Behavioural Brain Research 244 (2013) 120–129

Contents lists available at SciVerse ScienceDirect

Behavioural Brain Research

journal homepage: www.elsevier.com/locate/bbr

Research report

Role of the ventrolateral orbital cortex and medial prefrontal cortex in incentive downshift situations

Leonardo A. Ortega[a], Amanda C. Glueck[a], Megan Uhelski[b], Perry N. Fuchs[b], Mauricio R. Papini[a,*]

[a] Texas Christian University, United States
[b] University of Texas at Arlington, United States

HIGHLIGHTS

- The surprising omission of an incentive induces emotional activation and learning.
- Lesions of the ventrolateral orbital cortex (VLO) reduce behavioral suppression in the consummatory negative contrast.
- VLO lesions also eliminate behavioral activation induced by partial reinforcement.
- The medial prefrontal cortex do not seem to play a role in either of these situations.

ARTICLE INFO

Article history:
Received 26 July 2012
Received in revised form 24 January 2013
Accepted 25 January 2013
Available online xxx

Keywords:
Incentive contrast
Partial reinforcement
Ventrolateral orbital cortex
Medial prefrontal cortex
Rats

ABSTRACT

The present research evaluated the role of two prefrontal cortex areas, the ventrolateral orbital cortex (VLO) and the medial prefrontal cortex (mPFC), on two situations involving incentive downshifts, consummatory successive negative contrast (cSNC) with sucrose solutions and Pavlovian autoshaping following continuous vs. partial reinforcement with food pellets. Animals received electrolytic lesions and then were tested on cSNC, autoshaping, open-field activity, and sucrose sensitivity. Lesions of the VLO reduced suppression of consummatory behavior after the incentive downshift, but only during the first downshift trial, and also eliminated the enhancement of anticipatory behavior during partial reinforcement, relative to continuous reinforcement, in autoshaping. There was no evidence of specific effects of mPFC lesions on incentive downshifts. Open-field activity was also reduced by VLO lesions, but only in the central area, whereas mPFC lesions had no observable effects on activity. Animals with mPFC lesions exhibited decreased consumption of the lowest sucrose concentration, whereas no effects were observed in animals with VLO lesions. These results suggest that the VLO may exert nonassociative (i.e., motivational, emotional) influences on behavior in situations involving incentive downshifts. No clear role on incentive downshift was revealed by mPFC lesions.

The prefrontal cortex (PFC) is a structurally and functionally complex cortical region. The limits of the PFC can be defined by bidirectional connections to thalamic areas, which are relevant for PFC development [1]. Several cortical fields within the rat PFC can be roughly divided in three regions: dorsolateral, medial, and orbital. Not surprisingly, different areas within the PFC are associated to different behaviors and a particular area can be associated to more than one behavior. For instance, lesions of the ventromedial PFC (including infralimbic areas) retarded fear conditioning extinction [2], while lesions of the orbitofrontal cortex impaired the formation of a negative incentive value for a conditioned stimulus paired with food (unconditioned stimulus), when the food was later devaluated by pairing it with lithium chloride [3]. In addition, lesions of the orbitofrontal cortex impaired autoshaping acquisition [4].

The PFC is connected, among others, with thalamic nuclei, basal ganglia, and sensory and motor cortices [1]. Miller and Cohen suggested that networks associated with the PFC are in an exceptional location to coordinate a wide array of neural processes and control various types of behaviors [5]. Furthermore, the PFC may be especially relevant for the control of behavior in a top-down manner, as in situations requiring dynamic responses that in turn may involve the organization of sensory/internal inputs, cognitive information, and motivated responses. Thus, the PFC may underlie the coordination of some of the behavioral and motivational adjustments that occur in situations involving incentive downshifts, such as those studied in the present experiment.

* Corresponding author at: Department of Psychology, Texas Christian University, Box 298920, Fort Worth, TX 76129, United States. Tel.: +1 817 257 6084.
E-mail address: m.papini@tcu.edu (M.R. Papini).

0166-4328/$ – see front matter © 2013 Elsevier B.V. All rights reserved.
http://dx.doi.org/10.1016/j.bbr.2013.01.029

In incentive-downshift situations the organism is presented with a reward that has unexpectedly become less valuable than the one previously experienced [6]. The present experiment assessed the role of the ventrolateral orbital cortex (VLO) and medial prefrontal cortex (mPFC) in two situations involving incentive shifts: consummatory successive negative contrast (cSNC) and partial reinforcement acquisition effect (PRAE) in a Pavlovian situation. In cSNC, a group previously given access to 32% sucrose is downshifted to 4% sucrose and its consummatory behavior is compared to that of an unshifted control always given access to 4% sucrose. The cSNC effect involves greater consummatory suppression in downshifted animals relative to unshifted controls [7]. In the PRAE, a group receives pairings between a conditioned stimulus and an unconditioned stimulus (CS and US) in which a random half of the trials involve CS-only presentations. The acquisition performance of this partial reinforcement group is compared to that of a group in which all acquisition trials involve CS–US pairings (i.e., continuous reinforcement). The PRAE involves higher anticipatory responding during acquisition under partial reinforcement than under continuous reinforcement [8].

The role of the PFC on cSNC has not been thoroughly studied. Three prefrontal areas have been implicated in the response to incentive downshifts. Lin et al. [9] reported that excitotoxic lesions of the insular cortex completely eliminated the cSNC effect. Insular lesions resulted in a gradual reduction of performance following reward downshift to the level of unshifted controls. Two other prefrontal areas may play a role in recovery from incentive downshift. Using a reward downshift paradigm similar to cSNC, rats undergoing excitotoxic lesions of the mPFC performed similarly to sham controls during the first downshift trial, but showed higher levels of sucrose consumption during the second half of an extended postshift phase (12 trials) [10]. However, no differences were observed in a second downshift with the same animals. Unfortunately, no unshifted controls were included, making it difficult to determine whether the effects of mPFC lesions were related to the downshift event or to sucrose consumption. Finally, Ortega et al. [11] reported that electrolytic lesions of the anterior cingulate cortex (ACC) had no effect on the first downshift trial, on preshift performance, or on unshifted controls, but retarded recovery from cSNC in subsequent trials. An analysis of the initial 100 s of each postshift trial indicated that animals with ACC lesions exhibited the cSNC effect earlier than sham controls. Within-trial analysis has been used to uncover subtle transient effects that are obscured by pooling data for the entire trial [11–13]. This early-trial effect emerging during the second downshift trial was interpreted as providing evidence that the impairment of ACC function facilitated the retrieval of the aversive memory of the incentive downshift first experienced in the previous trial.

To the best of authors' knowledge, there is no published information on the role of the PFC in the PRAE as assessed in response-independent, Pavlovian situations (or in any other training situation), such as the autoshaping procedure used in this experiment.

The effects of PFC lesions reviewed thus far suggest a top-down regulation of behavior in incentive downshift situations. This idea was first suggested by the disruptive effects of lesions of the amygdala and parabrachial nucleus on cSNC [14,15]. The parabrachial nucleus is part of the brainstem circuit regulating the taste-licking action pattern in rats [16–21]. The basic idea is that telencephalic structures, including the PFC and amygdala, are engaged by a mismatch between actual and expected incentives to modify consummatory behavior under the control of the taste-licking brainstem action pattern. Previous results on the behavioral functions of the VLO and mPFC areas from situations thought to be related to incentive downshift [22] provided some hints.

The VLO is related to pain-induced responses following the formalin test. For example, Xie et al. [23] reported that microinfusions of morphine, a nonselective opioid receptor agonist, into the VLO attenuated pain-related behaviors induced by the formalin test. Both formalin-induced peripheral pain [24] and exogenous opioid administration [25] are known to modulate the cSNC effect. Furthermore, bilateral lesions of the orbitofrontal cortex (including the VLO and infralimbic cortex) impaired sign-tracking autoshaping acquisition and led to perseveration of the originally trained response in a discrimination reversal procedure, while mPFC lesions (including infralimbic and prelimbic cortices) did not affect autoshaping performance [4]. Although, lesions of the mPFC [26] and microinjections of amphetamine within the mPFC had no detectable effects on pain-related behavior after formalin administration [27], Pecoraro et al. [10] reported that mPFC lesions affected behavioral performance following reward downshift. Based on the attenuating effects of VLO lesions on pain-related behaviors and of the enhanced recovery from incentive downshift reported for animals with mPFC lesions, it was expected that rats with these two lesions would express reduced cSNC and PRAE in the current experiment.

