European Journal of Neuroscience, Vol. 22, pp. 2341–2346, 2005

Opposing effects of amygdala and orbital prefrontal cortex lesions on the extinction of instrumental responding in macaque monkeys

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Keywords: emotion, frustration, inhibitory control, perseveration, reversal learning

Abstract

Extinction is a well-known behavioural phenomenon that allows organisms to respond flexibly to a changing environment. Although recent work implicates the amygdala and orbital prefrontal cortex (PFo) in extinction of Pavlovian conditioned fear and aversion, much less is known about the neural bases of instrumental extinction. To explore the contribution of the macaque amygdala to flexible responding in the face of changing reward contingency, we tested the effects of selective, excitotoxic lesions of the amygdala on extinction of an instrumental response. For comparison, we evaluated the effects of ablation of PFo on the same task. Amygdala lesions facilitated the extinction of instrumental responses, whereas lesions of PFo had the opposite effect.

Introduction

Extinction is a well-studied behavioural phenomenon that permits flexibility in conditioned responses. Because extinction is neither unlearning nor an erasure of the original learning but, rather, a kind of new learning (for review see Bouton, 2002), it has some importance both as a psychological process and as a tool for studying the neuroscience of learning and memory. Recent studies have implicated both the amygdala and the ventromedial prefrontal cortex (including the orbitofrontal cortex, PFo) in the extinction of Pavlovian conditioned fear and aversion (e.g. Quirk *et al*., 2000; Gottfried & Dolan, 2004; Paré *et al*., 2004; Phelps *et al*., 2004; Likhtik *et al*., 2005; Milad *et al*., 2005), which is potentially relevant to the treatment of clinical conditions such as post-traumatic stress disorder. There has been less work, however, on the extinction of instrumental responses, which might provide information on the neural bases of goal-directed behaviour.

In monkeys, aspiration removals of the amygdala (Weiskrantz, 1956) and of the PFo (Butter *et al*., 1963) have been reported to retard the extinction of instrumental responses. Douglas & Pribram (1966) later reported no significant effect of aspiration amygdala lesions on extinction of a discrimination problem with 70–30% reward probability, although on average the amygdalectomized monkeys displayed longer response latencies in extinction relative to sham-operated controls. Although the latter finding is seemingly at odds with the impairment reported by Weiskrantz (1956), the results of Weiskrantz and of Butter *et al*. were nevertheless generally accepted. Given the obvious similarity between tests of instrumental extinction and reversal learning, both of which test the ability to learn about changing reward contingencies and require the avoidance of a previously learned response, it seemed unsurprising at the time that aspirative amygdala lesions and PFo lesions also yielded impairments on object reversal learning (Schwartzbaum & Poulos, 1965; Barrett, 1969; Jones & Mishkin, 1972). Indeed, Butter (1969), citing the known anatomical connections between the amygdala and PFo, remarked on the similar behavioural effects of damage to these two regions on extinction and object discrimination reversal performance, thereby raising the possibility that a functional interaction of the amygdala and PFo underlies the performance of intact monkeys on these tasks.

Most information regarding the contribution of the amygdala to visual learning for food reward in macaque monkeys has been derived from studies that used aspiration removals, yet the effects of aspirative lesions and fibre-sparing excitotoxic lesions of this structure often differ (Baxter & Murray, 2000). For example, monkeys with excitotoxic lesions of the amygdala learn visual discriminations for auditory secondary reinforcement at the same rate as controls (Malkova *et al*., 1997), results which contradict previous reports following aspirative lesions (Gaffan & Harrison, 1987). Given the paucity of information regarding the neural basis of instrumental extinction, together with the problems inherent in interpretation of the effects of aspirative amygdala removals, the present study re-investigated the amygdalar contribution to extinction. Five monkeys with bilateral excitotoxic amygdala lesions were trained on an instrumental response and then evaluated for extinction of that response. For comparison, we studied three monkeys with bilateral removals of PFo and ten unoperated controls.

If the amygdala is required for extinction of instrumental responses, then monkeys with selective amygdala lesions should exhibit slow (i.e. impaired) extinction. Based on earlier work (Butter *et al*., 1963, 1969; Butter, 1969), the monkeys with PFo lesions were expected to extinguish responding slowly. Finally, if both operated groups displayed impaired extinction, this would support the idea that the amygdala and PFo functionally interact in extinction, as they do in other settings (Baxter *et al*., 2000).

