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Short communication

Pre-surgical training ameliorates orbitofrontal-mediated impairments in spatial reversal learning

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ABSTRACT

We recently reported that orbitofrontal cortical (OFC) lesions impaired reversal learning of an instrumental two-lever spatial discrimination task, a deficit manifested as increased perseveration on the pre-potent response. Here we examine whether exposure to reversal learning test pre-operatively may have a beneficial effect for future reversal learning of OFC-lesioned animals. Rats were trained on a novel instrumental two-lever spatial discrimination and reversal learning task, measuring both 'cognitive flexibility' and constituent processes including response inhibition. Both levers were presented, only one of which was reinforced. The rat was required to respond on the reinforced lever under a fixed ratio 3 schedule of reinforcement. Following attainment of criterion, two reversals were introduced. Rats were then matched according to their reversal performance and subjected to bilateral excitotoxic OFC lesions. Following recovery, a series of four reversals was presented. OFC lesions impaired neither retention nor reversal phases. These data, together with the previously reported reversal deficit following OFC lesions, suggest that OFC is not needed when task experience has been gained but it is necessary when task demands are relatively high.

1. Introduction

An essential element of intelligence is the ability to adjust appropriately to changing surroundings. The abilities to learn and relearn the significance of stimuli that predict reward and punishment, and the ability to withhold responses once they become inappropriate, are crucial for successful environmental and social interactions. Orbitofrontal cortex (OFC) has been implicated in cognitive flexibility and constituent processes including response inhibition.

Recent evidence suggests that OFC lesions in various species cause an inability to withhold inappropriate responses particularly when learned behaviour must be modified to reflect changes in the likely outcome or consequence of responding. Consequently, OFC is not necessary for acquisition of simple discriminations problems, but should be critical for reversals of those problems [human: 11,22,24,25; monkey: 3,8,14,17; rat: 1,2,18,20,27,28]. These studies also suggest that impairments upon reversal are partially due to an increased perseveration to the previously relevant stimulus. Where perseveration is noted during reversal learning, the impairment appears to arise early rather than later. Consequently, such OFC lesion-induced reversal deficits are more likely to result from either a specific loss of the ability to inhibit the pre-potent response, or a failure to inhibit a previously relevant stimulus-reward association, or a failure to use the new negative affective information to counter previous positive affective information.

We have recently found that orbitofrontal (but not infralimbic and prelimbic) cortical lesions on animals with no pre-operative training impair reversal learning performance of an instrumental two-lever spatial discrimination task, a deficit manifested as increased perseveration of the pre-potent response [2]. Several studies on the effects of pre- and post-operative training have produced quite equivocal results. OFC lesions have been shown to impair performance or pre-trained animals on several discrimination tasks [9,10], while other reports have demonstrated the opposite finding when OFC-lesioned rats were tested following no pre-operative training on the task [7,27].

Thus the aim of this study was to assess the contribution of the rodent OFC on reversal performance when reversal learning experience has been gained prior to OFC lesions. To this end, rats were given selective cell body, fibre-sparing lesions of the OFC after they had been tested pre-operatively on two spatial discrimination reversals. Reversal training was resumed post-operatively with a series of four further reversals.

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2. Methods

2.1. Subjects

Twenty-four male Lister Hooded rats (Charles River, UK) weighting 280–320 g at the start of experiment, were pair-housed under a reversed light cycle (lights on from 19.00 to 07.00). Prior to the beginning of training, rats were handled for ≈3 min daily for 5 days and were put on a food-restriction schedule (15–18 g of Purina lab chow per day). Water was available *ad libitum* and testing took place between 13.00 and 16.00 six to seven days per week. The work was carried out under UK Home Office licence (PPL 80/1767) in accordance with the UK Animals (Scientific Procedures) Act 1986.

2.2. Apparatus

The behavioural apparatus consisted of seven operant conditioning chambers (30 cm × 24 cm × 30 cm; Med Associates, Georgia, VT), each enclosed within a sound-attenuating wooden box fitted with a fan for ventilation and masking of extraneous noise. Each chamber was fitted with two retractable levers located on either side of a centrally positioned food magazine, into which an external pellet dispenser could deliver 45 mg sucrose pellets (Noyes dustless pellets; Sandown Scientific, Middlesex, UK), a light emitting diode (LED), which was positioned centrally above each lever, a magazine light, and a houselight. Magazine entry was detected by an infrared photocell beam located horizontally across the entrance. The apparatus was controlled by Whisker control software (www.whiskercontrol.com) and the task was programmed in Visual C++ (v.6).