In the present experiment, electrolytic lesions in the VLO and mPFC were administered before the start of training. We chose to use electrolytic lesions because they produce easily localizable lesion boundaries and complete damage of the area. However, these lesions also damage fibers of passage, which tend to be spared in neurotoxic lesions, at least at low toxin doses [28]. Based on the reviewed results, it was expected that VLO lesions would impair recovery from cSNC, having an effect similar to that of ACC lesions, as manipulations on both ACC and VLO resulted in attenuation of formalin-induced pain behavior [23,29]. Whereas the role of the mPFC in pain modulation is unclear, mPFC lesions affected consummatory performance following reward downshift [10]. The addition of unshifted controls (i.e., 4% lesion and 4% sham groups) in the present experiment would allow an assessment of the extent to which the lesion effects are specific to the cSNC effect versus generally related to consummatory behavior. As usual in the case of brain lesion studies, the effects of PFC lesions extend to other behavioral functions besides those of specific concern in this research. For example, lesions of the mPFC, but not the lateral PFC, increase exploratory behavior of the central area in the open field test [30]. To assess the possibility of modulation of activity, relevant to the search stage of cSNC, rats with both VLO and mPFC lesions were also tested in the open field. Moreover, deep brain stimulation in the ventromedial PFC (including prelimbic and infralimbic cortices) attenuated the suppression of sucrose consumption following footshock stress in a model of learned helplessness [31]. These results suggest that the mPFC may play a role in the detection of sucrose solutions. Thus, a sucrose sensitivity test was also administered to all animals in the present experiment.

Autoshaping acquisition following continuous or partial reinforcement was also evaluated after VLO and mPFC lesions in the present experiment. Chudasama and Robbins [4] reported impaired autoshaping acquisition following orbitofrontal lesions. However, there was no evaluation of the effects of orbitofrontal lesions on autoshaping acquisition under partial reinforcement. Behavior under partial reinforcement acquisition may also be related to recovery from cSNC. In a selective breeding study that targeted recovery rates from cSNC, three strains of rats were bred for 5 filial generations according to their rate of recovery: high, low, or random. Whereas the low and random lines continued to show significant cSNC effects across generations, the high line exhibited a progressive reduction in the size of the cSNC effect across generations. When animals from the 5th filial generation were tested under partial vs. continuous reinforcement conditions, the emerging pattern of results was consistent with their cSNC performance.

Thus, rats in the random breeding condition showed higher acquisition performance after partial rather than continuous reinforcement training (i.e., PRAE). However, rats selectively bred for higher recovery rates from cSNC showed no acquisition differences under partial and continuous reinforcement (Ortega, Norris, Lopez-Seal, Ramos, & Papini, in preparation). Traditionally, the PRAE has been interpreted as reflecting emotional activation induced by incentive uncertainty leading to the invigoration of dominant responses [32–34]. The reduction of cSNC and PRAE in high recovery rats from the 5th filial generation are consistent with an interpretation based on reduced emotional (frustration) activation. Therefore, a similar design was used in the present experiment to determine whether VLO and mPFC lesions had similar effects, if any, on both cSNC and PRAE.

1. Method

1.1. Subjects

Fifty-eight Long–Evans male rats were used. Animals were experimentally naïve to all the procedures administered during the experiment. The animals were purchased from Harlan Laboratories (Indianapolis, IN). The subjects were housed in individual wire-bottom cages with free access to water. Each cage contained a rodent retreat for enrichment. During the experiment, animals were under a 12 h light/12 h dark schedule (lights on at 07:00 h), in a noise-controlled room with constant temperature (22–23 °C) and humidity (50–65%). They were fed with standard laboratory rat chow.

1.2. Surgery

When rats reached 90 days of age, they were randomly assigned to one of three surgery conditions: VLO lesions ($n = 19$), mPFC lesions ($n = 19$), or sham surgery ($n = 20$). Animals were deeply anesthetized with ketamine (50 mg/kg, ip) and xylazine (2.6 mg/kg, ip), and were then positioned in a stereotaxic frame with blunt-tipped ear bars. A midline incision was made in the scalp and two burr holes were drilled to insert a single electrode twice, one for the VLO or mPFC in each hemisphere. Bilateral electrolytic lesions of the VLO were performed by passing a 0.5 mA current, for 15 s, using a 0.3 mm electrode (AP 3.0–3.7; ML 1.5–2.5; DV 4.0–5.0). Bilateral electrolytic lesions of the mPFC were performed by passing a 0.5 mA current, for 15 s, using a 0.3 mm electrode (AP 3.0; ML 0.4; DV 4.9; at a 15° angle. All coordinates were from Paxinos and Watson [35]. Half of the animals in the sham group were given simulated lesions of the VLO and the rest simulated lesions of the mPFC. Sham operations involved all steps, including the insertion of the electrode, except that current was not administered. Rats were allowed 5–8 days to recover from surgery. Antibiotics were applied as needed. Food and water were continuously available in the cage.

1.3. Food deprivation

After recovery from surgery, average free-food weights were calculated from 3 consecutive days. Thereafter, animals were deprived of food to 81–84% of their average free-feeding weight; they received some amount of food every day during this deprivation procedure. Food was provided every day at about the same time, at least 15 min after behavioral testing. Water was continuously available during the course of the experiment. Animals were observed for signs of illness and weighed daily during the entire experiment. Behavioral training started when the weight of all rats reached the target range, which took approximately 5–7 days. All statistical tests were calculated with the SPSS package. In all cases, the alpha value was set at the 0.05 level. Statistical data for nonsignificant results was omitted for brevity.

1.4. cSNC test

cSNC was conducted in 4 conditioning boxes (MED Associates, St. Albans, VT) made of aluminum and Plexiglas ($29.3 \times 21.3 \times 26.8$ cm, $L \times H \times W$). The floor consisted of steel rods running parallel to the feeder wall. A tray with corncob bedding was placed below the floor to collect feces and urine. In the feeder wall was a hole 1 cm wide, 2 cm long, and 4 cm from the floor through which a sipper tube, 1 cm in diameter, was inserted. When fully inserted, the sipper tube was flush against the wall. Diffuse light was provided by a house light located in the center of the box's ceiling. A computer located in an adjacent room controlled the presentation and retraction of the sipper tube. When the rats made contact with the sipper tube, a circuit involving the steel rods in the floor was closed and the signal was recorded by the computer. This provided a measure of cumulative contact with the sipper-tube, called goal-tracking time (measured in 0.05-s bins). A trial lasted 5 min from the first detection of a sipper tube contact. Each conditioning box was placed in a sound-attenuating chamber containing a speaker to deliver white noise and a fan for ventilation. Together, the speaker and fan produced noise with an intensity of 80.1 dB (SPL, scale C). Boxes were swept immediately after each trial with a wet paper towel.

Within each lesion condition, animals were randomly assigned to one of two groups depending on the concentration of the sucrose solution received during preshift trials. In Groups 32/VLO, 32/mPFC, and 32/Sham, rats had access to 32% sucrose during Trials 1–10 (preshift), but this solution was replaced by 4% sucrose during Trials 11–15 (postshift). In Groups 4/VLO, 4/mPFC, and 4/Sham, animals received 4% sucrose during Trials 1–15. Solutions were prepared weight/weight, by mixing 32 g (or 4 g) of sucrose for every 68 g (or 96 g) of distilled water. cSNC testing involved two types of control conditions, namely, a behavioral control with groups not exposed to the incentive downshift (i.e., unshifted controls, 4% sucrose) and a surgery control with groups exposed to all the surgical procedures except for the electrolytic lesion.

1.5. Sucrose sensitivity test

This test assessed possible changes in sucrose sensitivity due to the lesions. Following cSNC testing and during 3 consecutive days, three different sucrose concentrations were administered in two-bottle tests, 23 h per sucrose concentration, in the home cage. The remaining hour was used to measure consumption, clean the bottles, and replace them as needed. One bottle contained 0.5%, 1%, or 2% sucrose (weight/volume; e.g., 0.5% was prepared by mixing 5 g of sucrose for every liter of distilled water). The other bottle contained distilled water. The order of the sucrose concentrations and the position of the two bottles in the cage were counterbalanced across subjects. Sucrose sensitivity was measured in terms of the ratio of sucrose consumption over total consumption (sucrose plus distilled water) in mL.

1.6. Open field test

The open field test was administered the day following the sucrose sensitivity test. This test was designed to assess possible changes in motor function following lesions in the VLO and mPFC. The open-field chambers were specifically designed for this purpose and were located in the same room where cSNC testing had been administered. Open-field and cSNC testing were never carried out simultaneously. Four open field chambers were used (Med Associates, St. Albans, VT). The dimensions of each chamber were $43 \times 30 \times 43$ cm ($L \times H \times W$). Testing took place between at 10:00 and 16:00 h. Rats were tested in squads of four. At the start of the trial, each rat was placed in the center of the open field. Overall and center locomotor activity were automatically recorded in 5-min bins during a single 20-min trial. The open field was swept immediately after each trial with a wet paper towel.

1.7. Autoshaping test

Autoshaping was administered to test whether VLO and mPFC lesions affect behavior in a different type of incentive downshift situation. The conditioning boxes were different from those used in cSNC testing and were also located in a different room. Four standard conditioning boxes were used (MED Associates, St. Albans, VT). The dimensions of each chamber were $28.0 \times 20.5 \times 20.1$ cm ($L \times H \times W$). The floor was made of steel rods running parallel to the feeder wall. A tray with corncob bedding was placed below the floor to collect feces and urine. A recessed magazine, 2 cm from the floor, was located in the center of the front wall, into which the pellets (45-mg Noyes, rat formula A/I) were delivered automatically. A photocell located inside the magazine detected head entries (goal tracking). A retractable lever made of aluminum (4.8 cm wide, 1.9 cm deep, and 7 cm above the floor) was located 2 cm to the left of the magazine. Insertion and retraction of the lever took 0.2 s. The lever was set so that minimal force would cause a downward movement that could be detected as a lever-pressing response. A light bulb (GE 1820) attached to the ceiling of the chamber and positioned opposite to the magazine, provided diffuse illumination. Each conditioning box was placed in a sound-attenuating chamber containing a speaker to deliver white noise and a fan for ventilation (SPL 80.1 dB, scale C). Conditioning boxes were swept immediately after each session with a wet paper towel.

