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Cognitive Inflexibility after Prefrontal Serotonin Depletion Is Behaviorally and Neurochemically Specific

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We have previously demonstrated that prefrontal serotonin depletion impairs orbitofrontal cortex (OFC)-mediated serial discrimination reversal (SDR) learning but not lateral prefrontal cortex (PFC)-mediated attentional set shifting. To address the neurochemical specificity of this reversal deficit, Experiment 1 compared the effects of selective serotonin and selective dopamine depletions of the OFC on performance of the SDR task. Whereas serotonin depletions markedly impaired performance, OFC dopamine depletions were without effect. The behavioral specificity of this reversal impairment was investigated in Experiment 2 by examining the effect of OFC serotonin depletion on performance of a modified SDR task designed to distinguish between 3 possible causes of the impairment. The results showed that the reversal deficit induced by prefrontal serotonin depletion was not due to a failure to approach a previously unrewarded stimulus (enhanced learned avoidance) or reduced proactive interference. Instead, it was due specifically to a failure to inhibit responding to the previously rewarded stimulus. The neurochemical and behavioral specificity of this particular form of cognitive inflexibility is of particular relevance to our understanding of the aetiology and treatment of inflexible behavior apparent in many neuropsychiatric and neurodegenerative disorders involving the PFC.

Keywords: dopamine, marmoset, obsessive-compulsive disorder, orbitofrontal cortex, Parkinson's disease, reversal learning

Introduction

We have previously demonstrated that different forms of cognitive flexibility, dependent upon distinct regions of the prefrontal cortex (PFC), are differentially modulated by serotonin (5-hydroxytryptamine [5-HT]) (Clarke and others 2005). Thus, 5-HT depletion impairs the ability to switch responding between one of the two visual stimuli on a serial discrimination reversal (SDR) task, an ability previously shown to depend upon the orbitofrontal cortex (OFC) in humans (Rolls and others 1994; Hornak and others 2004) and nonhuman primates (Butter 1969; Iversen and Mishkin 1970; Jones and Mishkin 1972; Dias and others 1996a, 1996b; Clarke and others 2004). In contrast, 5-HT depletion leaves intact the higher order ability to shift an attentional set (Clarke and others 2005) that has previously been shown to depend upon lateral PFC circuitry (Dias and others 1996a, 1996b; Rogers and others 2000). This pattern of findings is opposite to that shown for catecholamine depletion, which disrupts the development of a higher order attentional set but has no apparent effect on discrimination reversal learning (Roberts and others 1994; Crofts and others 2001). Together, these results raise the possibility that dopamine (DA) and 5-HT modulate distinct aspects of PFC processing. However, there are at least two potentially confounding factors that should be considered before the roles of PFC DA and 5-HT in reversal learning can be dissociated fully.

First, in previous studies of DA depletion on reversal learning, NA was depleted alongside DA in the PFC despite attempts to protect the NA fibers (Roberts and others 1994; Crofts and others 2001). Second, the DA depletions were greater in the lateral PFC than the OFC, so that the failure of such lesions to impair serial reversal learning may have been due to insufficient depletions of DA from the OFC. To address this issue of neurochemical specificity, Experiment 1 compared directly the effects of depletions of 5-HT and DA from within the OFC on performance of a SDR task.

A second issue, addressed in Experiment 2, is the behavioral nature of the reversal deficit induced by prefrontal 5-HT depletion. Although our previous reversal studies have shown that 5-HT-lesioned monkeys make more perseverative responses to the previously rewarded stimulus compared with controls, there are still several possible behavioral explanations for such responding (Clarke and others 2004, 2005). First, it could reflect the inability to cease responding to the previously rewarded stimulus. Second, it could reflect a difficulty in initiating responding to the previously unrewarded stimulus (enhanced learned avoidance of the previously incorrect stimulus). Third, the finding that the deficit induced by 5-HT depletion occurred on the 2nd and 3rd reversals, but not the first, could reflect an attenuation of the effects of proactive interference. Thus, at the start of reversal 2, competing memories of the original discrimination may bias responding toward the previously incorrect (but now correct) stimulus to accelerate learning of reversal 2 in controls but not following 5-HT depletion (Connor and Meyer 1971; Mackintosh 1974). In order to distinguish between these alternative explanations, we used a modified serial reversal paradigm whereby on the 2nd reversal, a novel stimulus replaced either the previously unrewarded stimulus (perseveration test) or the previously rewarded stimulus (learned avoidance test). In the perseveration test, the monkey has to learn to respond to the novel stimulus and inhibit responding to the previously rewarded stimulus. In the learned avoidance test, the monkey has to learn to respond to the previously unrewarded stimulus, without the need to inhibit responding to a previously rewarded stimulus. The differential pattern of performance of 5-HT-lesioned and control monkeys in these two conditions will reveal the specificity of the behavioral deficit. Thus together, Experiments 1 and 2 investigate the neurochemical and behavioral specificity, respectively, of the reversal deficit induced by prefrontal 5-HT depletions.

