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Research report

Consistent rewarding or aversive effects of the electrical stimulation of the lateral parabrachial complex

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Abstract

Electrical stimulation of the external lateral parabrachial subnucleus (LPBe) may induce rewarding or aversive behaviors in animals subjected to two different learning discrimination tasks. Statistical analysis found no significant differences between the group receiving electrical stimulation of the brain and the non-stimulated control group. However, rewarding or aversive behaviors were consistent and positively correlated between the two discrimination tasks in the stimulated group.

Thus, these tests differed in the gustatory stimuli used, in the right/left position of stimulation-associated/non-associated flavors, and in the cage in which experiments were performed. This behavioral consistency and corresponding correlation were not observed in the non-stimulated control group. These results suggest the existence of aversive and reward systems that are differentiated but anatomically very close. Therefore, the activation of aversive or rewarding systems may depend on the precise location of the electrode implanted in the LPBe of each animal.

Keywords: Electrical brain stimulation; Parabrachial nucleus; Reward; Taste preference

1. Introduction

The external lateral parabrachial subnucleus (LPBe) is at the ventral lateral end of the parabrachial complex and has been implicated in the processing of visceral and gustatory information [1,2]. The LPBe receives gustatory information through the rostral nucleus of the solitary tract (NST) [2–4], whereas it receives both vagal and visceral information [5] by means of its connections with the caudal NTS and area postrema (AP) [1,6,7].

The LPBe has been related to taste aversion learning induced by aversive agents (e.g., abdominal irritants, body rotation, or copper sulfate) or even by drugs of abuse (e.g., cocaine, amphetamines, or morphine) [8–12], mostly when these gustatory–visceral stimuli are contiguously presented [9,13]. Furthermore, this LPBe subnucleus has also been related to the spino(trigemino) pontoamygdaloid system and would be involved in the transmission of nociceptive information and in the affective-emotional, autonomic, and visceral processing of these negative events [14–24].

The LPBe may also participate in the processing of rewarding substances. Thus, the intraduodenal injection of glucose [25] or intragastric administration of lactose or sucrose, among others, generates C-Fos immunoreactivity in this area [11,12]. Moreover, lesions in this parabrachial subnucleus block taste preferences induced by the intragastric administration of rewarding food [26]. In this regard, some substances related to food intake and nutritional metabolism may exert their functions through this region, as in the case of cholecystokinin (CCK) [27,28], galanin, neuropeptide Y [29–31], and leptin [32]. The same has been found for certain drugs that increase the hedonic value of intake, e.g., benzodiazepines [33]; agents that reduce food intake, e.g., fenfluramine [27,34–36]; and antimetabolic substances, e.g., mercaptoacetate, 2.5-anhydro-D-mannitol, methyl palmoxirate [37–40,75].

Finally, it has been demonstrated that some drugs of abuse implicated in the reduction or increase of food intake [41–44], e.g., amphetamines [10] or opiates [10,27,35,45,46], may also be processed *via* the LPBe. In relation to the opiate system, it has been shown that the number of opiate receptors of this parabrachial area can be modified by food restriction [47] and, conversely, that drug manipulation of opiate receptors in this area can modulate intake [48,49].

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Taken together, the above data suggest that the LPBe nucleus may be related to both aversive and rewarding motivational processes. For this reason, we expected that LPBe electrical stimulation, an appropriate procedure for inducing preference/rewarding or aversive behaviors [50–52], might generate these appetitive and/or aversive responses in a random but consistent manner. These results might also serve as a behavioral criterion to identify the aversive or rewarding effects of LPBe electrical stimulation, especially the latter (preferences), given that lever-press self-stimulation has not been obtained with these animals [53], or at least not as readily as in the lateral hypothalamus, for example [54]. Therefore, in this study, it was decided to use two different learning discriminative tasks by which the animals could associate a stimulus with its rewarding or aversive consequences [26,51,52,55–59]. Furthermore, the two flavors presented, the right/left position of the stimulation-associated flavor, and the cages used by each animal were modified in these tests. According to our hypothesis, the animals would still prefer or avoid, in each individual case, the stimulus associated with intracerebral electrical stimulation, despite the modifications introduced and possible interferences among tasks, although global differences might not be found between stimulated and non-stimulated groups.