Rats within each lesion condition were matched by weight and cSNC experience, and then randomly assigned to one of two groups differing in terms of acquisition training. One group within each lesion condition received 50% partial reinforcement training while the other received continuous reinforcement training. Each session started with the onset of the house light and ended when the house light was turned off. A programming error discovered after training was completed resulted in rats in the continuous reinforcement condition receiving 9 trials per session, rather than the 10 trials originally planned. Rats in the partial reinforcement condition received 10 trials per sessions. A total of 5 sessions, one per day, were administered. Thus, continuously reinforced rats received a total of 45 CS–US pairings, whereas partially reinforced rats received 25 CS–US pairings and 25 CS-only trials. Within each session, trials were separated by a variable intertrial interval averaging 90 s (range: 60–120 s). Each trial began with the insertion of the retractable lever for 10 s. A computer recorded lever-pressing responses and goal tracking while the lever was inserted in the chamber. CS–US trials ended with the retraction of the lever and the delivery of 5 pellets in the magazine cup (one pellet per 0.2 s). CS-only trials ended with the retraction of the lever; no pellets were delivered. The dependent variables were lever pressings per minute and

total magazine entries; mean responses per trial were calculated for each animal. The purpose for recording goal tracking was to determine whether changes in lever-pressing responses could be related to competition from goal approach. Therefore, goal tracking was recorded only during lever presentations.

1.8. Histology

At the end of autoshaping testing, animals were sacrificed with CO_2 and their brains removed and stored in 10% formaldehyde for at least 24 h. All brains were then embedded in 30% sucrose for at least 24 h. Using a cryostat, 80 μm coronal sections were sliced, mounted on gelatin-coated glass slides, and stained with thionin. An experimenter blind to behavioral outcomes performed the histological analysis under 40× magnification to determine the location and extent to tissue damage relative to plates form the atlas of Paxinos and Watson [35]. Animals whose lesions were not located in the target structure were discarded from all the analyses.

2. Results

2.1. Histology

In the group of rats with VLO lesions, 12 animals had at least 75% bilateral damage and were included in the analyses reported below (i.e., 7 were discarded due to insufficient or misplaced damage). Histological analysis indicated that the anterior-posterior extent of the damage for the largest percentage of animals was localized between 4.7 and 2.7 mm relative to bregma. More than 75% of the animals had damage between 4.2 and 3.2 mm relative to bregma. The mean anterior–posterior distance was 1.25 mm (SEM = 0.21) for Group 4/VLO and 1.42 mm (SEM = 0.37) for Group 32/VLO. The extent of lesion was well localized to the VLO, but there was minor damage to the ventral/medial aspect of the agranular insular cortex in three animals with some additional damage to the medial/ventral region of the primary motor cortex in one of these animal. The distribution of damage for animals in the 32–4% versus 4–4% downshift conditions was similar (Fig. 1).

In the group with mPFC lesions, 13 animals had at least 75% bilateral damage to the medial prefrontal cortex (i.e., 6 were discarded due to insufficient or misplaced damage). Histological analysis indicated that the average anterior–posterior extent of damage for the largest percentage of animals was localized between 4.2 and 2.2 mm relative to bregma. The mean anterior–posterior distance was 1.38 mm (SEM = 0.13) for Group 4/mPFC and 1.50 mm (SEM = 0.17) for Group 32/mPFC. More than 75% of the animals had damage between 3.7 and 2.7 mm relative to bregma. The extent of lesion was well localized to the mPFC, but there was some damage to the medial/ventral region of the cingulate cortex (Cg1) in 4 animals and minor encroachment of the most anterior region of Cg2 in 2 animals. The distribution of damage for animals in the 32–4% versus 4–4% downshift conditions was similar (Fig. 1).

None of the sham-operated animals showed signs of damage other than that produced by the electrode.

2.2. cSNC test

Trial averages for each group are shown in Fig. 2. One rat in Group 32/Sham failed to acquire consummatory behavior during the preshift and was discarded from the analysis. Preliminary Sham (VLO, mPFC) × Contrast (32%, 4%) × Trial analyses of variance (ANOVA) of data from both preshift and postshift trials revealed that none of the factors involving sham groups was significant, $Fs < 1$. Thus, VLO and mPFC sham groups were pooled together in all subsequent analyses.

During preshift trials, rats learned to drink the sucrose solutions, presenting differential acquisition for the 32% vs. 4% solutions. This effect was similar for all lesion conditions, as indicated by a Lesion (VLO, mPFC, Sham) × Contrast (32%, 4%) × Preshift Trial (1–10) analysis of variance (ANOVA), which only revealed significant effects for trial, contrast, and the trial by contrast interaction, $Fs > 8.82$,

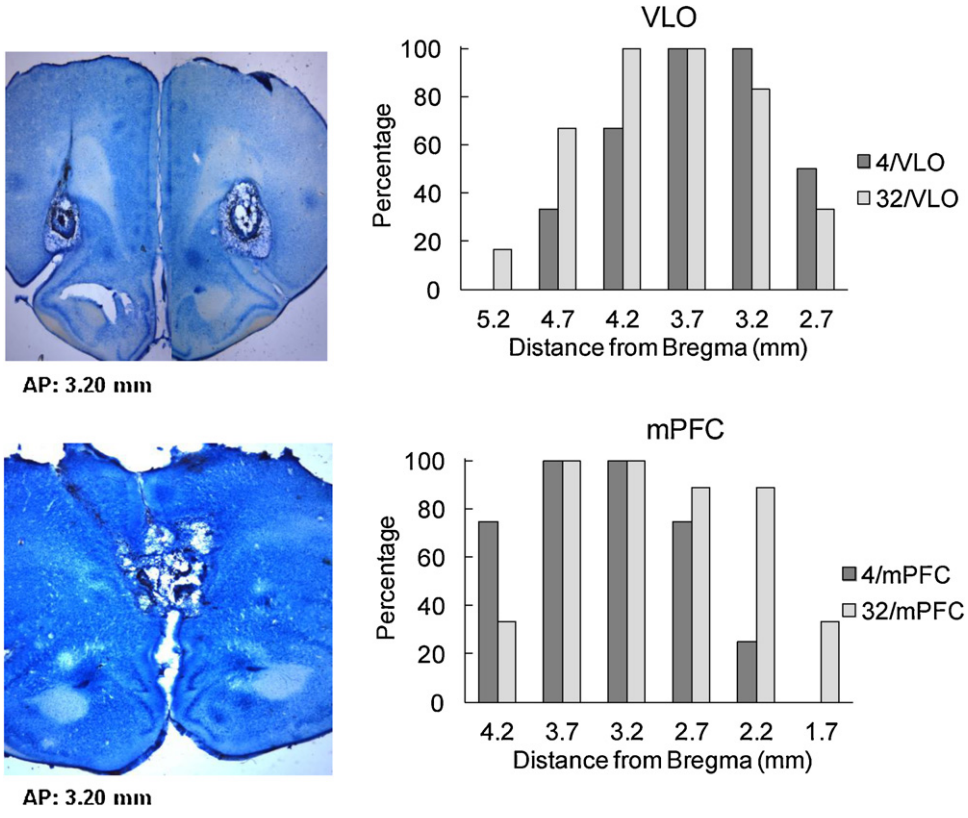

Fig. 1. Examples of VLO (top) and mPFC lesions (bottom). The histograms illustrate the percentage of animals with damage of the VLO (top) and mPFC (bottom) based on the stereotaxic plates of Paxinos and Watson [32] for animals in the downshifted and unshifted conditions. For both VLO and mPFC lesions, the anterior–posterior extent of the lesion was similar for the downshifted and unshifted conditions.