General Materials and Methods

Subjects and Housing

Twenty-eight naive common marmosets (*Callithrix jacchus*; 11 females, 17 males) bred on site at the Medical Research Council research

colony were housed in pairs. All monkeys were fed 20 g of MP.E1 primate diet (Special Diet Services [SDS], Withams, Essex, UK) and 2 pieces of carrot 5 days a week after the daily behavioral testing session, with simultaneous access to water for 2 h. At weekends, their diet was supplemented with fruit, rusk, malt loaf, eggs, treats, and marmoset jelly (SDS), and they had free access to water. Their cages contained a variety of environmental enrichment aids that were regularly varied, and all procedures were performed in accordance with the UK Animals (Scientific Procedures) Act 1986.

Apparatus

Behavioral testing took place within a sound-attenuated box in a dark room (for full experimental details, see Roberts and others 1988). The animal sat in a perspex transport box, one side of which was removed to reveal a color visual display unit (VDU; Microtec, Model 1440, Bradford, UK). The marmoset reached through an array of vertical metal bars to touch stimuli presented on the VDU, and these responses were detected by an array of infrared beams (Microvitec Touchtec 501) attached to the screen. A reward of cooled banana milkshake (Nestlé, York, UK) was delivered to a centrally placed spout. Presentation of reward was signaled by a 4 kHz tone played through loudspeakers located on either side of the VDU and was dependent upon the marmoset licking the spout to trigger a peristaltic pump that delivered the milkshake. The test chamber was lit with a 3 W bulb. The stimuli presented on the VDU were abstract, multicolored visual patterns (32 mm wide × 50 mm high) which were displayed to the left and right of the central spout. The stimuli were generated on an Acorn Archimedes computer, which also controlled the apparatus and recorded responding.

Behavioral Training and Testing

As described previously (Clarke and others 2004, 2005), all monkeys were trained initially to enter a perspex transport box for marshmallow reward and familiarized with the testing apparatus. Monkeys then received the following sequence of training: familiarization with a milkshake reward, learning of a tone-reward contingency, and responding on the touch screen until they were reliably and accurately making 30 responses or more to a square stimulus presented to the left and right of the licker in 20 min.

Behavioral testing consisted of a series of 2-choice discriminations composed of abstract colored stimuli. A response to the correct stimulus resulted in the incorrect stimulus disappearing from the screen, although the correct stimulus remained present for the duration of a 5 s tone that signaled the availability of 5 s of reinforcement. Failure to collect the reward was scored as a missed reinforcement. Following a response to the incorrect stimulus, both stimuli disappeared from the screen, and a 5 s timeout period ensued during which the houselight was extinguished. The intertrial interval was 3 s, and within a session the stimuli were presented equally to the left and right sides of the screen. Each monkey was presented with 30 trials per day, 5 days a week, and progressed to the next discrimination after attaining a criterion of 90% correct in the immediately preceding session. If a monkey showed a significant side bias (10 consecutive responses to one side), a rolling correction procedure was implemented whereby the correct stimulus was presented on the nonpreferred side until the monkey had made a total of 3 correct responses.

Behavioral Measures

The main measure of the monkeys' performance on the visual discriminations was the total number of errors made prior to achieving criterion of ⩾90% correct (excluding the day on which the criterion was attained) on each discrimination. Additional measures recorded for each trial were 1) the latency to respond to the stimuli presented on the VDU (response latency), 2) the latency to collect the reward from the spout (lick latency), and 3) the left/right location of the response. In addition, the type of errors that were made during each reversal was classified as "perseverative" (where responding to the "previously" correct stimulus was significantly above chance), "chance," or "learning" (where responding to the "newly" correct stimulus was at, or above chance, respectively) using signal detection theory (for a detailed explanation of these calculations, see Clarke and others 2004, 2005).