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Received 17 May 2005, revised 18 August 2005, accepted 6 September 2005

doi:10.1111/j.1460-9568.2005.04434.x

Materials and methods

Subjects and apparatus

Eighteen experimentally sophisticated, male rhesus monkeys (*Macaca mulatta*) were used. They weighed 6.8–14.6 kg at the beginning of the study, were housed individually in rooms with automatically regulated lighting (12-h light–dark cycle, lights on at 07:00 h), and were maintained on primate chow (#5038, PMI Feeds Inc., St Louis, MO, USA) supplemented with fresh fruit. Monkeys were maintained on a controlled diet to ensure reliable responding in the test apparatus and a healthy body weight. Water was available *ad libitum*. Three monkeys had received bilateral orbital prefrontal cortex lesions (Group PFo), five monkeys had received bilateral amygdala lesions (Group Amyg) and ten monkeys were retained as unoperated controls (Group Con).

Before entering the present study, all monkeys had extensive experience with visual object discrimination problems and had been assessed for emotional responses to objects and humans, and for food preferences as well (Izquierdo *et al*., 2004, 2005). Although the training histories of Groups Amyg and PFo were not identical, they were highly similar. In fact, Groups PFo and Amyg were each tested with a concurrently running control group ($n = 6$ and $n = 4$, respectively) which, for the present purposes, were considered as a single group (see Results).

Monkeys were trained in a modified Wisconsin General Testing Apparatus (WGTA) located in a darkened room. The test compartment was illuminated with two incandescent 60-W bulbs, whereas the monkey's compartment remained unlit. The test tray, measuring 19.2 cm (width) × 72.7 cm (length) × 1.9 cm (height), contained three food wells spaced 180 mm apart (centre to centre), aligned 160 mm in front of the animal's cage. A single object, novel at the beginning of the study, was used throughout testing. Food rewards consisted of half peanuts.

All procedures were reviewed and approved by the NIMH Animal Care and Use Committee.

Surgery

After induction with ketamine hydrochloride (10 mg/kg, i.m.), anaesthesia was maintained with isoflurane (1.0–3.0%, to effect). The animals received 0.45% sodium chloride plus 5% dextrose (i.v.). Aseptic procedures were employed. Heart rate, respiration rate, blood pressure, expired CO, and body temperature were monitored throughout the procedure. Surgeries were performed in two stages with the site of first surgery (left or right hemisphere) balanced within groups; all monkeys had received a bilateral lesion before entering the present study.

The pre- and postoperative treatment regimen consisted of dexamethasone sodium phosphate (0.4 mg/kg, i.m.) and Cefazolin antibiotic (15 mg/kg, i.m.) for 1 day before surgery and 1 week after surgery, to reduce swelling and prevent infection, respectively. At the end of surgery, and for two additional days, the monkeys received the analgesic ketoprofen (10–15 mg, i.m.); ibuprofen (100 mg) was provided for five additional days.

Amygdala lesion by ibotenic acid injection

We used the methods described previously (Malkova *et al*., 1997; Baxter *et al*., 2000; Izquierdo & Murray, 2004). Briefly, after noting the location of the sagittal sinus as the landmark for mediolateral coordinates, we calculated 18–22 injection sites based on magnetic resonance imaging (MRI) scans performed an average of 5.1 days prior to surgery. At each site, roughly 2 mm apart in each plane, we injected 0.6–1.0 μL ibotenic acid (10 μg/μL, 0.2 μL/min, Biosearch Technologies) into the amygdala via the 30-gauge needle of a Hamilton syringe. The needle remained in place 2–3 min after each injection to limit diffusion of the toxin up the needle track. The intended lesion (see Fig. 1) included the entire amygdala.