2. Materials and methods

2.1. Subjects

Thirty-one male Wistar rats (255–315 g each at time of surgery) from the University of Granada animalarium were used in this study. They were randomly assigned to one of two groups: (a) ES-LPBe: intermittent (30″ on/30″ off) ($n = 10$) or continuous ($n = 12$) electrical stimulation and (b) US-control: unstimulated control ($n = 9$). In the former group, the total duration of stimulation at each session was 15′ in all cases. Since no significant differences were found between the two subgroups, the results were analyzed together.

On arrival at the laboratory, animals were individually housed in 30 cm × 15 cm × 30 cm methacrylate cages that served as training chambers. The room temperature was maintained between 21 and 24 °C, and light–dark periods lasted 12 h each, with lights on at 8:30 a.m. All experimental and test procedures were conducted during the light phase.

Subjects were allowed a 5-day adaptation period during which they remained in their home cage with food and water available *ad libitum*. All behavioral procedures and surgical techniques were conducted in agreement with animal care guidelines established by Spanish Royal Law 23/1988.

2.2. Surgery

Under general anesthesia (sodium pentothal, 50 mg/kg., B. Braun Medical S.A. Barcelona, Spain), the ES-LPBe group was stereotaxically implanted (Stoelting Co. Stereotaxic 51600, USA) with a 00 stainless steel electrode aimed at the LPBe {Coordinates: AP = −0.16; $V = 3$; $L = \pm 2.5$; [76]}. After surgery, subjects were returned to their home cages where they stayed for at least 7 days of recovery with water and food *ad libitum*.

Animals from the US-control group had similar periods of adaptation and recovery but did not undergo surgical intervention.

2.3. Apparatus

As mentioned above, experimental procedures were conducted in the same methacrylate chambers that served as home cages. The front part of each cage had two 1.6-cm holes, each at the same distance from the center and sides and at the same height from the floor. Through those orifices, the animal had access to spouts attached to graduated burettes in which the flavors were offered.

Electrical stimulation was *delivered* using a LI12100 stimulator (Letica, Barcelona, Spain). At a current selected to be below the threshold for producing undesired behavioral effects [60], 66.6 Hz, 0.1 ms, 57–115 μA, cathodal rectangular pulses were applied to the LPBe. The stimulation process was monitored with a DM63 oscilloscope (Textronic Ltd., London, U.K.), which allowed constant visualization of the electrical pulses administered to animals during experimental sessions.

2.4. Behavioral procedure

2.4.1. Pretraining

During two pretraining sessions, all animals were water deprived for 23 h 50 min and allowed to drink tap water for 10 min from graduated burettes. The position of the burettes was alternated across sessions to avoid development of positional preferences. Once the water was withdrawn, animals had access to 15 g of food.

The experiment began after the 2-day pretraining period and comprised two phases separated by a 14-day interval. In each phase, animals underwent a discriminative learning task. The gustatory stimuli used were strawberry 'S' and coconut 'C' for phase I and lemon 'L' and vanilla 'V' for phase II (0.5% diluted in water, McCormick & Co. Inc. San Francisco, CA), which were always presented in the same right/left position.

In each phase, four learning sessions were performed in which the two different gustatory stimuli were offered on alternate days. For half of the animals, intake of one flavor (for 7 min) was immediately followed by 15 min of electrical stimulation of the LPBe, whereas intake of the other flavor was not followed by stimulation. For the remaining animals, the opposite process was carried out (for details, see Table 1). On day 5, a two-bottle free-choice test was conducted by placing both burettes in the cage simultaneously. Animals were allowed to freely drink the flavored solutions for 7 min and the total amount ingested was recorded.

Table 1
Behavioral procedure

Random distribution

Phase I	Day 1	Day 2	Day 3	Day 4	Test
~~Phase I~~					
Group A 50% of animals	Strawberry L + St. (15 min)	Coconut R + Non-St. (15 min)	=1st day	=2nd day	Strawberry L, coconut R (7 min)
Group B 50% of animals	Strawberry L + Non-St. (15 min)	Coconut R + St. (15 min)	=1st day	=2nd day	Strawberry L, coconut R (7 min)
Phase II					
Group A 50% of animals	Lemon L. + St. (15 min)	Vanilla R + Non-St. (15 min)	~~*0 Day~~	=2nd day	Lemon L, vanilla R (7 min)
Group B 50% of animals	Lemon L + Non-St. (15 min)	Vanilla R + St. (15 min)	~~*# Day~~	=2nd day	Lemon L, vanilla R (7 min)

Diagram of the balanced experimental conditions used in the two phases of this experiment. Strawberry and coconut were used as gustatory stimuli in the first phase and vanilla and lemon in the second phase. The unstimulated control animals (US-control) were also assigned one flavor with sham stimulation and another with non-"stimulation", although control animals never received electrical stimulation.