Surgical Procedure

Subjects were premedicated with ketamine hydrochloride (Pharmacia and Upjohn, 0.05 ml of a 100 mg/ml solution, intramuscularly), anesthetized with Saffan (alphaxalone 0.9% w/v, alphadolone acetate 0.3% w/v; Schering Plough; 0.4 ml intramuscularly), and given a 24-h prophylactic analgesic (Rimadyl; 0.03 ml of 50 mg/ml Carprofen, subcutaneously; Pfizer, Kent, UK), prior to being placed in a stereotaxic frame especially modified for the marmoset (David Kopf, Tujanga, CA, USA). Anesthesia was closely monitored and maintained with additional doses of Saffan when necessary.

To localize the effects of selective prefrontal serotonergic depletion to the orbital surface, injections were restricted to the OFC and were made using 5,7-dihydroxytryptamine (5,7-DHT, Fluka Biochemika; 9.92 mM) in saline/0.1% L-ascorbic acid. To protect the noradrenaline (NA) and dopamine (DA) innervation, respectively, the NA uptake blocker nisoxetine (25 mM; Sigma, UK) and the DA uptake blocker GBR 12909 (1.0 mM; Sigma, UK) were administered concomitantly in the infusate. Lesions of the dopaminergic innervation of the OFC were made using a procedure similar to that described by Crofts and others (2001). Twenty minutes prior to anesthesia, monkeys were premedicated with the monoamine oxidase inhibitor pargyline (Sigma; 50 mg/kg intraperitoneally) to enhance the efficacy of the dopaminergic neurotoxin 6-hydroxydopamine (6-OHDA) hydrobromide. To protect the serotonergic and noradrenergic innervation of the OFC from the 6-OHDA, monkeys received peripheral injections of the NA uptake blocker talsupram (Lundbeck, Copenhagan, Denmark; 20 mg/kg subcutaneously) and the selective serotonin reuptake inhibtor citalopram (Lundbeck; 5 mg/kg subcutaneously) 30 min before the injections of 6-OHDA commenced.

Injections (0.04 μl/20 s) were made into 5 sites on each side within the OFC, using a 30-gauge cannula attached to a 2-μl Hamilton syringe. All injections were made 0.7 mm above the base of the brain. The coordinates and volumes used were anteroposterior (AP) +16.75: lateromedial (LM) ± 2.5 (0.4 μl) and LM ± 3.5 (0.4 μl), AP +17.75: LM ± 2.0 (0.4 μl) and LM ± 3.0 (0.4 μl), and AP +18.5: LM ± 2.0 (0.6 μl) having been adjusted where necessary in situ according to cortical depth as described previously (see Dias and others 1996b). Sham surgery was identical to the above except for the omission of the toxin from the infusion. Postoperatively, all monkeys received the analgesic Metacam (Meloxicam, 0.1 ml of a 1.5 mg/ml oral suspension; Boehringer Ingelheim, Germany) before being returned to their home cage for 10 days of "weekend diet" and water ad libitum to allow complete recovery before returning to testing.

Postmortem Lesion Assessment

The specificity and extent of the selective 5-HT and DA lesions of the OFC were assessed by postmortem tissue analysis of monoamine levels in cortical and subcortical regions 4–11 months (Experiment 1) and 8–14 months (Experiment 2) after administration of the neurotoxin as described previously (Clarke and others 2004). In order to determine the longevity of the lesion, 2 additional animals that received unilateral 5-HT lesions using the same surgical procedure as described earlier were assessed for postmortem cortical and subcortical monoamine levels 2 weeks postoperatively. Tissue samples were homogenized in 200 μl 0.2 M perchloric acid for 1.5 min and centrifuged at 6000 rpm for 20 min at 4 ^{o}C. The supernatant (75 μl) was subsequently analyzed using reversed-phase high-performance liquid chromatography and electrochemical detection as described previously (Clarke and others 2005).

Experiment 1: Comparison of the Effects of Selective 5-HT or DA Depletions Within the OFC on Serial Reversal Learning

Methods

After touch screen training, 12 marmosets (5 females, 7 males) were given the following series of discriminations (see Fig. 1, Experiment 1).