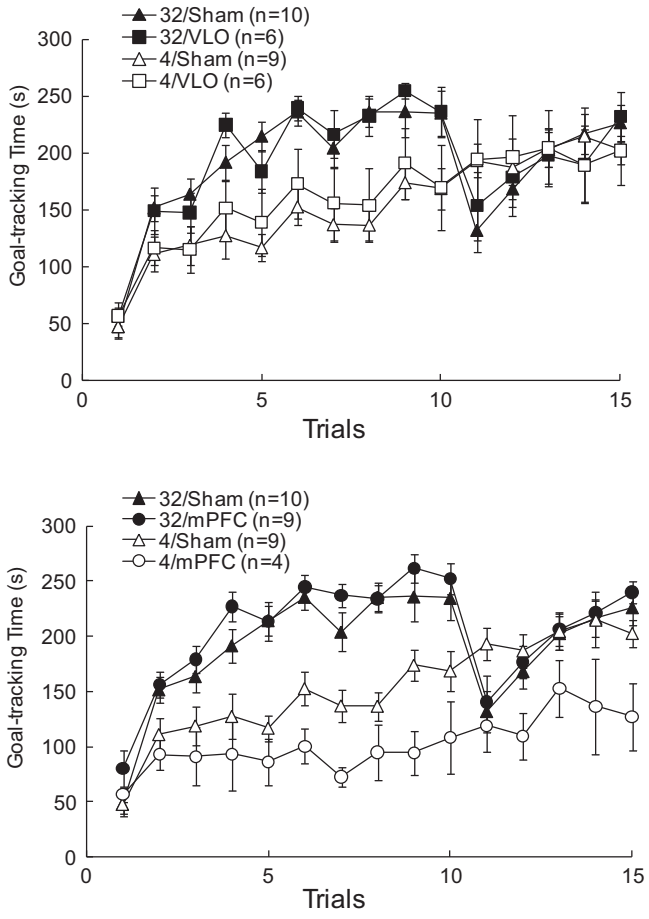

Fig. 2. Mean (±SEM) goal-tracking times for VLO (top) and mPFC groups (bottom), for the entire trial, during cSNC testing. Groups 32 received 32% sucrose during preshift trials (1–10) and were downshifted to 4% sucrose during postshift trials (11–15). Groups 4 received 4% sucrose during preshift and postshift trials (1–15). VLO: ventro-lateral orbital cortex. mPFC: medial prefrontal cortex. All lesions were bilateral and electrolytic. Sham groups received a similar surgical treatment but no current was passed through the electrode into brain tissue.

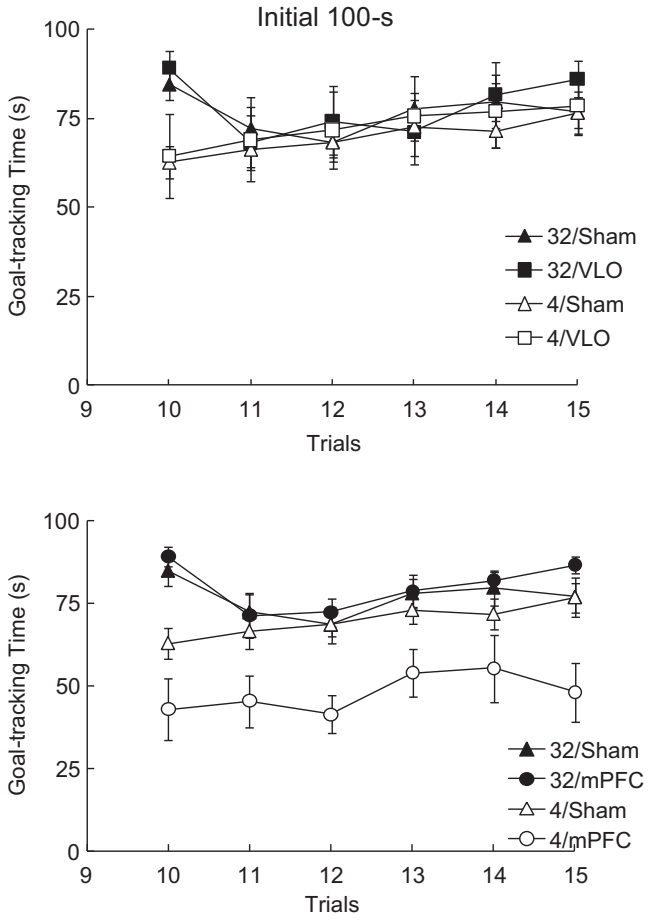

Fig. 3. Mean (±SEM) goal-tracking times for VLO (top) and mPFC groups (bottom) during the initial 100 s on Trials 10–15.

$ps < 0.01$. All other effects and interactions were nonsignificant. A borderline (but nonsignificant) effect was observed for the lesion by contrast interaction, obviously caused by the relatively poor performance of rats in Group 4/mPFC. These animals produced consistently lower goal-tracking times throughout the testing period (Fig. 2, lower panel).

During postshift trials, a cSNC effect is supported by a trial by contrast interaction and a trial effect, $Fs > 7.30$, $ps < 0.01$. However, no evidence for effects of the VLO or mPFC lesions on cSNC was found, as revealed by nonsignificant effects for all other factors. As above, the largest nonsignificant effect was that of the lesion by contrast interaction.

Visual inspection of the postshift results presented in Fig. 2 suggests that VLO and mPFC lesions had different effects on consummatory behavior. To determine whether this was the case, downshifted and unshifted groups were compared independently while holding constant the lesion condition by computing Contrast (32%, 4%) × Trial (11–15) ANOVAs for Sham, VLO, and mPFC pairs of groups. Where the interaction was significant, LSD pair wise comparisons at each trial were calculated with the error term derived from the main analysis. For the sham groups, the contrast by postshift trial interaction and the trial effect were significant, $Fs > 3.87$, $p < 0.008$; the contrast effect was not significant. LSD comparisons between contrast groups at each trial indicated that downshifted rats performed significantly below unshifted controls on Trial 11, $F(1, 17) = 6.42$, $p < 0.03$. For VLO groups, only the trial effect was significant, $F(4, 40) = 2.68$, $p < 0.05$; other effects were not significant. For mPFC groups, there was a nonsignificant, but marginal interaction, $F(4, 44) = 2.56$, $p < 0.06$, and significant main effects for contrast and trial, $Fs > 5.38$, $p < 0.02$. Notice that the contrast effect in mPFC animals is in the opposite direction: unshifted controls performed significantly *below* downshifted rats.

Within-trial analysis has been used to uncover subtle, transient effects that are obscured by pooling data for the entire trial [11,35,36]. Moreover, early trial performance may be reasonably assumed to reflect the effectiveness of the memory retrieval process induced by tasting the sucrose solution. For example, the cSNC effect is usually not observed in intact animals during the initial 100 s of downshift trials; however, administration of the memory-enhancing drug D-cycloserine immediately after Trial 11 increases consummatory suppression early on Trial 12, the following day [13]. Late-trial performance may reflect a mixture of memory retrieval and within-trial motivational factors affecting consummatory behavior during the postshift trials. Fig. 3 shows the performance of VLO (top) and mPFC (bottom) groups during the initial 100 s of trials 10–15 (Trial 10, the last preshift trial, was included only as a reference). As shown here, none of these lesions caused the cSNC effect to emerge early on trials 11–15. The only observable effect of the mPFC lesion was in the unshifted controls, which exhibited consistently lower performance on all the trials. A Lesion × Contrast × Trial (11–15) ANOVA indicated significant lesion by contrast interaction, contrast effect, and trial effect, $Fs > 3.33$, $ps < 0.05$; all other effects were not significant. LSD pairwise contrasts with the error term from the main analysis indicated

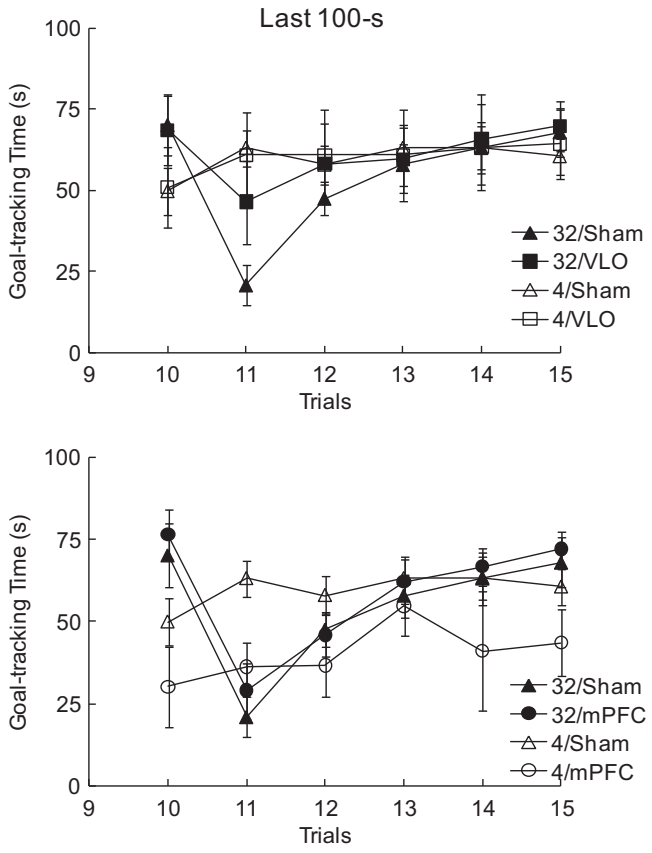

Fig. 4. Mean (±SEM) goal-tracking times for VLO (top) and mPFC groups (bottom) during the last 100 s on Trials 10–15.

