrose acceptance than the OF/VEH group in the second trial with the downshifted sucrose solution ($p < 0.05$). Contact with the sipper in groups CTRL/VEH and OF/SCOP was statistically similar during the second trial. All groups exhibited similar scores during the third encounter with the devalued solution. The main implication of these results is that SCOP blocked the facilitating effect of OF on negative contrast, during the second post-shift (Justel et al., 2014b, 2014c).

3.5. Experiment 4. Scopolamine's effect on OF consolidation in the second trial of incentive devaluation

This experiment assessed, during the second downshift trial, the effect of SCOP on the consolidation of the open field related memory.

As depicted in Fig. 4, the data demonstrates that, during the second post-shift trial, animals that explored the OF and received VEH administration (OF/VEH group) exhibited less time in contact with the sipper (s) than those that explored the OF but were administered SCOP (OF/SCOP group) or than those spared from OF and SCOP treatment (i.e., CTRL/VEH group). The ANOVA for the post-shift phase yielded a significant main effect of Trials [$F(2, 56) = 113.3$, $p < 0.0001$ ($\eta^2p = 0.80$)], and significant interactions between Trials and Treatment [$F(2, 56) = 9.81$, $p < 0.0001$ ($\eta^2p = 0.26$)] and between Treatment and Drug [$F(1, 28) = 13.58$, $p < 0.001$ ($\eta^2p = 0.33$)]. Guided by our a priori hypothesis, and the visual inspection of the graph, we conducted the post hoc comparisons for trial 2. These analyses indicated that the OF/VEH group exhibited significantly lower contact with the sipper than the CTRL/VEH group and the OF/SCOP group ($p < 0.05$, Fig. 4),

Groups	Trials 1-5	Trial 6	Trials 7-8
CTRL/0.1	32%	SCOP 0.1 → CTRL → 4%	4%
CTRL/0.5	32%	SCOP 0.5 → CTRL → 4%	4%
CTRL/1.0	32%	SCOP 1.0 → CTRL → 4%	4%
CTRL/VEH	32%	VEH → CTRL → 4%	4%
OF/0.1	32%	SCOP 0.1 → OF → 4%	4%
OF/0.5	32%	SCOP 0.5 → OF → 4%	4%
OF/1.0	32%	SCOP 1.0 → OF → 4%	4%
OF/VEH	32%	VEH → OF → 4%	4%