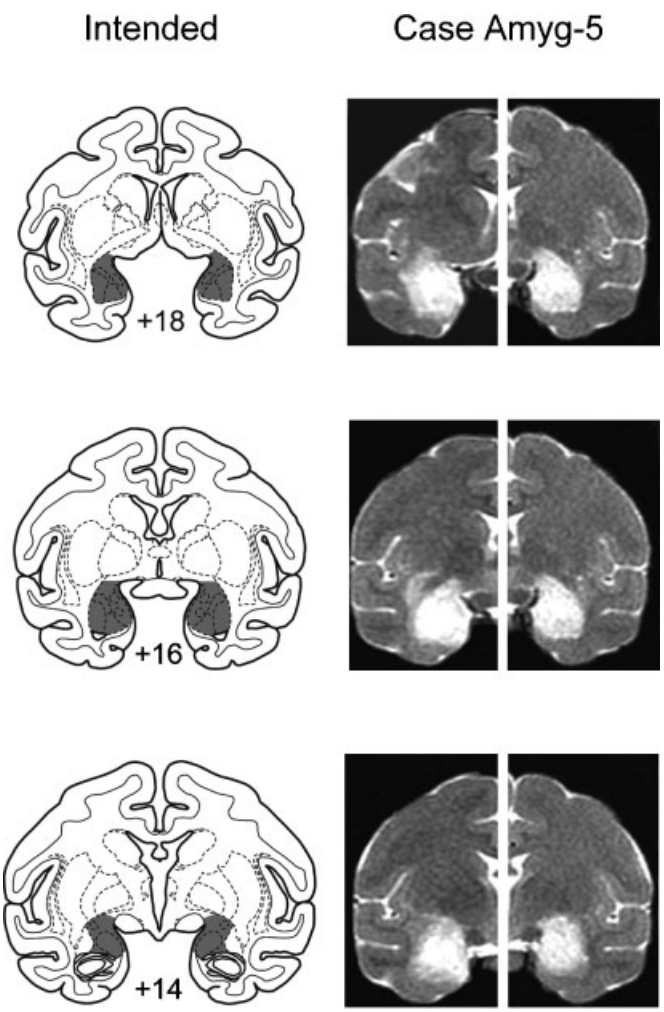

FIG. 1. Left: location and extent of intended lesion (shaded region) on standard coronal sections through the amygdala. Right: T2-weighted MR images from animal Amyg-5 obtained after injection of the excitotoxin ibotenic acid. The injections were carried out in two stages separated by 3 months. The MR images for each hemisphere are from scans obtained 8 days after the injections of ibotenic acid into the amygdala. The regions of hypersignal (white area) reveal oedema resulting from the injections. Numerals (+18, +16, +14) indicate location (mm) rostral to the interaural plane (0).

Orbital prefrontal cortex lesion by aspiration

Using a combination of suction and electrocautery, PFo was removed by subpial aspiration. The intended lesion (see Izquierdo *et al*., 2004) extended from the fundus of the lateral orbital sulcus to the fundus of the rostral sulcus. The rostral limit of the lesion was a line joining the anterior tips of the lateral and medial orbital sulci, and the caudal limit of the lesion was approximately 5 mm rostral to the junction of the frontal and temporal lobes. Thus, the lesion included Walker's areas 11, 13 and 14 and the caudal part of area 10 (Walker, 1940).

Assessment of the lesions

The lesions in all eight operated monkeys were quantitatively assessed from postoperative MRI scans. The extent of amygdala damage was evaluated from T2-weighted scans obtained within 12 days of surgery and the extent of PFo damage from T1-weighted scans obtained an average of 11.3 months after surgery.

Details for the methods of lesion assessment are provided elsewhere (Izquierdo & Murray, 2004). In brief, for amygdala lesions, the region of hypersignal evident in the T2-weighted MRI scan was plotted onto standard sections. Owing to our failure to obtain a postoperative MRI scan, only one hemisphere could be evaluated for animal Amyg-2. For the PFo lesions, the extent of the lesion visible in the T1-weighted scan was plotted. We then measured the volume of the lesion as a function of the total volume of the structure in the standard brain.

For the five monkeys in Group Amyg, the damage was essentially as intended. Monkeys in this group sustained a mean of 93.4% (range 85.2–100%) damage to the total volume of the amygdala. Each of the monkeys with amygdala lesions sustained some inadvertent damage to adjacent structures. Amyg-1 and Amyg-5 sustained slight bilateral unintended damage to anterior portions of the entorhinal cortex and hippocampus and to portions of the ventral claustrum, substantia innominata and piriform cortex. The remaining monkeys in this group sustained only minor and unilateral damage to a subset of these regions. Figure 1 shows a representative case. In all three of the monkeys in Group PFo, damage was also essentially as intended. The monkeys sustained a mean of 78.5% (range 69.2–88.9%) damage to the total volume of the PFo. MR images from one representative case have been published elsewhere (see Fig. 1 in Izquierdo *et al*., 2004).