2.3. Surgery

Subjects were divided into two groups, matched for their pre-operative performance during reversal phases. Animals were anaesthetized using 100 ml/kg Avertin [10 g of 2,2,2-tribromoethanol (Sigma, Poole, UK) in 5 g of tertiary amyl alcohol, diluted in a solution of 40 ml of ethanol and 450 ml of PBS] and secured in a stereotaxic frame fitted with atraumatic earbars. The incisor bar was set at −3.3 mm relative to the inter-aural line for a flat skull position. Bilateral excitotoxic lesions were made using either 0.09 M (OFC lesions) quinolinic acid, dissolved in 0.1 M phosphate buffer; the pH was adjusted with 0.1 M NaOH to between 6.5 and 7.0. Infusions (0.1 μl/min) were made according to the following coordinates [23]: OFC: site 1 AP, +4.0, L, ±0.8, DV, −3.4, 0.2 μl, site 2 AP, +3.7, L, ±2.0, DV, −3.6, 0.3 μl, site 3 AP, +3.2, L, ±2.6, DV, −4.4, 0.2 μl. Infusions were made 1 min after lowering the injector into the target region. The injector was left for a further 3 min after each infusion to allow for diffusion. Sham-operated animals received the same surgical procedure as the lesioned groups, except that they were infused with phosphate buffer 0.01 M. After surgery, animals were allowed for seven to ten days to recover prior to behavioural re-testing, during which time subjects were returned to their home cages.

2.4. Histology

After the completion of behavioural testing, animals were given a lethal dose of sodium pentobarbitone (1.5 ml/rat; Euthatal, 200 mg/ml; Genus Express, UK) and perfused transcardially with 0.01 M PBS followed by 4% paraformaldehyde. The brains were removed, postfixed in 4% paraformaldehyde for 24 h, and dehydrated in 20% sucrose in 0.01 M PBS overnight. Coronal sections mounted on double-subbed glass slides and stained with Cresyl Violet were used to verify lesion placement and to assess the extent of the lesion-induced neuronal loss.

2.5. Behavioural procedure

Rats were trained on the instrumental two-lever spatial discrimination and serial reversal learning task as described and illustrated previously [2]. Briefly, rats were initially trained to nose poke in the central magazine to trigger presentation of

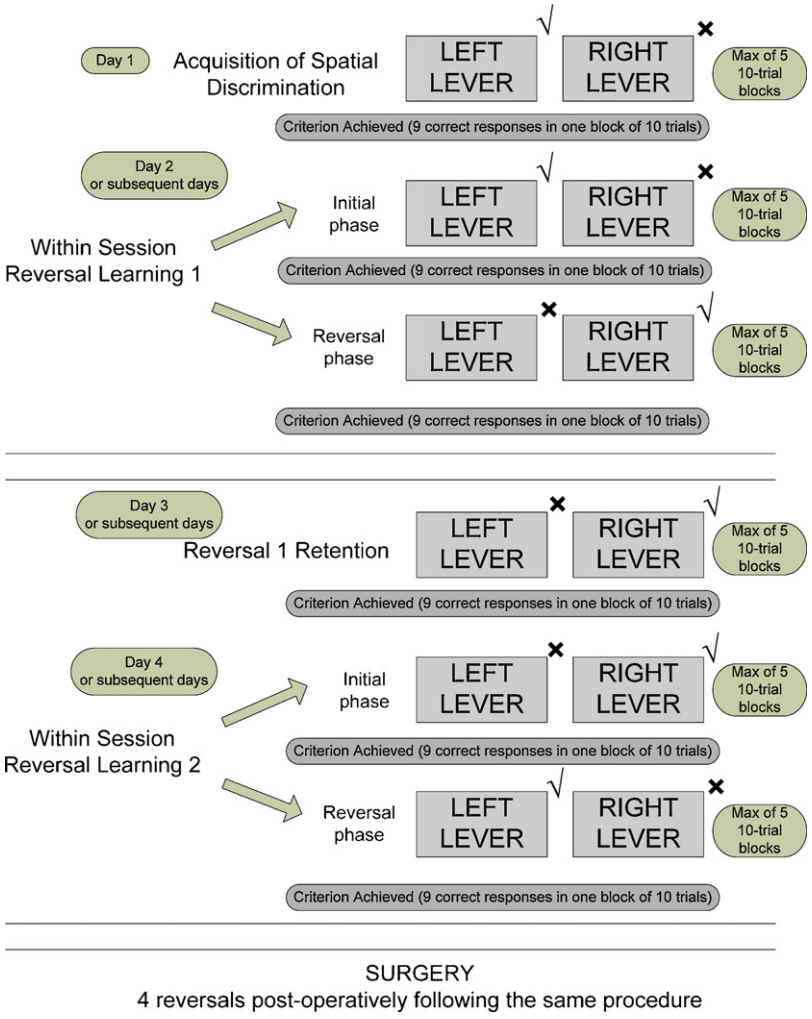

Fig. 1. Flow diagram of the behavioural procedure. The √ and × symbols indicate which lever was correct and incorrect at each stage. The correct lever was counterbalanced across rats.