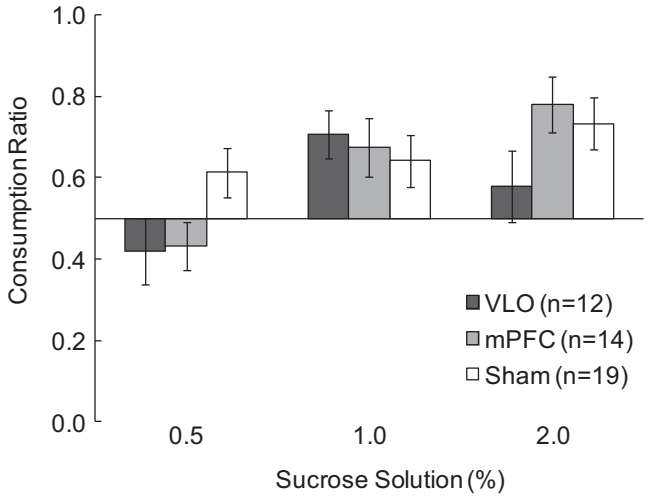

Fig. 5. Mean (±SEM) sucrose consumption ratio in VLO, mPFC, and Sham groups. Sucrose sensitivity was measured in terms of the proportion of sucrose consumption over total fluid consumption (mL) in the two-bottle test.

that the source of the interaction was the significantly lower performance of Group 4/mPFC relative to 32/mPFC, $F(1, 38) = 11.252$, $p < 0.003$. The difference between unshifted and downshifted groups was not different for the VLO and Sham conditions.

Fig. 4 shows the analogous results for the last 100 s of Trials 10–15 (again, Trial 10 serves only as a reference point). A similar analysis indicated significant interaction between contrast and postshift trial and a significant trial effect, $Fs > 9.59$, $ps < 0.001$; none of the other effects were significant. LSD pairwise tests indicated that the source of the interaction was significantly lower performance of downshifted groups than unshifted controls on Trial 11, $F(1, 38) = 7.84$, $p < 0.009$, but the opposite result on Trial 15, $F(1, 38) = 4.64$, $p < 0.04$. There was an apparent effect on the goal-tracking measure of VLO downshifted animals restricted to Trial 11 that might have been obscured in the general analysis by the performance on subsequent trials (see Fig. 4, top panel). To determine whether this effect reached significant level, a second analysis restricted to the VLO vs. Sham comparison, and only to Trials 11–12 was calculated. The triple interaction was now significant, $F(1, 38) = 4.74$, $p < 0.04$. Pairwise LSD tests indicated that downshifted differed from unshifted on Trial 11 in the sham groups, $F(1, 27) = 14.22$, $p < 0.002$, but not in the VLO groups. There were no differences on Trial 12. Thus, VLO lesions eliminated the cSNC effect during the final 100 s of Trial 11.

2.3. Sucrose sensitivity test

An overall Lesion × Sucrose analysis did not yield any significant results. Additional one-way analyses were performed comparing VLO vs. Sham and mPFC vs. Sham for each sucrose concentration (0.5, 1.0, and 2.0%). These analyses were intended to highlight potential effects that could be obscured in the overall analysis. Fig. 5 shows the preference for each sucrose concentration by each lesion condition. VLO rats showed nonsignificant effects for all concentrations. Although visual inspection suggests otherwise, rats in the mPFC condition actually showed a significantly lower sucrose preference than sham rats for the 0.5 sucrose concentration, $Fs(1, 32) > 4.46$, $p < 0.04$, but nonsignificant effects for the other concentrations. These results provided no evidence for an effect of VLO lesions on sucrose sensitivity. However, mPFC lesions seemed to have disrupted preference for sucrose at the lowest tested concentration, 0.5% solution. If this effect were genuine, it may relate to the unusually low level of consummatory behavior in Group 4/mPFC during cSNC testing (see Fig. 2, lower panel).

2.4. Open field test

Overall and center ambulatory distance were evaluated independently with Lesion (VLO, mPFC, Sham) × Bin (1–4) ANOVAs. Due to equipment malfunction, data from three rats were lost. As seen in Fig. 6, all rats showed a decreasing level of overall and center ambulation as the open-field session advanced (i.e., habituation of exploratory behavior). For overall and center performance, lesions did not affect ambulatory behavior. In both measures, there was significant decreasing activity across 5-min bins, $Fs(3, 117) > 136.00$, $ps < 0.01$; none of the other effects was significant.

Lesion × Bin analyses were calculated also for VLO and mPFC separately to determine whether a restricted effect was obscured in the overall analyses. Four separate ANOVAs were computed: VLO center activity, VLO overall activity, mPFC center activity, and mPFC overall activity. The Lesion × Bin interaction was significant in only one case: VLO lesion, center activity, $F(3, 81) = 2.74$, $p < 0.05$. The reduction in activity across bins was significant in all cases, $Fs > 86.67$, $ps < 0.001$. All other interactions and the main effect of lesion were nonsignificant. Thus, the habituation rate of locomotor activity was faster in VLO animals than in sham animals for the central area of the open field.

2.5. Autoshaping test

The acquisition of lever-pressing behavior under CR and PR conditions is shown for VLO (top), mPFC (middle), and Sham (bottom) groups in Fig. 7. The PRAE, or higher response level in the PR than CR groups, was clearly observed in Sham and mPFC

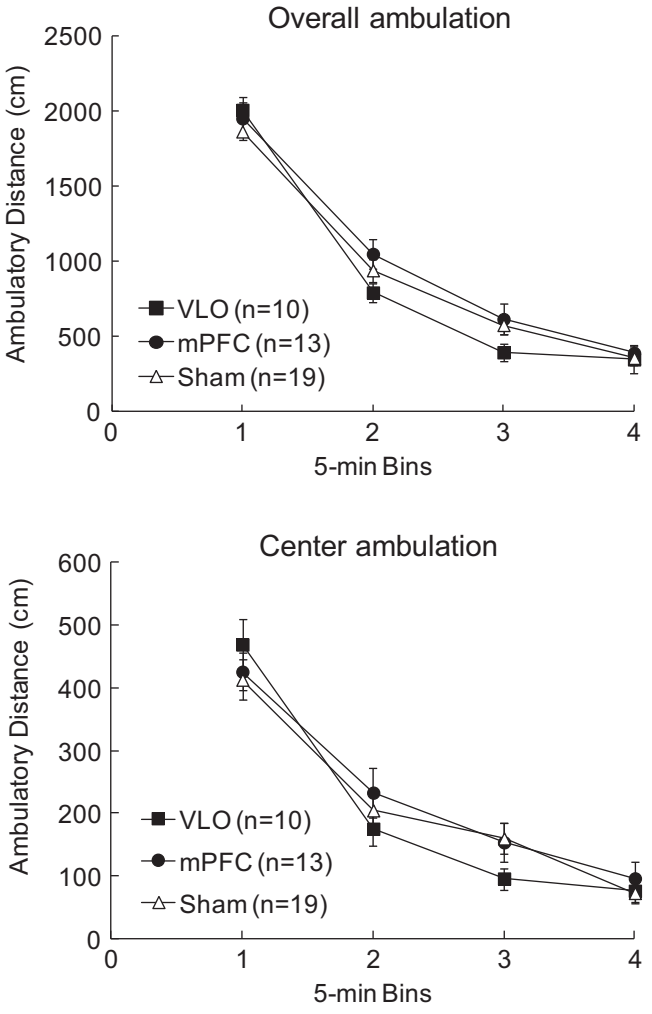

Fig. 6. Mean (±SEM) overall (top) and center (bottom) ambulatory distance during a 20-min open-field test in VLO, mPFC, and Sham groups.

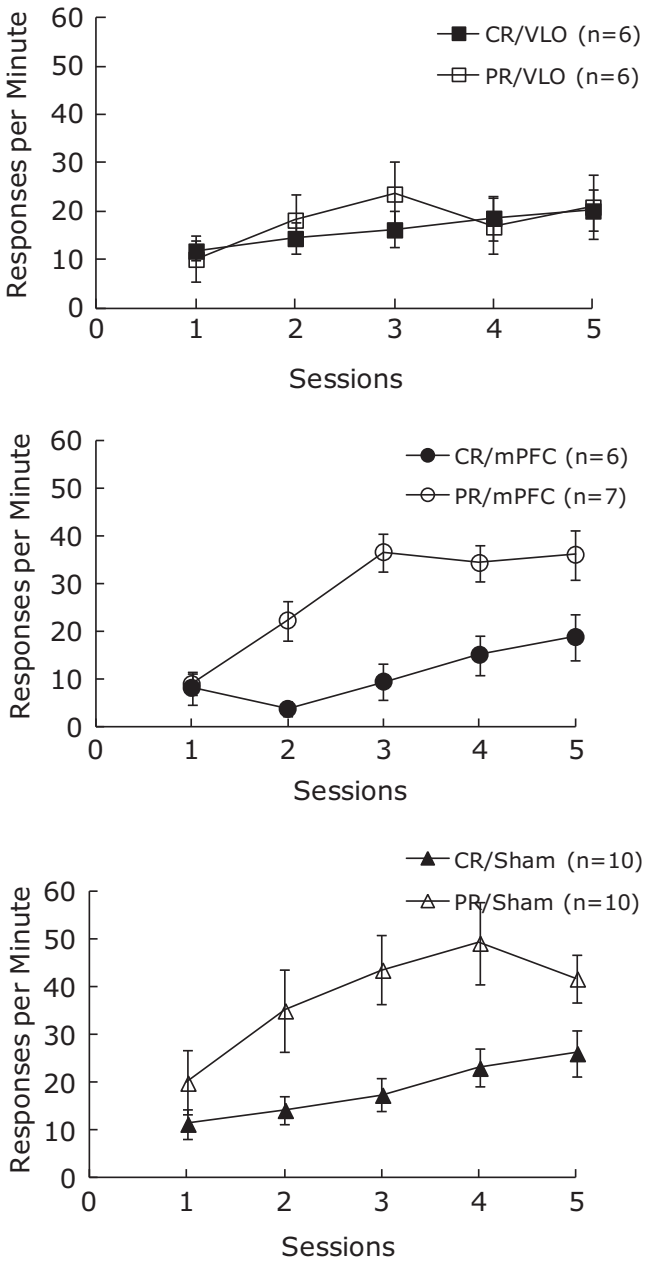

Fig. 7. Mean (±SEM) lever-pressing responses per minute for each autoshaping session for partial reinforcement (PR) and continuous reinforcement (CR) groups of rats with VLO (top), mPFC (middle), or Sham lesions (bottom).