Behavioural testing

Acquisition

Monkeys were required to displace a single three-dimensional 'junk' object overlying the central well of a three-well test tray to obtain a food reward hidden underneath. Monkeys were given a maximum of 30 s to displace the object. If monkeys displaced the object within the 30-s limit, the trial was scored as correct. If monkeys did not displace the object within 30 s, the trial was scored as incorrect (i.e. an omission). In either case, the trial continued until 30 s had elapsed, after which the screen was lowered and the intertrial interval initiated. Monkeys received a total of 30 trials per session, each separated by 15 s. A criterion was set at 28 or more correct responses in 30 trials for each of five consecutive days.

Extinction

After reaching the above criterion on acquisition, monkeys were given five consecutive sessions of extinction. In these sessions, the trials were exactly the same as in acquisition except no food reward was located underneath the object. On each trial, the experimenter scored whether the monkey displaced the object within the 30-s time limit.

Results

We first examined the performance of the two control groups that had been run concurrently with Groups Amyg and PFo. There was no difference between the two control groups on the number of omissions scored during acquisition (one-way ANOVA, $F_{1,8} = 2.342$, $P = 0.164$), nor was there a difference in the number of unrewarded object displacements in extinction (one-way ANOVA, $F_{1,8} = 0.289$, $P = 0.605$). Consequently, the two groups were collapsed and analysed as one (Group Con).

Acquisition

Our primary measure of the rate of acquisition was the total number of omissions (i.e. trials in which monkeys failed to displace the object) scored by each monkey in attaining the criterion, including those made in the sessions comprising the criterion run. During acquisition, both operated groups made fewer omissions than controls. Whereas Group Amyg and Group PFo averaged only 1.0 ± 0.775 and 0.67 ± 0.333 omissions, respectively, Group Con averaged 25.4 ± 7.377 omissions. An analysis of omissions confirmed the group differences (one-way ANOVA, $F_{2,15} = 4.083$, $P = 0.038$) and *post-hoc* Bonferroni comparisons showed that although the two operated groups did not differ from each other ($P = 0.980$), both scored fewer omissions during the acquisition phase than controls (Amyg vs. Con, $P = 0.026$; PFo vs. Con, $P = 0.055$).

The operated groups also required fewer total sessions to attain the criterion (including the sessions comprising the criterion run) than did the controls (Group Amyg mean, 5.0 ± 0 sessions; Group PFo mean, 5.0 ± 0 sessions; Group Con, 7.5 ± 0.601 sessions). As was the case for omissions, a one-way ANOVA on the total sessions to reach the criterion revealed a main effect of group ($F_{2,15} = 6.410$, $P < 0.010$), and *post-hoc* Bonferroni comparisons revealed that although the two operated groups did not differ from each other ($P = 1.0$), both required fewer sessions to attain the criterion than did controls (Amyg vs. Con, $P = 0.007$; PFo vs. Con, $P = 0.021$).

Extinction

Group performance on the last session of acquisition and the five sessions of extinction is shown in Fig. 2. A repeated-measures ANOVA on the number of unrewarded object displacements across the five sessions of extinction revealed a significant main effect of group ($F_{2,15} = 4.702$, $P = 0.026$) and a significant within-subjects effect of session ($F_{4,60} = 12.451$, $P < 0.001$). The interaction of session by group, however, failed to attain significance ($F_{8,60} = 1.331$, $P = 0.246$). *Post-hoc* tests (all sessions collapsed) yielded a significant difference between Group PFo and Group Amyg ($P = 0.008$) and between Group PFo and Group Con ($P = 0.067$), but not between Group Amyg and Group Con ($P = 0.118$).

An analysis of the first session of extinction – the session on which Group Amyg appeared most divergent – was performed to investigate further the effect of amygdala lesions on extinction. As illustrated in Fig. 3, the 30 trials of session 1 were divided into six blocks of five trials each. A repeated-measures ANOVA on the number of unrewarded object displacements revealed a main effect of group ($F_{2,15} = 6.474$, $P = 0.009$), a significant within-subject effect of block ($F_{5,75} = 10.914$, $P < 0.001$) and a marginally significant block-by-group interaction ($F_{10,75} = 1.922$, $P = 0.055$). Although *post-hoc* comparisons showed no group differences on the first two blocks, Group Amyg differed significantly from Group Con ($P = 0.0128$) on the third block, and then differed from both Group PFo and Group Con on all subsequent blocks (all P-values < 0.05).