the retractable levers and to respond on them under a fixed ratio 3 (FR-3) schedule for food delivery (pre-training). The FR-3 schedule was used to preclude the possibility of reinforcing single, accidental presses on the correct lever (animals cannot detect reversal following a single response) and to make the reversal task more difficult.

2.5.1. Acquisition of spatial discrimination

Training continued with the acquisition of a two-lever discrimination task. Now both levers were presented at trial onset and the rat had to learn that three consecutive lever presses on only one of these levers would result in reward.

Each session lasted 20 min and consisted of a maximum of five 10-trial blocks. Each trial began with the presentation of both levers and a visual stimulus (a lit LED). The lit LED was used as a distractor and its location (left/right) varied from trial to trial according to a pseudo-random schedule so that the light was presented an equal number of times on each side for the session. This element was included to allow for the possible future addition of an extra-dimensional shift in our procedure (shift to the visual stimulus modality). Thus, the only stimulus with informational value for the discrimination was the spatial position of the retractable levers. Throughout the session, three consecutive lever presses on one lever (lever A) would produce a single pellet reward and the retraction of both levers, whereas one single response on lever B would result in lever retraction without reward delivery. The position of the reinforced lever (left or right) was kept constant for each rat but was counterbalanced between subjects.

Each rat had one training session per day and was trained to a criterion of nine correct trials in one block of 10 trials (binomial distribution $p < 0.01$, likelihood of attaining criterion in a 10-trial block). Once this criterion was reached, this *initial* discrimination phase was considered complete, and the animal was returned to the home cage. If the criterion was not achieved this phase was repeated the next day till criterion achievement (Fig. 1).

2.5.2. Within session serial reversal learning task

In the next training session, reversal learning was introduced. By definition, reversal learning presupposes retention of a previously acquired discrimination. In serial reversals, in the first instance this would involve recall of the initially acquired discrimination described above. In subsequent reversals it would involve retention of the preceding reversal phase.

Accordingly, in the reversal session, animals were again exposed to the initial discrimination task described above (with the same lever rewarded as before: Discrimination retention in the first instance, latest reversal retention in subsequent runs). This initial retention phase preceding reversal also comprised a maximum of five 10 trial blocks and once the criterion of nine correct trials in a 10-trial block was achieved, the position of the reinforced lever was reversed (*reversal phase*). The reversal phase also consisted of a maximum of five 10-trial blocks. The learning criterion was the same as in the initial phase (nine correct trials in a 10-trial block). Animals required more than one session to reach criterion on reversal phase. Thus, they received multiple, separate training sessions that were summed together to produce the final results. During these sessions the initial contingency was determined by retention performance. For example:

REVERSAL 1
Day 1: A+, B− (retention without reversal − criterion achieved).
Day 2: A+, B− (retention preceding reversal − criterion achieved).
A−, B+ (reversal phase − criterion not achieved).
Day 3: A+, B− (retention preceding reversal − criterion achieved).
A−, B+ (reversal phase − criterion achieved).
REVERSAL 2
Day 4: A−, B+ (retention without reversal − criterion achieved).
Day 5: A−, B+ (retention preceding reversal − criterion achieved).
A+, B− (reversal phase − criterion achieved), etc.

A series of two reversals was given prior to surgery and four reversals following surgery. Between successive reversals, animals were always given a single intervening day session of up to five 10-trial blocks where they were required to show retention of the previous reversal phase by reaching the 9 of 10 correct criterion in one 10-trial block (retention phase without reversal: same procedure as acquisition of spatial discrimination described; Fig. 1).

2.6. Statistical analysis

The main measures of the animals' ability to learn the discriminations were: (i) the number of trials to criterion, and (ii) the number of errors to criterion (i.e. incorrect trials). Additional measures recorded for each trial were (iii) the choice latency, (iv) the latency to collect the reward and (v) the number of omissions.