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Table 2
Design of positions occupied by experimental and control animals

Phase 1								
Subject	1	2	3	4	5	6	7	8
Position	Cage 1		Cage 2		Cage 3		Cage 4	
Phase II								
Subject	4	3	8	7	2	1	6	5
Position	Cage 1		Cage 2		Cage 3		Cage 4	

Procedure for the distribution of the animals in different cages during phases I and II of the experiment. This procedure (amplified) was used for the 18 animals in the ES-LPBe group and the 9 in the US-control group.

In the case of the unstimulated control group (US-control), intake of the two gustatory stimuli was never followed by brain electrical stimulation.

In the interval between phases, animals received food and water *ad libitum*. At the start of the second phase, conditions of the new discrimination test were modified with regard to the gustatory stimuli used, the right/left position of the electrical stimulation-associated stimulus, and the cage in which experiments were conducted (Table 2).

2.5. Histology

After conclusion of the experiment, all animals were deeply anesthetized with an overdose of sodium pentothal and intracardially perfused with isotonic saline and 4% paraformaldehyde. Electrolytic lesions (0.5 mA of cathodic current for 5 s) were made to verify placement of electrodes in the LPBe. Their brains were removed, stored in paraformaldehyde, and laminated in 50-μ sections. Sections were mounted, stained with cresyl violet, and photographed (VMZ-4F stereoscopic magnifying glass and PM-6 camera, Olympus, Tokyo, Japan) (see Figs. 1 and 2).

2.6. Data analysis

Statistica 6.0 software (Statsoft Inc., OK) was used for the statistical analysis.

A mixed bifactorial (group × flavor) ANOVA was used to analyze differences between stimulated and control groups.

To demonstrate the intra-subject consistency of data, comparisons were performed using correlation coefficients of the differential data (difference between intake of electrical LPBe stimulation-associated flavor [Flavor + St.] and intake of the flavor not associated with this stimulation [Flavor + Non-St.]) obtained for each animal in phases I and II tests. In the US-control group, one of the flavors was randomly selected before each learning phase to be sham-associated with the electrical LPBe stimulation (animals in this group never received this stimulation).

Classification and selection criteria can be developed from these data according to the behavior of these animals. Thus, animals were grouped into: those with a >50% consumption of the stimulation-associated flavor in the two tests, designated "positive" group, those with <30% consumption of the stimulation-associated flavor in the two tests, designated "negative" group; and those with 30–50% consumption of this flavor in one or both phases, designated "neutral" group.

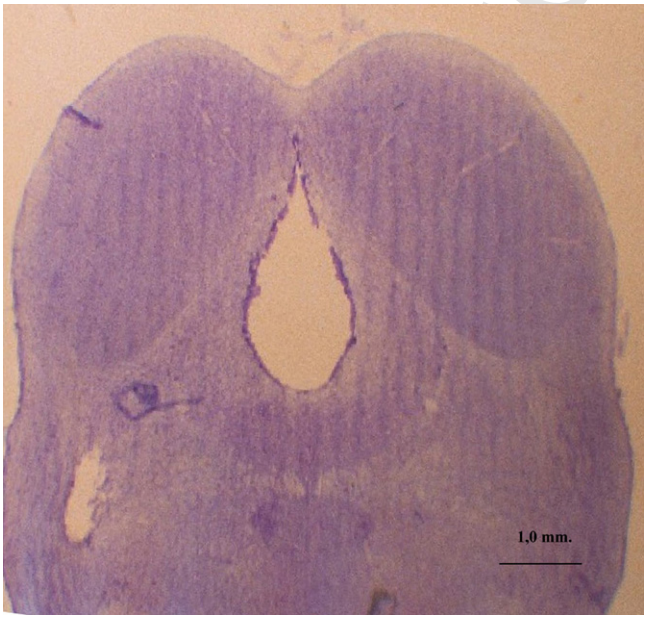

Fig. 1. Histological preparation stained with cresyl violet, showing the localization (as small lesion) of the area occupied by the end of the electrode, representative of observations in the animals in this experiment.