We also examined the rate of extinction, defined as the number of trials taken to achieve four omissions in a row. In general, the extinction rate measure provided a picture similar to that for the number of omissions scored over the five sessions, with Group Amyg showing the fastest extinction rate and Group PFo the slowest (Group Con, 49.0 ± 12.157 trials; Group Amyg, 16.8 ± 2.311 trials; Group

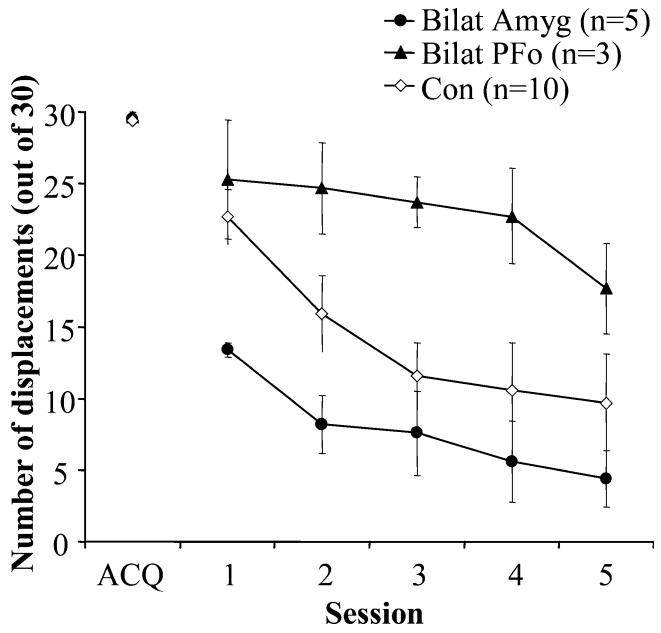

FIG. 2. Curves showing the group mean number of rewarded object displacements made during the last day of acquisition (ACQ) and the mean number of unrewarded displacements made during the extinction phase, plotted as a function of session.

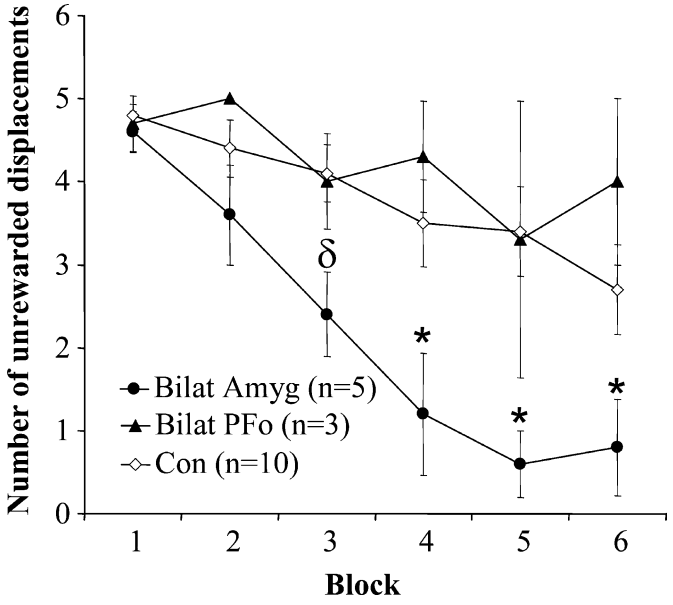

FIG. 3. Curves showing the group mean number of unrewarded displacements made during the first session of extinction, in blocks of five trials. δ, Group Amyg differs from Group Con, $P = 0.013$; *, Group Amyg differs from both Group PFo and Group Con, all P-values < 0.050.

PFo, 93.7 ± 38.912 trials). A one-way ANOVA revealed a main effect of group ($F_{2,15} = 3.711$, $P = 0.0491$) and *post-hoc* Bonferroni comparisons showed that only Groups Amyg and PFo differed on this measure ($P = 0.016$).

It was also of interest to determine if the rate of extinction was related to the number of trials completed during acquisition. The rate of extinction was not significantly correlated with the number of trials completed in acquisition for either Group Amyg or Group Con ($-0.112 < r < 0.080$; $0.874 < P < 0.831$); an analysis could not be carried out for Group PFo because of the small number of subjects ($n = 3$).