1. Acquisition of a novel discrimination (D1).
2. Acquisition of a second novel discrimination (D2).

Having reached criterion on the second discrimination (D2), 4 monkeys received 5,7-DHT lesions of the OFC, 4 monkeys received 6-OHDA lesions of the OFC, and 4 monkeys received sham control

procedures (2 controls in the style of the 6-OHDA lesion and 2 controls in the style of the 5,7-DHT lesion). After 2 weeks recovery, they received the following series of discriminations:

3. A retention test of the discrimination learned immediately prior to surgery (D2 retention).
4. Acquisition of a third novel discrimination (D3). From this stage onward the reward contingencies were counterbalanced so that one stimulus of the pair was rewarded for half the monkeys in each group and the other stimulus was rewarded for the other half. This prevented differences in performance being an artifact of any innate stimulus preference.
5. A series of 4 reversals, whereby for each reversal the previously incorrect stimulus became rewarded and the previously rewarded stimulus became incorrect (Reversals 1–4).

Results

Postmortem Depletions of Serotonin and DA Within Selected Regions of the PFC following 5,7-DHT and 6-OHDA Lesions of the OFC

The 5,7-DHT injections into the OFC produced substantial depletions of 5-HT in both the orbital and lateral regions of PFC 4–11 months postoperatively but left the adjacent medial and dorsal regions of the PFC and the motor/premotor cortices intact (Fig. 2*A*). Pretreatment with the NA and DA reuptake blockers nisoxetine and GBR 12909 successfully protected NA and DA, respectively, with their levels remaining the same as controls. No significant depletions of 5-HT, DA, or NA were seen in any other frontal or striatal regions, including the primary motor and premotor cortex, the pre- and postgenual cingulate cortices, and the caudate nucleus (see Table 1). The 6-OHDA injections into the OFC produced substantial depletions of DA restricted to the OFC, with the talsupram and citalopram pretreatments successfully protecting 5-HT and NA levels, respectively (Fig. 2*B*).

For the purpose of statistical analysis, levels of 5-HT, DA, NA, and 5-hydroxyindoleacetic acid (5-HIAA) were square root transformed to eliminate the heterogeneity of variance between groups (demonstrated using Levene's test) and then compared across groups (5-HT lesion, DA lesion, and sham-operated control) within 18 brain regions using a one-way analysis of variance (ANOVA). To correct for multiple independent ANOVAs, the results of each analysis were corrected for 18 contrasts using the Šidák correction (P values corrected for n comparisons such that $P_{corrected} = 1 - [1 - P_{uncorrected}]^n$). This revealed significant main effects of group for 5-HT levels in the OFC ($F_{2,9} = 51.224$, $P_{corrected} < 0.0178$) and lateral PFC ($F_{2,9} = 27.461$, $P_{corrected} < 0.0178$) and for DA levels in the OFC ($F_{2,9} = 14.211$, $P_{corrected} = 0.0354$). No other regions showed significant group differences for any neurotransmitter measured.

These group differences were investigated further using Fisher's protected least significant difference test (performing 3 uncorrected