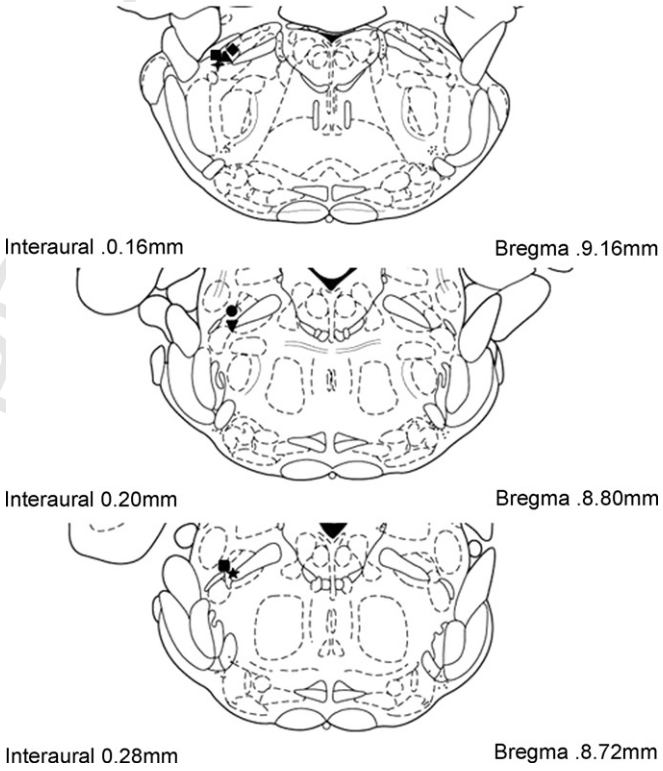

Fig. 2. Map of the localization of electrode tip in some experimental group animals (diamond, animal 1; inverted triangle, animal 2; four-point star, animal 6; five-point star, animal 8; square, animal 13; rounded square, animal 16; triangle, animal 17).

3. Results

Three animals in the ES-LPBe group were excluded from the statistical analysis because the implant became detached during

the behavioral procedure. Another subject of this same group was excluded for showing circling behavior.

There was wide intersubject variability in the intake of one or other flavor (Flavor + St. or Flavor + Non-St.) by animals in both groups (ES-LPBe and US-control), and the mixed bifactorial (group × flavor) ANOVA found no differences in phase 1 between groups [$F(1,25) = 0.2230$ $p < 0.6408$] in either flavor intake [$F(1,25) = 0.2490$ $p < 0.6221$] or interaction of the two factors [$F(1,25) = 0.2724$ $p < 0.6063$). Similar results were found for phase II [group: $F(1,25) = 1.0083$ $p < 0.3249$; flavor: $F(1,25) = 2.0877$ $p < 0.1609$; interaction: $F(1,25) = 0.0010$ $p < 0.9748$] (Fig. 3).

However, the comparison using Pearson correlation coefficient data for each animal in phases I and II showed a significant correlation ($r = 0.70508$; $p > 0.001$**) for the intake of stimulation-associated flavor values in both phases by the ES-LPBe group (Fig. 4). This was not the case for the US-control group, in which the correlation was not significant ($r = -0.07176$; $p < 0.8544$) (Fig. 5). When the criteria proposed above were applied to the 18 animals in the ES-LPBe group, 6 were assigned to the "positive" group (preference for stimulation-associated flavor) [mean current intensity of 87.1 μA], 7 to the "negative" group (aversion to stimulation-associated flavor) [mean intensity of 81.5 μA], and 5 to the "neutral" group [mean = 100 μA]. Hence, whereas 72% of animals in the stimulated group were consistent in their behavior, only two members of the "US-control" group showed a repeated preference for one of the gustatory stimuli presented, while the remaining 7 [77.7%] met the criterion established for the neutral group.