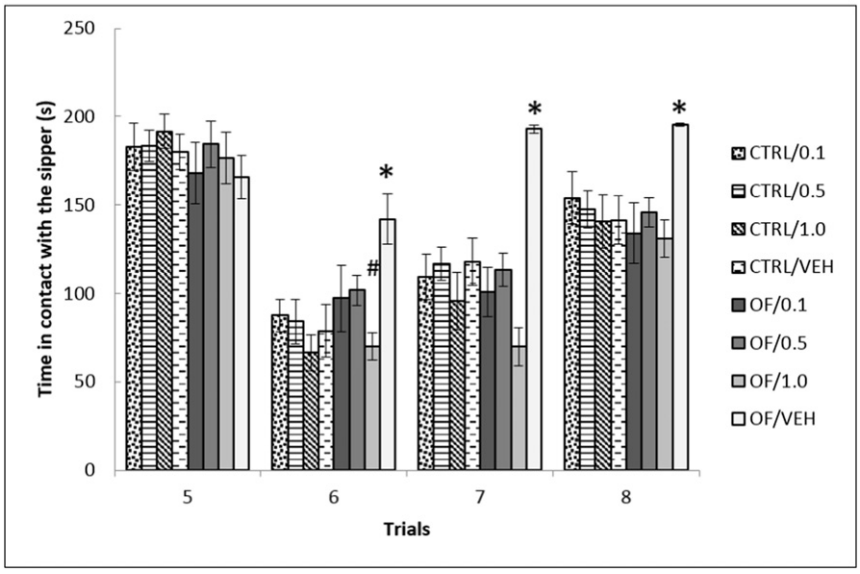

Fig. 1. Time in contact with the sipper (s) in animals exposed to incentive downshift. During pre-shift animals were given 5 daily, 5-min trials of access to 32% sucrose (only the last pre-shift trial is depicted in the figure, descriptive data for the other trials can be found in Table 1). During the 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 1 h before the first downshift trial (OF Groups) or were left in their homecages before the downshift (CTRL group). 20 min before OF exposure the subjects were administered scopolamine (0.1, 0.5 or 1.0 mg/kg, SCOP) or vehicle (VEH). Eight experimental groups were thus defined according to the pre-shift solution consumed and the open field exposure: CTRL/0.1 (n = 9), CTRL/0.5 (n = 9), CTRL/1.0 (n = 9), CTRL/VEH (n = 8), OF/0.1 (n = 8), OF/0.5 (n = 9), OF/1.0 (n = 8), OF/VEH (n = 9). The asterisk indicates a significant difference between the OF/VEH vs. the remaining groups, in a given trial. The pound sign indicates a significant difference between the OF/1.0 and the OF/0.5 group, during trial 6. Vertical lines represent standard errors of the mean.

thus suggesting that SCOP administration after OF exposure blocks the facilitating effect of novelty exposure during the second downshift trial.

3.6. Experiment 5. Effects of scopolamine and OF treatment in animals not exposed to incentive devaluation (i.e., unshifted)

As depicted in Fig. 5, time in contact with the sipper was fairly similar across sessions and groups. This was confirmed by the ANOVA, which revealed a lack of significant main effects or significant interactions. This implies that mere exposure to SCOP or the OF was ineffective to alter responsiveness to 4% sucrose. It seems that novelty only alters time in contact with a sipper providing 4% sucrose in the context of a frustration situation. Similarly, SCOP was devoid of unspecific, enhancing or detrimental, effects. The experiment helps us rule out the possibility of unspecific effects of the drug or the apparatus in the consummatory behavior of the 4% sucrose solution.

4. Discussion

These experiments evaluated the modulatory role of OF exploration on frustration and the participation of the cholinergic system in this phenomenon. In the present work, as in previous experiments (Justel et al., 2014b, 2014c), OF exploration before the first or the second trial of incentive downshift significantly modulated frustration expression. Specifically, subjects exposed to the apparatus before the first trial with the downshifted solution exhibited greater consummatory behavior of the downshifted reward than animals without OF exposure, which indicates an attenuated frustration effect (Experiments 1 and 2). On the other hand, animals exposed to the OF before the second downshift trial exhibited an increment in the frustration response. This was evident by the lower contact with the sipper exhibited by the animals exposed to the open field, when compared to unexposed counterparts (Experiment 3 and 4). The OF effect was blocked by the administration of scopolamine before and after OF exploration, a result indicating the participation of the cholinergic system in the acquisition and consolidation of the OF information. This result contrasts, to a certain extent, with that found in Blake et al. (2011), in which SCOP affected acquisition of a nose-poke task but did not modify the consolidation of a step-through avoidance learning.

These results are important to the cSNC literature, particularly in regards to the role played by novelty exposure and the cholinergic system. The rationale for using scopolamine was that several studies indicate that exposure to a novel open field heightens cortical and hippocampal levels of acetylcholine in rats (Aloisi et al., 1997; Giovannini