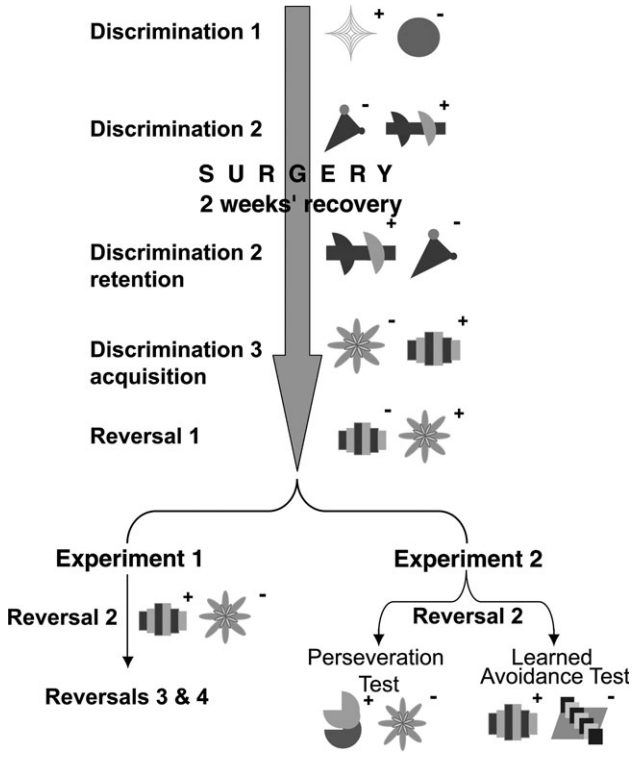

Figure 1. A schematic illustrating the different stages of the task used in Experiments 1 and 2. All marmosets performed identical visual discriminations up until reversal 2. At this stage, the marmosets in Experiment 1 performed 3 further serial reversals, whereas in Experiment 2, the visual discrimination reversal task diverged to allow the independent assessment of perseverative and learned avoidance behavior. Marmosets responded to stimuli on the touch screen to obtain banana milkshake reward. The "+" and "–" indicate which stimulus was correct and incorrect at each stage and were not visible to the marmosets. In Experiment 2 at reversal 2, half of each of the lesioned and control groups performed either the "perseveration" or "learned avoidance" tests. The correct and incorrect stimulus within the pairs were counterbalanced from D3 acquisition onward. All stimuli were multicolored.

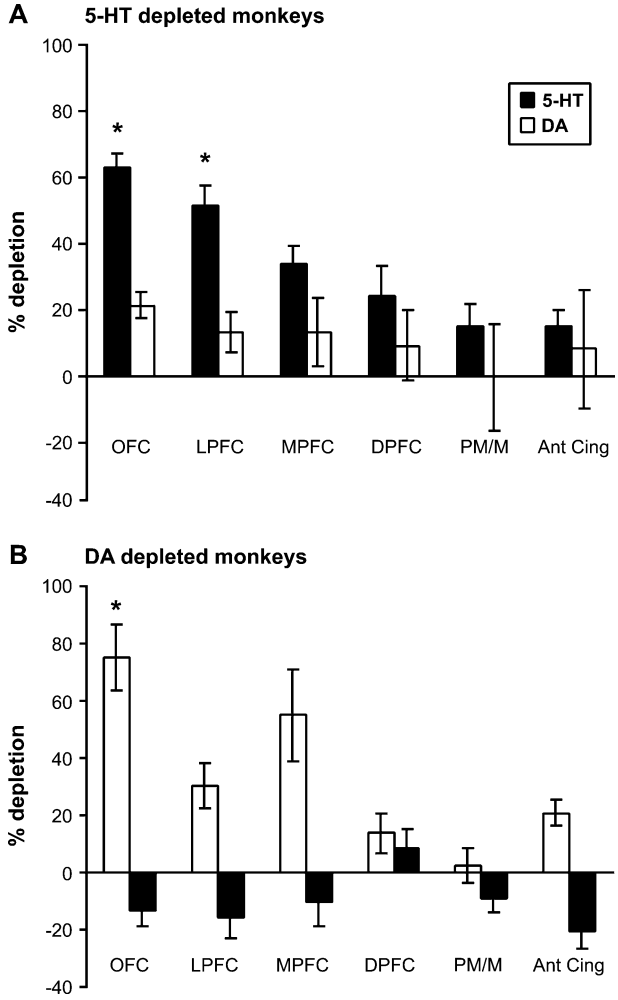

Figure 2. Mean percentage depletions (± standard error of the mean) of 5-HT and DA in the frontal cortex of marmosets with 5,7-DHT and 6-OHDA lesions of the OFC. OFC, orbitofrontal cortex (including granular, dysgranular, and agranular regions); LPFC, highly granular lateral PFC; MPFC, pregenual medial PFC; DPFC, dorsal granular PFC; M/PM, primary motor and premotor cortex; and C1, anterior cingulate cortex. *$P < 0.05$ (corrected), comparison of neurotransmitter levels in a given region between lesioned and control monkeys.

pairwise tests). In the OFC, 5-HT levels were lower in 5-HT-lesioned monkeys than in controls (63.2% depletion; $t_6 = 7.287$, $P = 0.002$) and DA-lesioned monkeys ($t_6 = 11.085$, $P < 0.001$); controls and DA-lesioned monkeys did not differ from each other ($t_6 = 1.295$, $P = 0.252$). Similarly, in the lateral PFC, 5-HT levels were lower in 5-HT-lesioned monkeys than in controls (51.6% depletion; $t_6 = 5.32$, $P = 0.002$) and DA-lesioned monkeys ($t_6 = 7.330$, $P < 0.001$); controls and DA-lesioned monkeys did not differ from each other ($t_6 = 1.409$, $P = 0.208$). In addition, DA levels in the OFC were lower in DA-lesioned monkeys than in controls (75% depletion; $t_6 = 4.172$, $P = 0.017$) and 5-HT-lesioned monkeys ($t_6 = 3.435$, $P = 0.038$); control and 5-HT-lesioned monkeys did not differ from each other ($t_6 = 2.487$, $P = 0.06$).