Discussion

We found that selective amygdala lesions facilitated and PFo lesions impaired the extinction of instrumental responses in monkeys. Thus, amygdala lesions and PFo lesions yield opposing effects on this task.

The finding of fewer omissions during acquisition of the instrumental response by the operated groups was unexpected and deserves further comment. In acquisition, a trial ended after 30 s had elapsed. This procedure was implemented to ensure that the only difference between trials in the acquisition and extinction phases was the presence (acquisition) or absence (extinction) of primary reinforcement hidden underneath the object. Before entering the present study, all monkeys had extensive experience with traditional visual discrimination learning tasks in which trials always ended immediately upon retrieval of the food reward, if one was available. By contrast, in the acquisition phase of the present experiment, once monkeys had displaced the object and retrieved the food reward – an act that typically required only 2–3 s – they were required to wait until the full 30 s had elapsed before the trial ended. Thus, the procedures used in acquisition had two main consequences: (i) the rate at which rewards could be obtained was lowered, and (ii) there was a prolonged exposure to the empty food well. The slow acquisition by the controls derived from their repeated refusal to displace an object to obtain food reward (i.e. omissions). Presumably, the controls, but not the operated groups, found either the newly instigated delay (i.e. the 30-s trial duration) or the prolonged exposure to the empty food well to be frustrating; rather than displacing the object to obtain food, they did not respond at all. Although lesions of the amygdala or PFo in monkeys disrupt emotional responses to aversive events, monkeys with such lesions are capable of expressing emotion (e.g. Meunier *et al*., 1999; Kalin *et al*., 2001; Izquierdo *et al*., 2005). Thus, the precise reason why the operated groups did not display these same signs of frustration is unclear. It appears that the emotional response to frustration is mediated by circuitry that includes the amygdala and PFo.

As indicated in the Introduction, monkeys with aspirative amygdala lesions have been found to be significantly slower than (Weiskrantz, 1956) or not different from (Douglas & Pribram, 1966) controls in tests of instrumental extinction in appetitive settings. Several differences – including lesion method and extent, reward schedule, and test apparatus – limit any comparison among the studies. These differences notwithstanding, the present results serve as an instance additional to that cited in the Introduction of selective, excitotoxic amygdala lesions yielding effects that qualitatively differ from those that follow aspirative lesions, probably because the latter type of lesion interrupts fibre pathways coursing near the amygdala (Goulet *et al*., 1998; Easton & Gaffan, 2001).

Weiskrantz (1956) also found that two amygdalectomized monkeys showed more rapid extinction than controls on a postoperatively acquired test of active avoidance, and the same two monkeys tended to recover more rapidly than controls during extinction of conditioned suppression; thus, some of his results support the idea that amygdala damage facilitates extinction not only of Pavlovian conditioned responses (e.g. conditioned suppression) but also of instrumental responses (e.g. active avoidance). Future studies along these lines should take into account the evidence for dissociable roles of the basolateral and central nuclei of the amygdala (Hatfield *et al*., 1996; Killcross *et al*., 1997; Parkinson *et al*., 2000).

Our results confirm earlier reports that monkeys with PFo lesions extinguish instrumental responses slowly (Butter *et al*., 1969; Butter, 1969), and thus support the idea that PFo functions in behavioural inhibition, at least to an extent (e.g. Fuster, 1997). Nevertheless, because there is a possibility that our aspiration lesions disrupted fibres en route to regions outside PFo (e.g. Morrison *et al*., 1982), firm conclusions regarding a role for PFo will have to await confirmation of the impairment with more selective lesion methods. This caveat aside, we note that the same operated subjects are also impaired on tests of reinforcer devaluation and object reversal learning (Izquierdo *et al*., 2004). Indeed, evidence from neuropsychological and neuroimaging studies suggests that PFo circuitry is engaged in both decision making and object reversal learning (for review see Clark *et al*., 2004), and instrumental extinction appears to share this circuitry. Taken together, these results are consistent with the idea that PFo neurons provide a common currency for the valuation of goals leading to response selection (see Holland & Gallagher, 2004; Izquierdo *et al*., 2005).