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

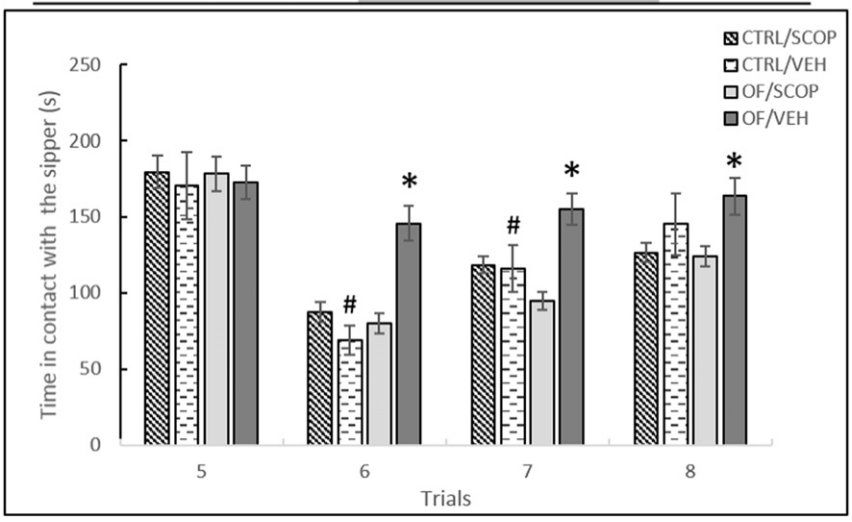

Fig. 2. Time in contact with the sipper (s) in animals exposed to incentive downshift. During pre-shift animals were given 5 daily, 5-min trials of access to 32% sucrose (only the last pre-shift trial is depicted in the figure, descriptive data for the other trials can be found in Table 1). During the 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 1 h before 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 pre-shift solution consumed and the open field exposure: CTRL/SCOP (n = 10), CTRL/VEH (n = 9), OF/SCOP (n = 10), OF/VEH (n = 10). The asterisk indicates significant differences between OF/VEH and CTRL/VEH groups, in trials 6 to 8. The pound sign indicates significant differences between OF/VEH and OF/SCOP groups, in trials 6 and 7.Vertical lines represent standard errors of the mean.

et al., 1998; Thiel et al., 1998; Popovic et al., 2015). The rationale for testing the effects of this specific antagonist in the first or second trial of incentive devaluation was that these two trials may exhibit functional differences. Amsel's (1992) postulates that exposure to the first downshift trial results in an aversive unconditioned response. This so-called *primary frustration* endows contextual stimuli with incentive salience, so that during the second downshift trial the memory of the primary frustration is reactivated, alongside with a memory of the reward received during the pre-shift trial. A prediction of these functional differences is that a given treatment may be effective in the first but not in the second trial or may exert opposite effects in these days (Ruetti and Justel, 2010). It has been found, for instance, that ethanol administration ameliorated cSNC during the second trial, but did not alter primary frustration (Becker and Flaherty, 1982, 1983). The present results offered mixed support for this prediction. The open field exposure exerted opposite effects on cSNC according to when it was applied, yet these differential effects were similarly blocked by SCOP.

The literature suggests that scopolamine may exert an amnesic-like effect on open field memory (McGaugh and Roozendaal, 2009), erasing or blocking the information acquired during OF exposure. It has been found that SCOP inhibits novelty-induced c-Fos, a general marker of neural activity, in neocortex and hippocampus (Wirtshafter, 2005). At the behavioral level, Blake et al. (2011) found that the novelty induced by exposure to a hole board apparatus inhibited the expression of an inhibitory avoidance. Specifically, animals exposed to the hole board exhibited a shorter latency, when compared to unexposed controls, to step into the compartment where the shock had been given. This effect was blocked by scopolamine. These results are very similar to the data presented in the present study, although animals subjected to the downshift are not exposed to explicit aversive stimuli (like exteroceptive nociceptive stimulation) but instead experience a downshift in the reward magnitude of a known reinforcer.