To confirm that the 5-HT and DA depletions were regionally selective for both group and brain region, a planned analysis was conducted of the 6 PFC regions of interest, using the model $\text{group}_3 \times (\text{region}_6 \times \text{S})$. For both 5-HT and DA, this revealed a significant group × region interaction (5-HT: $F_{10,45} = 7.988$, $P < 0.001$; DA: $F_{10,45} = 4.810$, $P < 0.001$), confirming that the depletions were neurochemically and regionally specific. There were no such differences in NA levels (group × region: $F < 1$; group: $F_{2,9} = 3.083$, $P = 0.96$) or 5-HIAA levels (group × region: $F < 1$; group: $F < 1$). A full regional analysis [using the model $\text{group}_3 \times (\text{region}_{18} \times \text{S})$] was not conducted as the inclusion of many nondepleted regions merely reduces the power to detect differences in regions of a priori interest (Cardinal and Aitken 2006).

Behavioral Assessment

Preoperative performance. Preoperatively, the 3 groups did not differ in the numbers of errors to reach the performance criterion on either discrimination (D1 and D2: F values <1; see Table 2).

Postoperative performance. Retention and acquisition. Postoperatively, there was no significant difference between the groups on their ability to remember the previously learned visual discrimination ($F < 1$) or the ability to acquire a new discrimination ($F < 1$; see Table 2). These findings suggest that both lesions had no effect on motoric ability or on general motivation.

Serial reversal. The 5-HT-lesioned monkeys made more errors than control monkeys and DA-lesioned monkeys across the series of reversals (Fig. 3*A*). Whereas control and DA-lesioned monkeys showed a steady decline in the number of errors to reach criterion from the 1st to the 4th reversal, 5-HT-lesioned monkeys did not. Close examination of the types of errors made by the 5-HT-lesioned monkeys revealed that they made more perseverative errors, but not more errors during the chance or learning stages, suggesting a selective effect of 5-HT depletion within the OFC and lateral PFC on perseverative responding (Fig. 3*B*). ANOVA of the square root–transformed errors to criterion using the model $\text{group}_3 \times (\text{error type}_3 \times \text{reversal}_4 \times \text{S})$, where "error type" = perseveration, chance, or learning stage, revealed significant main effects of error type ($F_{2,18} = 119.765$, $P < 0.001$) and of reversal ($F_{3,27} = 11.913$, $P < 0.001$) and an error type × group interaction ($F_{4,18} = 7.272$, $P < 0.001$), but no reversal × group interaction ($F_{6,27} = 2.189$, $P = 0.075$).

Simple main effects of group for each error type, collapsed across all 4 reversals revealed a significant difference between groups at the perseverative stage ($F_{2,9} = 31.103$, $P < 0.001$) but no such group difference at the chance and learning stages (F values <1). Post hoc analysis by independent samples t-tests revealed that the 5-HT-lesioned monkeys perseverated for longer than both control ($t_6 = 5.684$, $P = 0.001$; mean perseveration score across 4 reversals: control monkeys, 7.4 ± 2.9 errors; 5-HT lesioned monkeys, 57.4 ± 8.3 errors) and DA-lesioned monkeys ($t_6 = 5.897$, $P = 0.001$; mean perseveration score for DA-lesioned monkeys 7.5 ± 1.7 errors) and that there was no difference in perseveration between control and DA-lesioned monkeys ($t_6 = 0.18$, $P = 0.986$). Although the mean DA depletions of DA-lesioned monkeys was 75% (±11%), two of the 4 lesioned monkeys had DA depletions of 90.8% and 96.6%, but despite this their performance was still remarkably similar to controls (averaging 6.75 and 5.25 perseverative errors, respectively). Thus, the impairments seen in reversal learning were specific to 5-HT lesions of the OFC/lateral regions of the PFC and, as shown previously (Clarke and others 2004, 2005), were perseverative in nature (Fig. 3*B*).