groups, but not in VLO groups. Despite the apparent lesion by schedule interaction, a Lesion (VLO, mPFC, Sham) × Schedule (CR, PR) × Session (1–5) ANOVA only revealed significant effects for the schedule by trial interaction, schedule, and session, $Fs > 3.70$, $ps < 0.008$. Other effects were not significant. Separate ANOVAs were computed for each lesion group, as done with other dependent measures. It was expected that the schedule effect would be present in sham and mPFC groups, but not in VLO groups; the analyses supported these predictions. PR groups were significantly above CR groups in sham and mPFC animals, $Fs > 6.82$, $ps < 0.02$, but not in VLO animals. The session effect was also significant in sham and mPFC groups, $Fs > 9.02$, $ps < 0.001$, but not in VLO groups. Finally, the schedule by session interaction was only significant in mPFC groups, $F(4, 44) = 3.18$, $p < 0.03$.

An analysis on response rates during the first trial of each session, before the first outcome for the session was delivered, was computed to determine whether the PRAE would result from relatively more satiation in CR animals than in PR animals as a result of differences in the amount of food delivered during the session. Performance during the first trial was not influenced by food delivery because it occurred before the first outcome of the session, thus detecting selectively the ability of the CS to induce response activation. The results are shown in Fig. 8. Clearly, the same pattern of results was observed whether in the entire session or in the first trial of each session. Analyses indicated significantly higher response rate in PR than CR groups in sham and mPFC groups, $Fs > 4.85$, $ps < 0.05$, but not in VLO groups. The session effect was significant in all groups, $Fs > 2.78$, $ps < 0.04$, whereas the schedule by session interaction was significant only in the sham groups, $F(4, 68) = 3.11$, $p < 0.03$. Therefore, the PRAE was present already in the first trial of each session in sham and mPFC groups, but it was absent in VLO groups.

A similar analysis was calculated for goal tracking performance to determine whether the absence of the PRAE in VLO groups was related to competition from goal approach. The results are shown in Fig. 9 in terms of the session means for each group. Rats in all conditions showed higher goal tracking performance under PR than under CR, suggesting that increased response competition was not a factor in VLO groups. Thus, the failure of the PRAE to emerge in VLO animals was specific to lever-pressing behavior, as the effect developed normally in terms of goal tracking in all lesion conditions. These analyses indicated the following results.

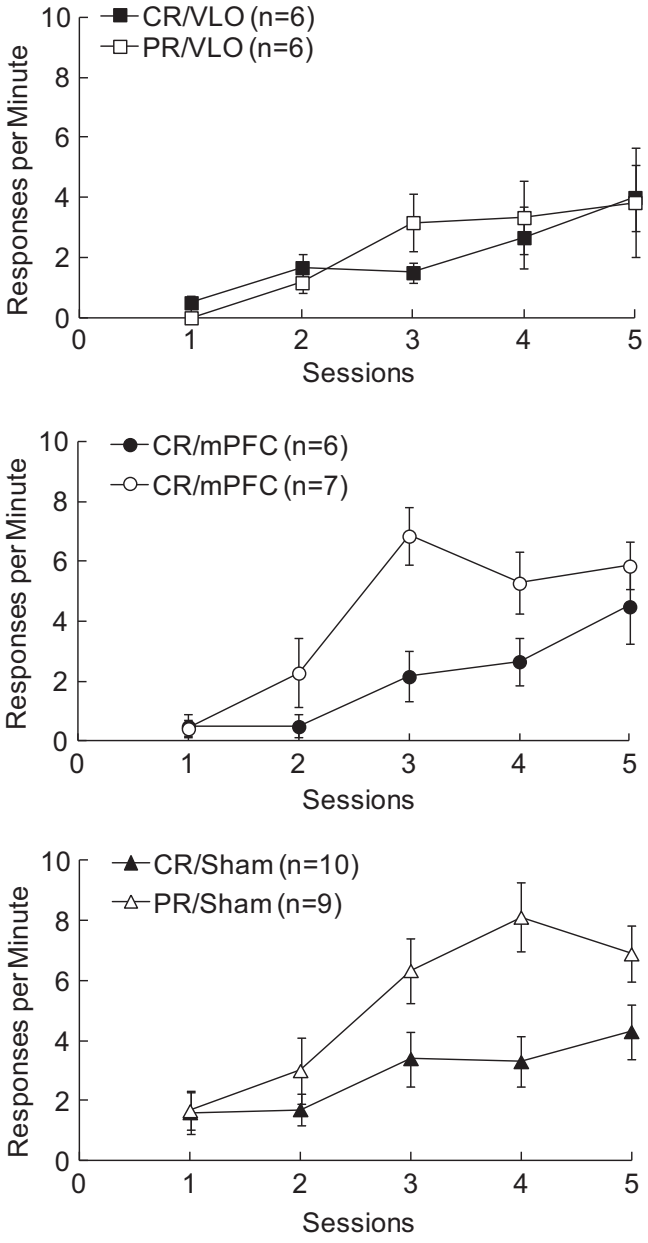

Fig. 8. Mean (±SEM) lever-pressing responses per minute during the first trial of each autoshaping sessions for partial reinforcement (PR) and continuous reinforcement (CR) groups of rats with VLO (top), mPFC (middle), or Sham lesions (bottom).

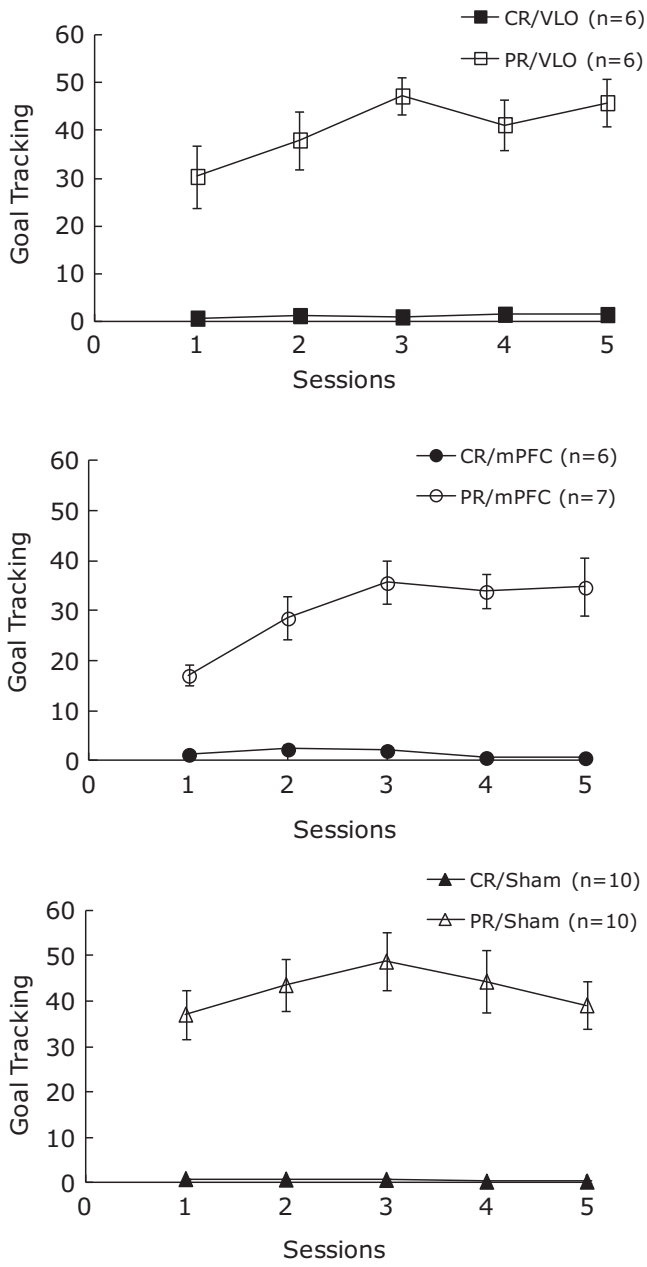

Fig. 9. Mean (±SEM) goal-tracking responses per trial for each autoshaping session for partial reinforcement (PR) and continuous reinforcement (CR) groups of rats with VLO (top), mPFC (middle), or Sham lesions (bottom).