An unexpected finding of the present study is that selective amygdala lesions and PFo lesions yield opposing effects on extinction. The behavioural effects of amygdala lesions generally parallel those of PFo lesions, and several investigators have suggested a single functional circuit (Jones & Mishkin, 1972; Aggleton & Passingham, 1981) underlying emotional changes and deficits in reversal learning (Schwartzbaum & Poulos, 1965; Barrett, 1969; Jones & Mishkin, 1972) and extinction (Weiskrantz, 1956; Butter, 1969) that accompany either aspirative (or radiofrequency) amygdala or PFo damage. Inasmuch as excitotoxic amygdala lesions and PFo lesions significantly disrupt emotional responses in adult macaques (Meunier *et al*., 1999; Izquierdo *et al*., 2005; acquisition in the present study), the opposing effects of the two lesions challenge models which predict that both groups should be impaired in extinction (Jones & Mishkin, 1972; Aggleton & Passingham, 1981; Rolls, 1999). Thus, at least partially dissociable neural substrates underlie the changes in emotional behaviour and impairments on cognitive tests such as reversal learning and extinction.

To our knowledge, the only other report of opposing effects of lesions to these two structures is by Winstanley *et al*. (2004), who studied temporal discounting. They found that rats with amygdala lesions behaved impulsively, choosing fewer large, delayed rewards and more small, immediate rewards relative to controls. By contrast, rats with PFo damage chose more large, delayed rewards than did controls. In the present study, monkeys with amygdala lesions withheld responses in the extinction phase to a greater extent than controls. Thus, an increase in impulsivity, *per se*, cannot account for the effects of amygdala lesions in the two sets of results.

We offer two possible accounts for the findings in both studies. As argued by Winstanley *et al*. (2004), amygdala damage might be expected to produce an impairment in using the representation of the incentive value of reward to guide behaviour; this deficit would have resulted in the direction of effects observed after amygdala lesions in the two studies. Specifically, in the present study, the object (i.e. the conditioned stimulus) might have supported responding by the controls to a greater extent than by the amygdalectomized monkeys during the extinction phase. Although both the amygdala and the PFo are known to contribute to conditioned reinforcement mechanisms, whereas amygdala lesions in monkeys disrupt the capacity for a conditioned stimulus to support instrumental responding in second-order schedules of reinforcement (Parkinson *et al*., 2001), PFo lesions have no such effect (Pears *et al*., 2003). Indeed, the monkeys with PFo lesions studied by Pears *et al*. (2003) responded on average more than controls during the more demanding second-order schedules. These findings are consistent with the facilitation and impairment of instrumental extinction after selective amygdala lesions and PFo damage, respectively, as in the present study. In this view, much as Winstanley *et al*. accounted for the disparate effects of basolateral amygdala and PFo lesions in rats performing a delay-discounting task, the facilitation after amygdala lesions might be due to an inability to maintain a representation of reward and the impairment after PFo lesions to a failure to update the representations of incentive value that guide response selection.

An alternative explanation of the two sets of results is that rats and monkeys with amygdala lesions are more sensitive than controls to the occurrence of nonreward, including delayed reward, perhaps because of competitive interactions within the prefrontal cortex. This idea gains support from a recent functional imaging study (Hurliman *et al*., 2005) which suggests that different sensory systems – specifically, visual (external) and juice (visceroappetitive or internal) cues – compete within the prefrontal cortex. Although the precise manner in which different cytoarchitectonic fields of the prefrontal cortex functionally interact with the amygdala remains to be elucidated (cf. Pezawas *et al*., 2005), these findings raise the possibility that PFo may operate more efficiently in the absence of the amygdala. Thus, the facilitation of extinction in our amygdalectomized monkeys and the increased choice of small, immediate rewards by rats with basolateral amygdala lesions might both have resulted from a more efficient processing relative to controls, within PFo, of visual (and perhaps temporal) information regarding the presence or absence of food reward. In this view, the opposing effects of amygdala and PFo lesions observed in the present study – and by extension the opposing effects reported by Winstanley *et al*. – resulted from manipulation (via enhancement or disruption) of a single process, namely the ability of PFo neurons to code the value of predicted rewards.

Acknowledgements

This research was supported by the Intramural Research Program of NIMH. R. Saunders and the staff of the NMR Facility, NINDS, helped obtain the MR scans, O. Sheinina, R. K. Suda and K. Wright helped with behavioural testing, and P-Y. Chen helped prepare the figures.

Abbreviations

MRI, magnetic resonance imaging; PFo, orbital prefrontal cortex.

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