Even though it is tempting to conclude that SCOP acted in the present work by inducing amnesia, the drug has several other effects that have to be taken into consideration (Hescham et al., 2014). There are studies that indicated that this cholinergic antagonist can increase or decrease locomotor activity (Klinkenberg and Blokland, 2010), or induce anxiety (Macedo Medeiros et al., 2014). Moreover, it could be suggested that the effects of scopolamine may be related to its antidepressant effects (Zhang et al., 2015). These are certainly plausible alternative possibilities, although they are lessened by the observation that, in the present study, motor activity patterns in the open field were not affected by SCOP. Specifically, we found that SCOP did not significantly alter overall locomotor activity or the frequency of entries into the central sections of the open field, at the doses tested.

It could also be thought that SCOP exerted unspecific enhancing or detrimental effects on consumption of the 4% sucrose solution. In Experiment 5, however, rats were given continuous exposure to 4% sucrose. These unshifted groups were exposed to SCOP and OF on the 6th trial, yet neither of these treatments significantly altered sucrose intake patterns. It seems that the results cannot be explained by unspecific effects of SCOP administration upon the consumption of 4% sucrose.

In summary, the results of the present study indicate that OF exposure attenuated and exacerbated incentive downshifts, when applied before the first and second downshift trial, respectively. These effects, which replicate previous research by Justel et al. (2014a,b,c), were blocked by scopolamine administration before or after OF exposure. These results pinpoint a significant, mediational role of the cholinergic system in downshift-induced frustration, and provide new information

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

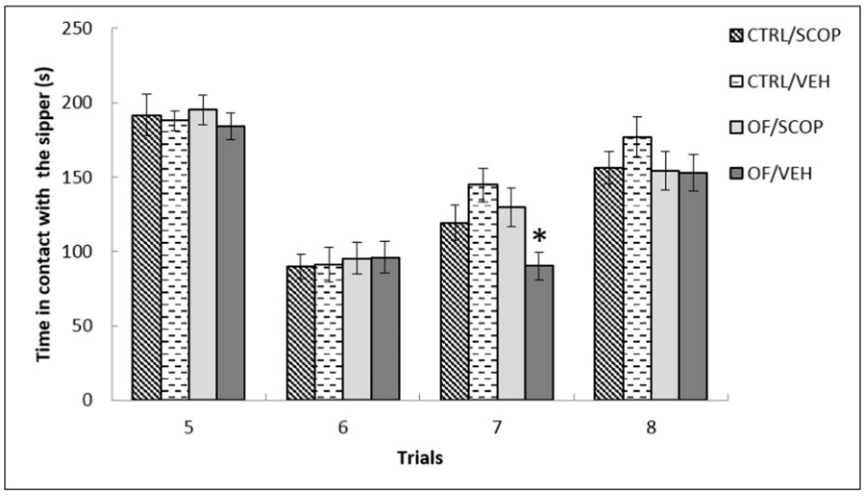

Fig. 3. Time in contact with the sipper (s) in animals exposed to incentive downshift. During pre-shift animals were given 5 daily, 5-min trials of access to 32% sucrose (only the last pre-shift trial is depicted in the figure, descriptive data for the other trials can be found in Table 1). During the 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 1 h before the second downshift trial (OF Groups) or were left in their homecages before the downshift (CTRL group). 20 min before OF exposure the subjects were administered with scopolamine 0.5 mg/kg (SCOP) or vehicle (VEH). Four experimental groups were thus defined according to the pre-shift solution consumed and the open field exposure: CTRL/SCOP (n = 10), CTRL/VEH (n = 9), OF/SCOP (n = 10), OF/VEH (n = 10).The asterisk indicates a significant difference between OF/VEH and CTRL/VEH groups, in trial 7. Vertical lines represent standard errors of the mean.