PR rats responded higher than CR rats in the three lesion conditions, $Fs > 92.73$, $ps < 0.001$. The schedule by trial interaction was not significant in sham and VLO animals, but significant in mPFC animals, $F(4, 44) = 2.98$, $p < 0.03$. Changes across sessions were significant for VLO and mPFC animals, $Fs > 2.83$, $ps < 0.04$, but not for sham animals. These results also suggest that at least in the autoshaping situation, the PRAE is not dependent upon response competition; in fact, PR sham animals responded at a high rate to both the lever (sign tracking) and the magazine (goal tracking), whereas CR animals showed less responding for both sign and goal tracking.

3. Discussion

The present experiment evaluated the role of two PFC regions (VLO and mPFC) on two effects involving incentive downshifts (cSNC and the PRAE), and on sucrose sensitivity and open-field activity. The results can be summarized as follows. First, VLO lesions eliminated the cSNC effect, but only on Trial 11 and during the ending part of the trial, and eliminated the PRAE in autoshaping. VLO lesions also accelerated the rate of habituation in the open field, but only in the central area. VLO lesions had no observable effects on sucrose sensitivity. Second, there was no evidence that mPFC lesions affected the cSNC effect, the PRAE, and open-field activity. However, mPFC lesions reduced consummatory behavior in the unshifted condition during cSNC testing. Perhaps related to the latter effect, mPFC lesions reduced preference for the lowest sucrose solution tested. The following paragraphs examine the limitations and implications of these conclusions.

Three major limitations are addressed next. First, electrolytic lesions are more clearly defined and possibly more effective at destroying neural tissue than chemical lesions, but they also destroy fibers of passage [28]. Axons interconnecting cortical areas

are probably significant in number and thus the extent to which the results reported here are due to this type of damage is unclear. However, further examination of the functional role of a given brain area on a specific behavioral effect can be safely postponed when electrolytic lesions fail to produce observable effects. This is because the area is unlikely to play a vital role in the behavior under examination given the generally extensive damage produce by such lesions. Second, behavioral tests were administered in the same sequence for all animals, thus preventing an evaluation of carry-over effects from one test situation to the next. The two situations involving incentive downshifts are known to be sensitive to sequential task effects. For example, the cSNC interacts with tests of anxiety (elevated plus maze and home-cage emergence tests [36]) and the effects of partial reinforcement are known to carry over to other tasks involving different environments, responses, and motivational states [37]. In the present experiment, the only concern would be whether exposure to the cSNC situation affected subsequent tests, because the PRAE was the last task presented to the animals. However, the cSNC effect in this particular experiment happened to be relatively small in size and short lasting. In sham animals, for example, the cSNC effect was clearly seen only on Trial 11. The strongest effect was the PRAE and it was observed last in the sequence of tests. Third, some of the sample sizes were smaller than usual for similar experiments due to lesion misplacement and size. For example, in the cSNC stage, Groups 32/VLO and 4/VLO included only 6 subjects each, and Group 4/mPFC included only 4 animals; the original target sample size was hoped to have been 10 per group. Small sample sizes usually conspire against group differences because of increase within-group variance and reduced degrees of freedom. The fact that these effects were statistically significant suggests that they are probably genuine. Still, these results should be taken with caution.

VLO lesions caused a transient, within-trial increase in consummatory performance during the later part of the first downshift trial (Trial 11). It is possible that such an effect of the VLO lesion is related to a decreased negative emotional response to the downshift that takes a few minutes to peak on Trial 11. This transient effect of the VLO lesions on cSNC may be related to the enhanced c-fos expression after the downshift trial for the orbitofrontal cortex [38]. Alternatively, divergent results between VLO lesions and orbitofrontal cortex activation on cSNC may be related to procedural differences across experiments in a manner analogous to studies on the nucleus accumbens and cSNC. Sucrose downshift enhanced c-fos expression in the nucleus accumbens [38] and blunted dopamine efflux during Trial 11 [39]. However, lesions in this area failed to produce detectable effects on cSNC [40,41].

The PRAE was absent in rats with VLO lesions, but only when measured in terms of lever pressing. There was a trend, albeit nonsignificant, toward decreased responding during both CR and PR in VLO rats, relative to sham rats, consistent with impaired acquisition of autoshaping following orbitofrontal lesions reported in previous studies [4]. The reduction of the cSNC effect on Trial 11 (Fig. 4) and the absence of the PRAE in lever pressing (Figs. 7 and 8) are consistent with an explanation in terms of frustration theory [33]. Under normal circumstances (e.g., sham animals), incentive downshift invigorates behavior by eliciting higher drive levels [42]. In the cSNC situation, increase drive may be responsible for the typically high levels of activity and searching behavior observed during the initial downshift trials [43], thus leading to reduced drinking. In the PRAE situation, the presence of a discrete stimulus with strong signal properties [44] may channel higher drive levels into the invigoration of lever pressing. VLO lesions seem to attenuate drive normally induced by incentive downshifts—a nonassociative process. Drive attenuation in VLO animals may also be responsible for the enhanced habituation of central-area activity in the open field. A drive function for VLO on both cSNC and the PRAE is also consistent with increased persistence in extinction of food-rewarded responses following VLO lesions [45].

There was no evidence for an effect of mPFC lesions on reward downshift, either in the cSNC or PRAE situation. An interpretation of the cSNC results is complicated by the effect of the mPFC lesion on unshifted performance. mPFC lesions decreased consummatory behavior to 4% sucrose, but did not seem to affect consummatory behavior to 32% sucrose. These data are partially consistent with Pecoraro et al. [10], who reported no effects of mPFC lesions on early postshift (postshift trials 1–3), but an increase of performance in an extended postshift phase. However, as noted above, unshifted controls were not included in that study, which leaves open the question of whether the effects reported by Pecoraro et al. are specific to the incentive downshift or to the consumption of low-concentration sucrose solutions. Notice, however, that the mPFC lesions in the present experiment were located mainly in the prelimbic cortex, whereas the mPFC lesions in the Pecoraro et al. [10] study were located mainly in the infralimbic cortex. Taken together, these data do not allow for a firm conclusion on the role of the mPFC (prelimbic and infralimbic cortices) in the cSNC situation. The fact that in the present experiment mPFC also failed to influence the PRAE suggests that it is premature to assign this area any specific role in incentive downshift situations. In addition, the lack of sensitivity for the lowest sucrose concentration in the sucrose preference test by mPFC animals is also partially consistent with a lower performance of animals exposed to 4% sucrose in the cSNC situation. This, however, must be taken with caution for two reasons. First, because the procedures for testing sucrose sensitivity and cSNC are very different (24 h vs. 5 min, choice vs. no choice). Second, because downshifted animals with mPFC lesions, exposed to 4% sucrose, display very different consummatory behavior from that of 4%, unshifted control. Note that such a difference in consumption of 4% sucrose (i.e., between downshifted and unshifted groups during postshift trials, all receiving access to 4% sucrose) cannot be explained exclusively in terms of reduced sensitivity for low sucrose solutions in animals with mPFC lesions.

Brain mechanisms underlying reward downshift can be described in terms of a top-down activation of the cortex and critical subcortical nuclei that reorganizes brainstem-based mechanisms for sucrose-related consummatory behavior [12,13]. PFC areas are in an exceptional location to coordinate several neural processes [5]. In the case of cSNC, it seems that the ACC [11] and the insular cortex [9] are two promising areas for the control of the behavioral mechanisms that underlie the sudden reorganization of consummatory behavior following cSNC. These areas also seem to exert opposite influences on consummatory behavior during incentive downshifts, with lesions of the ACC enhancing cSNC, whereas lesions of the insular cortex eliminating cSNC.

Flaherty's [46] multistage hypothesis may help clarify the neurochemical basis of cSNC, but it clearly needs greater specificity. Amsel's [33] frustration theory provides such specificity when applied to the cSNC situation [6,47]. Some effects of brain lesion and pharmacological studies are consistent with the hypothesis that different mechanisms underlie consummatory behavior during the first vs. second downshift trials, at least under the usual procedure. Trial selectivity has been observed for benzodiazepine anxiolytics and opioids [23,46], and also for ACC lesions [11]. Flaherty's rejection and search effects in the stage 1 of his multistage model are conceptually analogous to Amsel's aversive and drive-inducing properties of primary frustration—the unconditioned state triggered by surprising nonreward. Flaherty's conflict and recovery effects of stage 2 in his hypothesis are analogous to the more detailed concepts of approach-avoidance conflict and counterconditioning of frustration in Amsel's frustration theory. It remains to be seen whether these models can, on the one hand, handle all

the empirical evidence, and on the other, be translated into brain function. For example, both naloxone (an opioid-receptor antagonist) and ACC lesions enhance the cSNC effect [11,48], suggesting the possibility of a compensatory mechanism, perhaps mediated by opioidergic activity, that modulates the intensity of the emotional response to the incentive downshift, as is known to occur in situations involving physical pain and fear [49,50]. There is no provision in either model for such a compensatory mechanism.

Acknowledgments

The research reported in this article was partially supported by TCU/RCAF Grant # 60562 to MRP.