Data for each variable were subjected to a repeated measures ANOVA. Where significant interactions were found, they were further explored through separate ANOVAs or planned comparisons (contrast testing) to establish simple effects. The between-subject factor was Group (two levels: sham and OFC lesions) and the within-subject factors were either Retention phase (summed retention without reversal occurring + retention preceding reversal; four levels: Post-operative retention of pre-operative reversal 2, post-operative retention of post-operative reversals 1–3) or Reversal Phases (four levels: Post-operative reversals 1–4).

3. Results

3.1. Histological results

The cytoarchitectonic borders and nomenclature are taken from the atlas by Paxinos and Watson [23]. The largest and smallest of

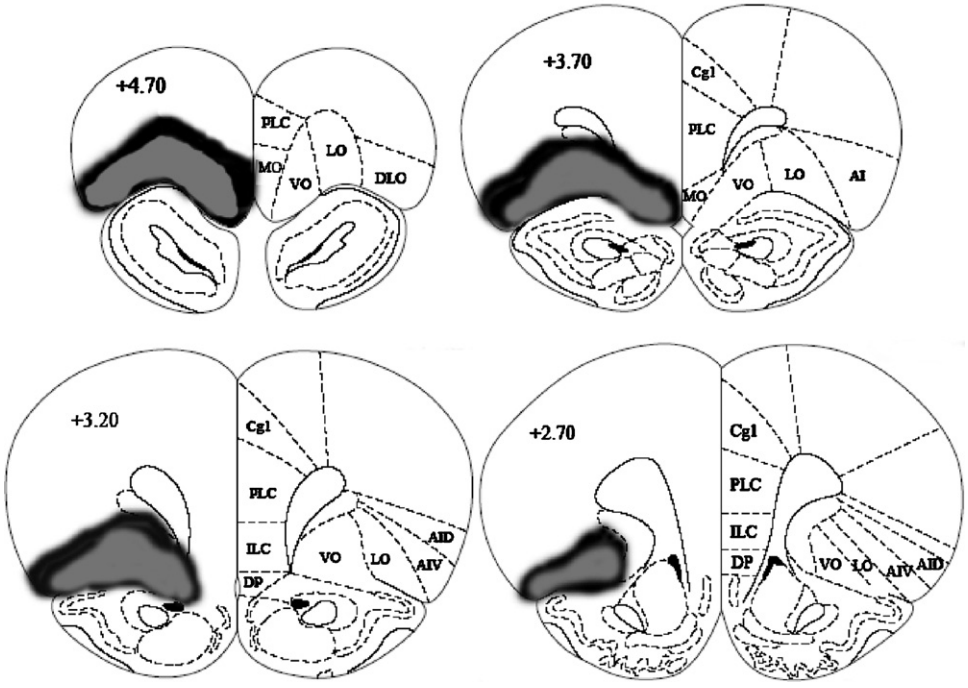

Fig. 2. Diagrammatic reconstructions of coronal sections [23] showing the largest (black shading) and smallest (grey shading) extent of OFC lesion. Numbers in each section indicate AP level anterior to bregma. VO, ventral orbital; LO, lateral orbital; MO, medial orbital; DP, dorsal peduncular; AID, Dorsal agranular insular cortex; AIV, ventral agranular insular cortex; Cg1, cingulate cortex, area 1; Cg2, cingulate cortex, area 2; DLO, dorsolateral orbital cortex.

the lesions for each group are depicted in Fig. 2. One animal died after surgery and examination of the Cresyl-Violet sections revealed that the lesions of four animals were incomplete, unilateral or extended into the anterior cingulate and prelimbic region, thus discarded from the behavioural analyses. The remaining 10 animals showed bilateral damage to the entire extent of the orbitofrontal region. Therefore, the final group numbers were: shams, 8 and OFC-lesioned, 10.

The lesion started at bregma +4.7 and included the most ventral orbital (VO) and in some cases the most medial (MO) regions. At this most rostral extent, the lesion encroached into the prelimbic cortex (PLC). The lesion then continued to include the ventral and lateral orbital (LO) cortex (at bregma +3.2), where the most lateral extent of the ILC was also damaged although for the most part, the ILC was entirely spared, as was the dorsal peduncular (DP) and the PLC. At its most caudal extent (bregma +2.7), the lesion included the VO and LO and the most ventral agranular insular (AIV) cortex (Fig. 2).

3.2. Behavioural results

3.2.1. Pre-operative performance

Pre-operatively, the un-operated animals showed a serial reversal effect, i.e. progressively improved performance following continued reversal learning and pre-operative Reversal 2 Phase was learned with fewer errors than pre-operative Reversal 1 Phase (data not shown). Following matching, the 2 groups did not differ in the number of trials or errors to criterion on either the discrimination, retention or reversal phases (Fs < 1).