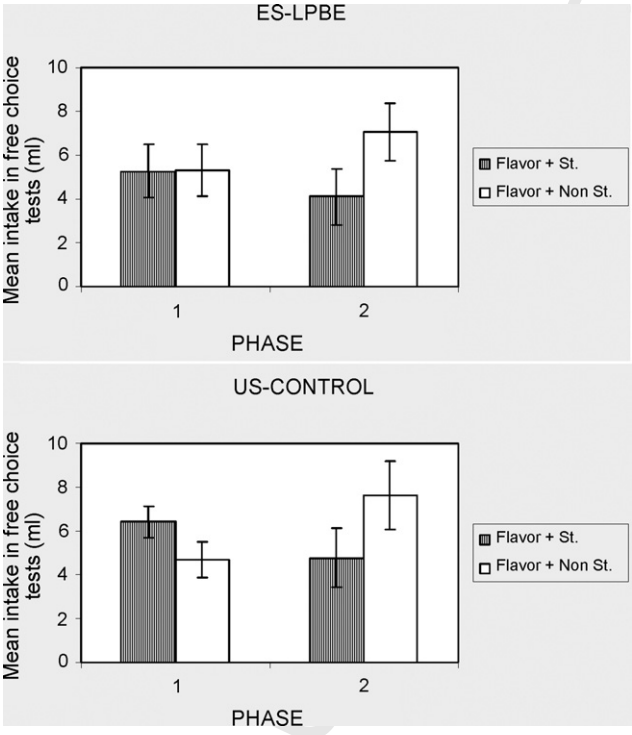

Fig. 3. Mean intake (in cc) by ES-LPBe (above) and US-control (below) of the flavor associated with electrical stimulation of the LPBe and the flavor not associated with this stimulation (Flavor + St., Flavor + Non-St.) during phases I and II of the experimental procedure in this experimental series.

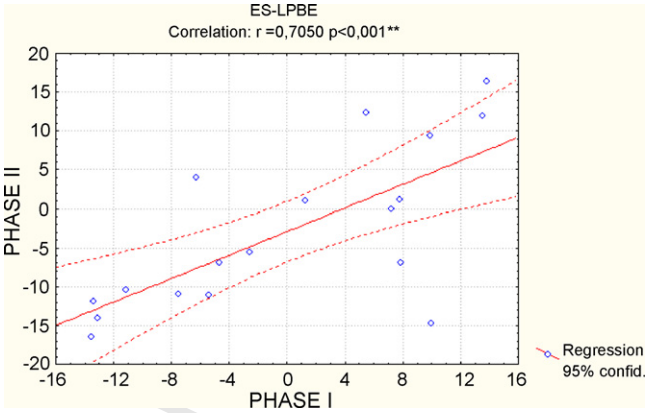

Fig. 4. Correlation matrix for the data of each ES-LPBE subject in phases I and II of the experiment ($r = 0.7050$, $p > 0.001$**). The area between the two curves represents the estimated surface area predicted to contain these data points from the performance of each subject in the two phases of the experiment, with a confidence interval of 95%.

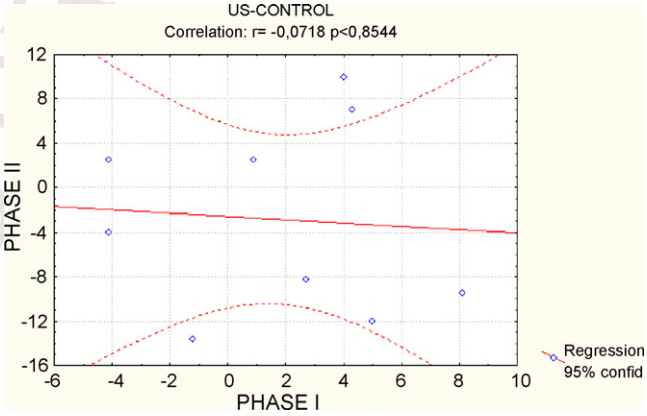

Fig. 5. Correlation matrix for the data of each subject of the US-control group in phases I and II of the experiment ($r = -0.0717$, $p < 0.8544$).