References

[1] Uylings HBM, Groenewegenb HJ, Kolb B. Do rats have a prefrontal cortex. Behavioural Brain Research 2003;146:3–17.
[2] Quirk GJ, Russo GK, Barron JL, Lebron K. The role of ventromedial prefrontal cortex in the recovery of extinguished fear. The Journal of Neuroscience 2000;20:6225–31.
[3] Gallagher M, McMahan RW, Schoenbaum G. Orbitofrontal cortex and representation of incentive value in associative learning. The Journal of Neuroscience 1999;19:6610–4.
[4] Chudasama Y, Robbins TW. Dissociable contributions of the orbitofrontal and infralimbic cortex to Pavlovian autoshaping and discrimination reversal learning: further evidence for the functional heterogeneity of the rodent frontal cortex. The Journal of Neuroscience 2003;23:8771–80.
[5] Miller EK, Cohen JD. An integrative theory of prefrontal cortex function. Annual Review of Neuroscience 2001;24:167–202.
[6] Papini MR. Comparative psychology of surprising nonreward. Brain, Behavior, and Evolution 2003;62:83–95.
[7] Vogel JR, Mikulka PJ, Spear NE. Effects of shifts in sucrose and saccharin concentrations on licking behavior in the rat. Journal of Comparative and Physiological Psychology 1968;66:661–6.
[8] Boughner RL, Papini MR. Survival of the partial reinforcement extinction effect after contextual shifts. Learning and Motivation 2006;37:304–23.
[9] Lin J, Roman C, Reilly S. Insular cortex and consummatory successive negative contrast in the rat. Behavioral Neuroscience 2009;123:810–4.
[10] Pecoraro N, de Jong H, Ginsberg AB, Dallman MF. Lesions of the medial prefrontal cortex enhance the early phase of psychogenic fever to unexpected sucrose concentration reductions, promote recovery from negative contrast and enhance spontaneous recovery of sucrose-entrained anticipatory activity. Neuroscience 2008;153:901–17.
[11] Ortega LA, Uhelski M, Fuchs PN, Papini MR. Impairment of recovery from incentive downshift after lesions of the anterior cingulate cortex: emotional or cognitive deficits. Behavioral Neuroscience 2011;6:988–95.
[12] Norris JN, Daniel AM, Papini MR. Spontaneous recovery of consummatory behavior, but not of consummatory successive negative contrast. Learning and Motivation 2008;39:296–312.
[13] Norris JN, Ortega LA, Papini MR. Posttrial D-cycloserine enhances the emotional memory of an incentive downshift event. Behavioural Brain Research 2011;223:348–55.
[14] Becker HC, Jarvis MF, Wagner GC, Flaherty CF. Medial, lateral amygdalectomy differentially influences consummatory negative contrast. Physiology & Behavior 1984;33:707–12.
[15] Grigson PS, Spector AC, Norgren R. Lesions of the pontine parabrachial nuclei eliminate successive negative contrast effects in rats. Behavioral Neuroscience 1994;108:714–23.
[16] Grill HJ, Norgren R. The taste reactivity test. I. Mimetic responses to gustatory stimuli in neurologically normal rats. Brain Research 1978;143:263–79.
[17] Grill HJ, Norgren R. The taste reactivity test. II. Mimetic responses to gustatory stimuli in chronic thalamic and chronic decerebrate rats. Brain Research 1978;143:281–97.
[18] Grill HJ, Norgren R. Chronically decerebrate rats demonstrate satiation but not bait shyness. Science 1978;201:267–9.
[19] Norgren R. Gustatory system. In: Paxinos G, editor. The Rat Nervous System. second edition San Diego, CA: Academic Press; 1995.
[20] Tabuchi E, Yokawa T, Mallick H, Inubushi T, Kondoh T, Ono T, et al. Spatiotemporal dynamics of brain activated regions during drinking behavior in rats. Brain Research 2002;951:270–9.
[21] Travers JB, Dinardo LA, Karimnamazi H. Motor and premotor mechanisms of licking. Neuroscience and Biobehavioral Reviews 1997;21:631–47.
[22] Papini MR, Wood M, Daniel AM, Norris JN. Reward loss as psychological pain. International Journal of Psychology and Psychological Therapy 2006;6:189–213.
[23] Xie YF, Wang JF, Huo Q, Jia H, Tang JS. μ but not d and k opioid receptor involvement in ventrolateral orbital cortex opioid-evoked antinociception in formalin test rats. Neuroscience 2004;126:717–26.
[24] Ortega LA, Daniel AM, Davis JB, Fuchs PN, Papini MR. Peripheral pain enhances the effects of incentive downshifts. Learning and Motivation 2011;42:203–9.
[25] Papini MR. Role of opioid receptors in incentive contrast. International Journal of Comparative Psychology 2009;22:170–87.
[26] Pastoriza LN, Morrow TJ, Casey KL. Medial frontal cortex lesions selectively attenuate the hot plate response: possible nocifensive apraxia in the rat. Pain 1996;64:11–7.
[27] Altier N, Stewart J. Intra-VTA infusions of the substance P analogue, DiMe-C7, and intra-accumbens infusions of amphetamine induce analgesia in the formalin test for tonic pain. Brain Research 1993;628:279–85.
[28] Frey S, Morris R, Petrides M. A neuroanatomical method to assess the integrity of fibers of passage following ibotenate-induced damage to the central nervous system. Neuroscience Research 1997;28:285–8.
[29] Donahue RR, LaGraize SC, Fuchs PN. Electrolytic lesion of the anterior cingulated cortex decreases inflammatory, but not neuropathic nociceptive behavior in rats. Brain Research 2001;897:131–8.
[30] Lacroix L, Spinelli S, Heidbreder CA, Feldon J. Differential role of the medial and lateral prefrontal cortices in fear and anxiety. Behavioral Neuroscience 2000;114:1119–30.
[31] Hamani C, Diwan M, Macedo CE, Brandão ML, Shumake J, Gonzalez-Lima F, et al. Antidepressant-like effects of medial prefrontal cortex deep brain stimulation in rats. Biological Psychiatry 2010;67:117–24.
[32] Amsel A. The role of frustrative nonreward in noncontinuous reward situations. Psychological Bulletin 1958;55:102–19.
[33] Amsel A. Frustration Theory: An Analysis of Dispositional Learning and Memory. Cambridge, MA: Cambridge University Press; 1992.
[34] Gray JA. Elements of Two-process Learning Theory. New York: Academic Press; 1975.
[35] Paxinos G, Watson C. The Rat Brain in Stereotaxic Coordinates. sixth edition New York: Academic Press; 2007.
[36] Flaherty CF, Greenwood A, Martin J, Leszczuk M. Relationship of negative contrast to animal models of fear and anxiety. Animal Learning and Behavior 1998;26:397–407.
[37] Ross RR. Positive and negative partial-reinforcement extinction effects carried through continuous reinforcement, changed motivation, and changed response. Journal of Experimental Psychology 1964;68:492–502.
[38] Pecoraro N, Dallman MF. c-Fos after incentive shifts: expectancy, incredulity, and recovery. Behavioral Neuroscience 2005;119:366–87.
[39] Genn RF, Ahn S, Phillips AG. Attenuated dopamine efflux in the rat nucleus accumbens during successive negative contrast. Behavioral Neuroscience 2004;118:869–73.
[40] Eagle DM, Humby T, Howman M, Reid-Henry A, Dunnett SB, Robbins TW. Differential effects of ventral and regional dorsal striatal lesions on sucrose drinking and positive and negative contrast in rats. Psychobiology 1999;27:267–76.
[41] Leszczuk MH, Flaherty CF. Lesions of nucleus accumbens reduce instrumental but not consummatory negative contrast in rats. Behavioural Brain Research 2000;116:61–79.
[42] Stout S, Boughner RL, Papini MR. Reexamining the frustration effect in rats: aftereffects of surprising reinforcement and nonreinforcement. Learning and Motivation 2003;34:437–56.
[43] Pellegrini S, Mustaca A. Consummatory successive negative contrast with solid food. Learning and Motivation 2000;31:200–9.
[44] Tomie A, Grimes KL, Pohorecky LA. Behavioral characteristics and neurobiological substrates shared by Pavlovian sign-tracking and drug abuse. Brain Research Reviews 2008;58:121–35.
[45] Butter CM, Mishkin M, Rosvold HE. Conditioning and extinction of a food-rewarded response after selective ablations of frontal cortex in rhesus monkeys. Experimental Neurology 1963;7:65–75.
[46] Flaherty CF. Incentive Relativity. New York: Cambridge University Press; 1996.
[47] Wood M, Daniel AM, Papini MA. Selective effects of the delta-opioid receptor agonist DPDPE on consummatory successive negative contrast. Behavioral Neuroscience 2005;119:446–54.
[48] Pellegrini S, Wood M, Daniel AM, Papini MR. Opioid receptors modulate recovery from consummatory successive negative contrast. Behavioural Brain Research 2005;164:239–49.
[49] Mizoguchi H, Watanabe C, Sakurada T, Sakurada S. New vistas in opioid control of pain. Current Opinion in Pharmacology 2012;12:87–91.
[50] McNally GP. The roles of endogenous opioids in fear learning. International Journal of Comparative Psychology 2009;22:153–69.