3.2.2. Post-operative performance

3.2.2.1. Retention and acquisition. Trials to criterion: A repeated measures analysis of the number of trials to criterion revealed no significant main effects of Group or Retention Phase ($F_{1,16} = 0.431$, $p = 0.521$; $F_{3,48} = 2.17$, $p = 0.104$) and no significant Group × Reversal Phase interaction ($F_{3,48} = 1.43$, $p = 0.245$; Fig. 3A).

Errors to criterion: The retention of each reversal by each group is shown in Fig. 4A. Both groups retained the pre-operatively acquired stimulus-reward contingencies ($F_{1,36} = 1.198$, $p = 0.290$). A repeated measures ANOVA (Group × Retention Phase) revealed no significant main effects of either Group or Retention Phase ($F_{1,16} < 1$; $F_{3,48} = 2.406$, $p = 0.079$, respectively), but a significant Group × Retention Phase interaction ($F_{3,48} = 2.92$, $p = 0.043$). Further investigation of this effect showed that OFC lesions did not impair rats' ability to retain spatial discriminations at a rate comparable to that of sham-operated controls. Actually, OFC-lesioned animals improved across successive discriminations more rapidly than controls (Retention of Reversal 3: sham vs. OFC contrast: $F_{1,16} = 7.705$, $p = 0.013$).

3.2.2.2. Serial reversals. Trials to criterion: A repeated measures analysis of the number of trials to criterion revealed no significant main effects of Group or Reversal Phase ($F_{1,16} = 0.959$, $p = 0.342$; $F_{3,48} = 2.60$, $p = 0.063$) or Group × Reversal Phase interaction ($F_{9,108} = 2.344$, $p = 0.085$; Fig. 3B).

Errors to criterion: Performance on post-operative serial reversals is shown in Fig. 4B. A repeated measures ANOVA of the number of errors to criterion yielded a significant main effect of Reversal phase and a significant Group × Reversal Phase interaction ($F_{3,48} = 2.853$, $p = 0.047$; $F_{3,48} = 3.456$, $p = 0.024$, respectively). Planned comparisons revealed a trend for sham-operated controls to be worse than OFC-lesioned animals in Reversal 4 Phase ($F_{1,16} = 3.83$, $p = 0.067$), but no other effects. Moreover, repeated measures analysis within the OFC-lesioned animals showed that OFC-animals improved significantly across reversals, whereas