4. Discussion

The results of this experiment show that LPBe stimulation may induce preferences or aversions towards associated stimuli in discrimination learning tasks. Analysis of the preferences shown for the flavor associated with the electrical brain stimulation in each task showed no significant results. However, a significant correlation was found between data obtained in the two tests by the stimulated animals [ES-LPBe] but not by the control animals [US-control]. This finding suggests that most animals in the stimulated group developed a preference for either the electrical stimulation-associated flavor or for the other one – and only a minority showed alternating behavior. Hence, this effect was consistent in the majority of the electrically stimulated animals, despite modifications introduced into the two discrimination learning tasks with regard to the gustatory stimuli presented, the left/right localization of the stimulation-associated flavor, and the experimental cage used, with the

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consequent egocentric and allocentric re-organization that these tests might have required. Therefore, these data appear to indicate that the effect is consistent within an individual but not among individuals.

The lateral end of the parabrachial nucleus, which includes the LPBe, receives visceral information from the caudal NTS and area postrema [1,2,6] and gustatory information from its connections with the rostral NTS [2,7]. This sensory information can be rewarding or aversive. Thus, it has been reported that the LPBe appears to participate in the development of learned preferences and aversions [9,26]. In this context, electrical stimulation of the LPBe can act as an adequate stimulus to induce one or other biological process (positive or negative reinforcement), as also found in other brain regions [50–52,61].

Previously published data have shown that a single anatomical structure can be the substrate for both appetitive and aversive motivational processes [62–65]: The same can be observed with some substances (e.g., corticotropin-releasing factor or κ agonists), whose rewarding or aversive effects may depend on the dose, the experimental situation, or the anatomic localization of the neurochemical systems involved [66,67]. In the present study, however, while the stimulated anatomical area appeared to be critical, no differences were found in preference/aversion behavior as a function of the electrical current parameters used.

In other words, it appears possible that the electrical stimulation of the LPBe could have affected positive or negative cells according to the precise localization of the electrode. This would modify the quality of the associated stimulus and would mean that the stimulus, initially neutral, acquires appetitive or aversive motivational properties. This interpretation is compatible with the identification in this LPBe area of cells that react to the hedonic properties of different gustatory stimuli [4], and of mutually inhibitory interactions between activity patterns of hedonic-positive and hedonic-negative cells [2,7,68,69].

Furthermore, various authors have detected C-Fos immunoreactivity in the LPBe after the intragastric administration of nutrients and of chemical substances that generate learned preferences (e.g., glucose, sucrose, lactose, maltose, polycose) [12,25] or aversions (e.g., cocaine, morphine, methamphetamine, hypertonic saline, LiCl, copper sulfate) [10,11].

The present observation of animals that found electrical stimulation of the LPBe to be aversive is also consistent with reports by other authors that the administration of some immune system-activating toxic agents (bacterial lipopolysaccharide) can produce immunoreactivity in the external part of the LPBe [70]. This aversive effect can also be explained as a consequence of the activation of an important relay of the spino-parabrachial pathway in the LPBe, whose participation in the processing of noxious information is well documented [14–24].

Finally, various authors have demonstrated that the behavioral effect of opiates may depend on the type of receptor on which they act. Thus, agonists of μ and δ receptors usually generate reinforcement, whereas substances that act on κ receptors do not favor its self-administration and may also induce aversive behaviors [71,72]. Some of these receptor types, i.e., μ and κ, have been identified in the LPBe [47]. It is likely that the electrical stimulation could have produced an activation of some or other receptors, generating positive or negative effects or even both simultaneously, which would explain the behavior of the "neutral" animals. Indeed, this explanation is compatible with data reported by Moufid-Bellancourt et al. [71], who achieved both rewarding and aversive effects from the intraparabrachial infusion of μ and κ agonists, respectively. Moreover, it cannot be ruled out that the electrical stimulation of the LPBe might also have activated a motivational system associated with deficit/satiation states [64] or brain reward.

To summarize, the present results show that electrical stimulation of the LPBe can generate, in different animals, consistent preferences or aversions to gustatory stimuli with which it is associated. These results may possibly depend on slight variations in the position of the end of the electrode, differentially activating some of the motivational subsystems present in this region. These different reward/aversion mechanisms could be anatomically very close together, allowing the establishment of learned associations between a stimulus and its positive or negative consequences, analogous to observations in humans [64,73,74].

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bbr.2008.02.036.

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