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

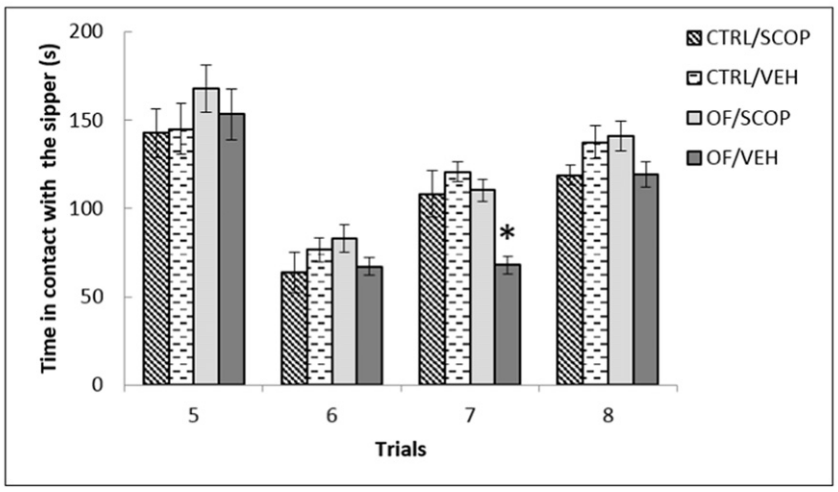

Fig. 4. Time in contact with the sipper (s) in animals exposed to incentive downshift. During pre-shift animals were given 5 daily, 5-min trials of access to 32% sucrose (only the last pre-shift trial is depicted in the figure, descriptive data for the other trials can be found in Table 1). During the 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 1 h before the second 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 pre-shift solution consumed and the open field exposure: CTRL/SCOP (n = 7), CTRL/VEH (n = 9), OF/SCOP (n = 8), OF/VEH (n = 8). The asterisk indicates a significant differences between OF/VEH vs. CTRL/VEH and OF/SCOP groups, in trial 7. Vertical lines represent standard errors of the mean.

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

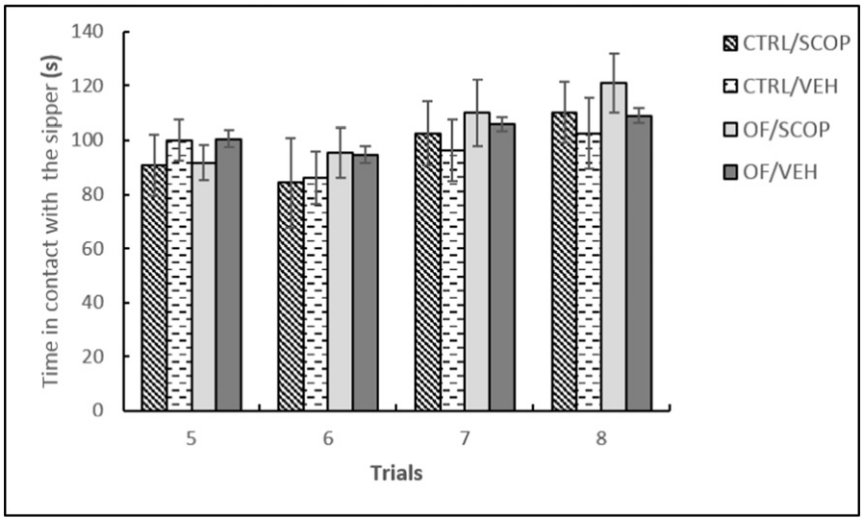

Fig. 5. Time in contact with the sipper (s) in animals unexposed to incentive downshift. Animals were given 8 daily, 5-min trials of access to 4% sucrose (only trials 5–8 are depicted in the figure, descriptive data for the other trials can be found in Table 1). Animals were given a single exposure to an open field 1 h before the sixth trial (OF Groups) or were left in their homecages (CTRL group). 20 min before OF exposure the subjects were given 0.5 mg/kg scopolamine (SCOP) or vehicle (VEH). Four experimental groups were thus defined: CTRL/SCOP (n = 10), CTRL/VEH (n = 10), OF/SCOP (n = 11), OF/VEH (n = 10). Vertical lines represent standard errors of the mean.

on functional and pharmacological dissociations during the first and second trials of frustration.

Acknowledgments

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