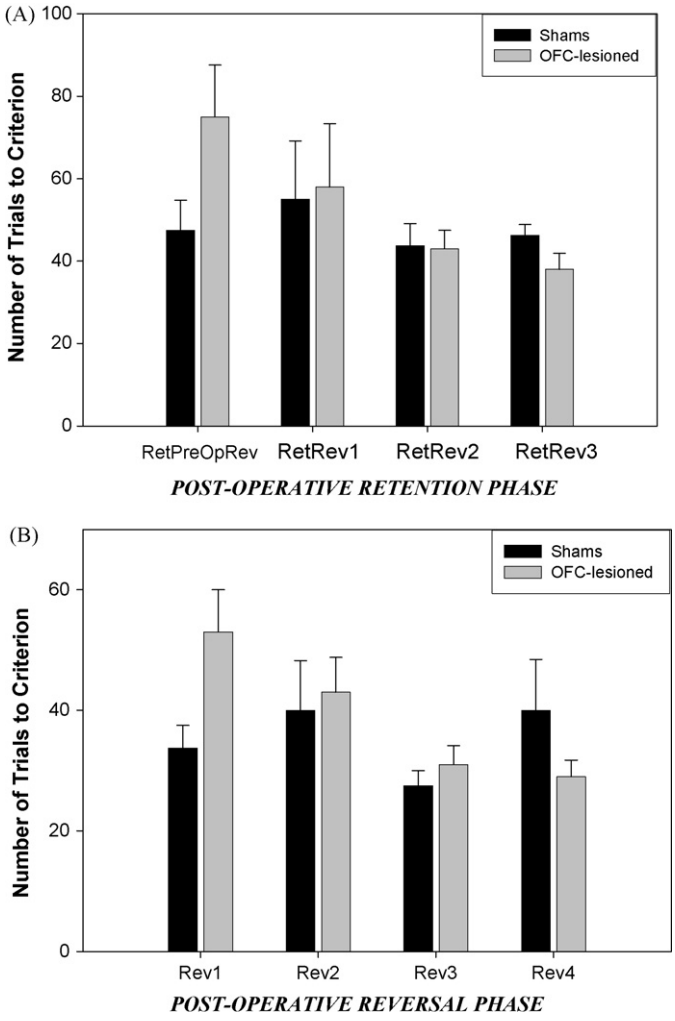

Fig. 3. (A) Data are means ± SEM of trials to criterion in post-operative retention phases (summed retention without reversal + retention preceding reversal). PreOpRev: post-operative retention of pre-operative reversal 2; RetRev1, RetRev2 and RetRev3: post-operative retention test of reversal 1, 2 and 3. (B) Data are means ± SEM of trials to criterion in post-operative reversal phases. Rev1, Rev2, Rev3 and Rev4: post-operative reversal 1–4 phases. Asterisks denote significant differences (ANOVA; $^{*}p < 0.05$) from sham-operated controls.

the same analysis within the sham-operated controls failed to show such a pattern ($F_{3,27} = 5.506$, $p = 0.004$; $F_{3,21} = 1.413$, $p = 0.267$, respectively).

Analysis of perseverative and learning errors: Data were further analyzed according to the method of Boulougouris et al. [2]. In this analysis, errors during reversal learning were broken down into two learning stages: errors committed before the attainment of chance level performance (50% correct) and errors committed between 50% and 85% correct trials. Errors made during the first stage of learning are indicative of perseverative responses to the previously reinforced stimulus. Thus, stage 1 errors are termed "perseverative errors" whereas stage 2 errors are termed "learning errors".

The number of perseverative errors is shown in Fig. 5A. A repeated measures ANOVA revealed that there was no significant main effects of Group or Reversal phase ($F_{1,16} = 0.16$, $p = 0.69$ and $F_{3,48} = 1.19$, $p = 0.33$, respectively) and no significant Group × Reversal phase interaction ($F_{3,48} = 1.89$, $p = 0.14$). The number of learning errors is shown in Fig. 5B. A repeated measures ANOVA revealed that there was no significant main effects of Group or Reversal phase ($F_{1,16} = 0.37$, $p = 0.55$ and $F_{3,48} = 1.41$, $p = 0.25$,

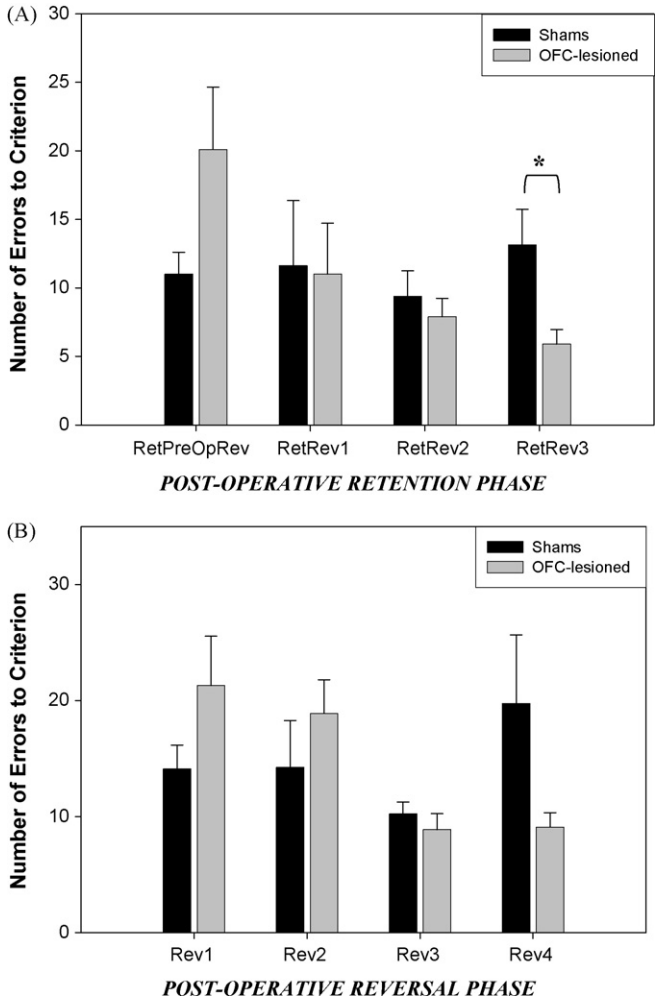

Fig. 4. (A) Values are means ± SEM of errors to criterion during post-operative retention phases (summed retention without reversal + retention preceding reversal). PreOpRev: post-operative retention of pre-operative reversal 2; RetRev1, RetRev2 and RetRev3: post-operative retention test of reversal 1, 2 and 3. (B) Data are means ± SEM of errors to criterion in post-operative reversal phases. Rev1, Rev2, Rev3 and Rev4: post-operative reversal 1–4 phases.

respectively) and no significant Group × Reversal phase interaction ($F_{3,48} = 2.15$, $p = 0.11$).

3.2.3. Latencies and omissions

Control and lesioned animals did not differ in their omissions and latencies to make correct or incorrect responses at any stage of the experiment, either pre-operatively or post-operatively (Fs < 1). Moreover, there were no differences in the latency to collect the reward following reinforced trials (Fs < 1).

4. Discussion

We have recently reported that orbitofrontal (but not infralimbic and prelimbic) cortical lesions on animals with no pre-operative training impair reversal learning performance of an instrumental two-lever spatial discrimination task. This deficit was manifested as increased perseveration of the pre-potent response, as OFC lesions impaired early, but not later, post-operative reversals [2]. In this study, we investigated the effects of pre- and post-operative training on reversal performance of OFC-lesioned animals. Pre-operatively rats performed well in acquiring and retaining the spatial discriminations and showed a serial reversal effect, i.e. with continued reversal training, performance improved and each new reversal was learned with fewer errors [19]. Post-operative testing showed no effect of OFC lesions on either retention or serial reversals, despite the requirement to inhibit the normal pre-potent tendency to respond during reversal phases. Moreover, OFC-lesioned rats performed significantly *better* than sham-operated controls during the final retention and reversal phase.

This improvement constitutes a paradoxical finding in view of the classical literature concerning effects of OFC lesions on reversal-type performance. OFC lesions impair reversal learning across tasks using different modalities, but only during early reversals [monkey: 3,5,8; rat: 2,20]. Later reversals are acquired progressively faster, suggesting that an involvement of OFC is required when task demands are relatively high. Consequently, OFC is not needed when task experience has been gained.

We have previously reported OFC-dependent reversal impairments when the OFC lesions were given before reversal learning training [2]. The lack of impairment of the OFC-lesioned animals during reversal phases in the present study suggests that the pre-operative training may have had a beneficial effect for future reversal learning of these animals. The different effects of pre-operative or post-operative training have also been reported by studies investigating the effects of OFC lesions on performance in

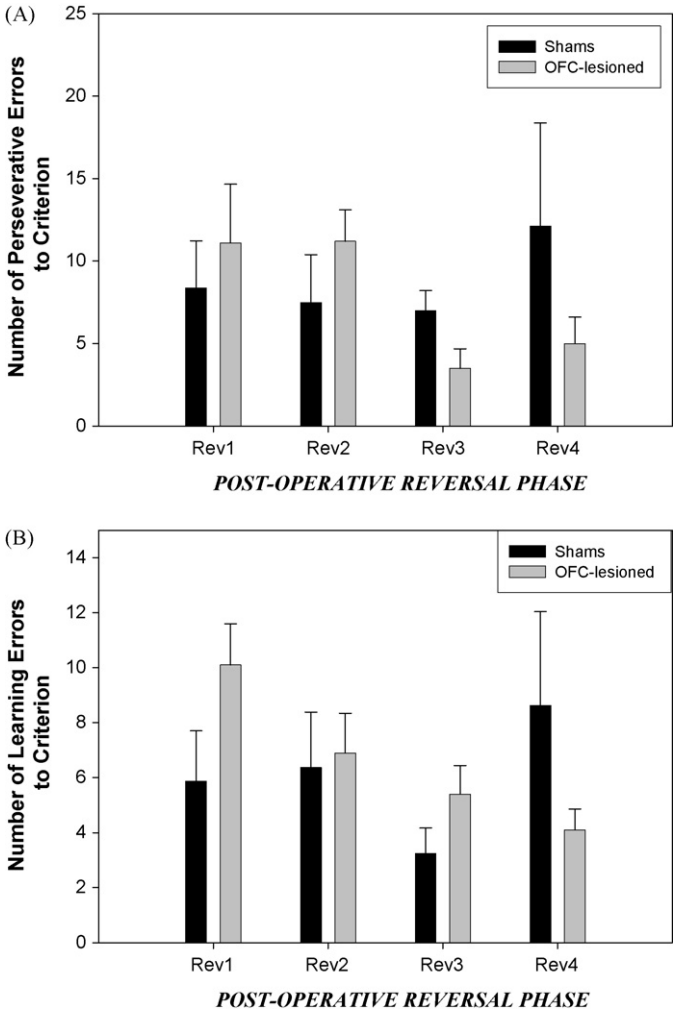

Fig. 5. (A) Values are means ± SEM of perseverative errors to criterion during post-operative Reversal phases. (B) Data are means ± SEM of learning errors to criterion in post-operative Reversal phases. Rev1, Rev2, Rev3 and Rev4: post-operative reversal 1–4 phases.

an odour-guided go, no-go discrimination task [9,10,27]. Eichenbaum et al. [9,10] tested the effects of aspiration lesions of the OFC on rats exposed to pre-surgical training on several discrimination problems, finding that the lesions resulted in impairment and perseverative responding. On the contrary, Schoenbaum et al. [27] reported the opposite finding after testing OFC-lesioned rats without pre-operative training on the task. Moreover, Dias et al. [7] compared effects of pre- and post-training lesions of OFC on discrimination learning and showed a trend toward impairment in animals given training before OFC lesions that was not apparent in animals given lesions prior to training. Finally, the differences between pre-training and post-training OFC manipulations have also been reported in the signal attenuation model of obsessive-compulsive disorder (OCD), as OFC inactivation in the post-training signal attenuation procedure results in a non-selective decrease in lever-pressing, whereas pre-training OFC lesions lead to a selective increase in 'surplus' lever-pressing [15,16]. Consequently, these findings suggest that task experience (pre- or post-surgical) is a crucial variable to be considered while testing the effects of OFC lesions. It should also be noted here that although there are many circumstances where OFC promotes response inhibition, some others have shown that it is not necessary for behavioural inhibition per se, but it is context dependent [4].

Another possible explanation of this lack of effect of OFC lesions may be the fact that rats in this study received negative feedback when they responded incorrectly. Although three responses on the reinforced lever were required for food delivery (correct trial), a single response on the non-reinforced lever immediately led to both levers being retracted and initiation of the inter-trial interval (ITI) without food delivery (incorrect trial). Therefore, rats may have used this 'negative feedback' as a cue to guide their behaviour. It has been suggested that feedback can have different effects in different contexts in humans [22]. Moreover, a recent study, using two cognitive procedural learning tasks, showed that Parkinson's patients off medication are better at learning to avoid choices that lead to negative outcomes than they are at learning from positive outcomes [13]. In our task, analysis of the number of approaches to the food magazine following an incorrect response might be indicative of whether animals used the negative feedback as a strategy. Such analysis revealed no differences between the two groups ($F < 1$, data not shown). However, it would therefore be interesting to investigate how OFC-lesioned animals use feedback in terms of reversal learning by comparing the present data with the performance of OFC-lesioned rats having positive feedback following an incorrect response while having negative feedback following a correct response.

The relatively poor performance of the control group in the final retention and reversal phase may be attributed to trace representations of the originally acquired stimulus-reward contingencies in the OFC that might interfere with new encoding across multiple reversals [26]. Likewise, one other possibility to account for the performance of sham-lesioned rats is that they suffered from interference from earlier reversals not observed in OFC-lesioned subjects. These interpretations are supported by Schoenbaum et al. [27] who reported that, although controls had problems with serial reversals of go, no-go odour discrimination compared with OFC-lesioned rats, specifically during the fourth reversal, they were significantly improved when a novel reversal problem was introduced. It should be noted here that this study differs from our own not only in terms of modality (odour vs. spatial discriminations) but also in terms of experimental design (between vs. within session reversal testing).

The same authors also interpreted the improvement of the OFC-lesioned rats as the emergence of a non-OFC-dependent strategy for solving reversals which is less susceptible to interference than processes supporting reversal learning in intact rats. Furthermore, it was suggested in that study that prefrontal functions might be subsumed by other structures with practice [21] and that these systems might operate in parallel with OFC to some extent. Parallel processing systems which subsume OFC functions in later stages of reversal learning might also account for the faster reversal learning of OFC-lesioned rats in the present study. However, this notion is speculative and needs further experimental support. Furthermore, this view is limited given the methodological differences in both studies. Nevertheless, together these findings render the idea that an intact OFC might hamper reversal learning in later stages, perhaps due to interference from original contingencies.

Improvement across serial reversals was also noted following collateral damage to striatal areas medial to the posterior OFC [12]. This improved performance did not generalize to a new odour discrimination. This may be related to interactions between the striatum and PFC, suggesting that striatal involvement in consolidating strategies in a way which is less bound to particular cues. In support of this hypothesis, Crofts et al. [6] reported that depletion of striatal dopamine led to response patterns that were closely bound to the currently relevant stimulus features, thus reflecting a role for the striatum in abstracting rules after extended experience.

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