Response Latencies and Lick Latencies

Control and lesioned monkeys did not differ in their latencies to make correct or incorrect responses at any stage of the experiment, either preoperatively [analyzed using the model $\text{group}_3 \times (\text{response type}_2 \times \text{stage}_2 \times \text{S})$, where response type refers to correct or incorrect responding; largest F value = 2.369, $P = 0.419$] or postoperatively [$\text{group}_3 \times (\text{response type}_2 \times \text{stage}_6 \times \text{S})$; all terms involving group: F values <1]. Similarly, control and lesioned monkeys did not differ in their latency to obtain reward following a correct response, either preoperatively or postoperatively [$\text{group}_3 \times (\text{stage}_2 \times \text{S})$; largest F value = 1.858, $P = 0.101$].

Experiment 2: Behavioral Characterization of the Reversal Deficit Induced by Prefrontal 5-HT Depletion

Methods

Sixteen common marmosets (*Callithrix jacchus*; 6 females, 10 males) were trained as described earlier. Once trained, the monkeys received the following series of discriminations, with progression onto the next

Table 1
Experiment 1: postmortem catecholamine tissue levels

Brain region	Serotonin			DA			Noradrenaline		
	Levels	% depletions		Levels	% depletions		levels	% depletions	
	Control	5-HT lesion	DA lesion	Control	5-HT lesion	DA lesion	Control	5-HT lesion	DA lesion
C2	0.7 ± 0.04	6.9 ± 3.7	−17.5 ± 8.6	0.4 ± 0.11	38 ± 8.8	41 ± 7.7	0.8 ± 0.2	−8.8 ± 13	13 ± 21
Ant par	0.9 ± 0.03	29 ± 2.5	−54 ± 38.7	0.4 ± 0.07	9.8 ± 8.7	22 ± 10	1 ± 0.21	10 ± 13	−0.02 ± 21
Post par	0.8 ± 0.08	14 ± 3.2	−20.5 ± 7	0.2 ± 0.01	32 ± 16	−10 ± 14	0.8 ± 0.1	−8 ± 17	9.5 ± 25
CAUD1	1.6 ± 0.28	−14 ± 10	16.3 ± 5.5	83 ± 5.3	10 ± 5.6	13 ± 6.4	1.4 ± 0.39	14 ± 33	37 ± 22
CAUD2	1.5 ± 0.18	1.8 ± 11	11.3 ± 17	92 ± 2.1	15 ± 4.2	0.6 ± 5.3	0.9 ± 0.19	−35 ± 41	−16 ± 45
CAUD3	1.7 ± 0.1	21.3 ± 7	43.8 ± 8	81 ± 0.55	20 ± 9.6	23 ± 4.5	0.9 ± 0.3	−64 ± 44	−60 ± 68
PUT1	1.9 ± 0.4	21.9 ± 2	15.8 ± 9.6	82.1 ± 5	41.6 ± 3	28.5 ± 9	0.9 ± 0.2	−30 ± 40	−9 ± 27
PUT2	1.9 ± 0.1	6.8 ± 5.4	−9 ± 10.8	76 ± 10	6 ± 2.5	−1.4 ± 11	1 ± 0.44	−1.5 ± 39	−16 ± 55
PUT3	1.9 ± 0.1	12 ± 7.7	27.5 ± 12	90 ± 2.5	29.7 ± 3	29 ± 12	1.3 ± 0.53	15 ± 24	−18 ± 60
NACC	2.7 ± 0.7	17.4 ± 8	−23.6 ± 14	39 ± 1.5	−12 ± 23	18 ± 26	2 ± 0.55	19 ± 23	−20 ± 33
HYP	3.1 ± 0.3	−22 ± 8.8	−18 ± 10.6	1.1 ± 0.1	−31 ± 50	27 ± 13	9.9 ± 0.8	−33 ± 9	10 ± 5.9

Note: Mean levels of 5-HT, DA, and NA (expressed as pmol/mg wet tissue weight ± standard error of the mean [SEM]) in the parietal cortex and striatum of the control group and their percent depletions (±SEM) in marmosets with 5,7-DHT and 6-OHDA lesions of the OFC. C2, mid-cingulate cortex; Ant Par, anterior parietal cortex; Post Par, posterior parietal cortex; CAUD1, anterior caudate; CAUD2, mid-caudate; CAUD3, posterior caudate; PUT1, anterior putamen; PUT2, mid-putamen; PUT3, posterior putamen; NACC, nucleus accumbens; and HYP, hypothalamus. 5-HIAA levels were also analysed but as no regions showed significant differences from controls, the data are not shown.

Table 2
Experiment 1: prereversal discrimination performance

Group	Errors (±SEM)			
	Before surgery		After Surgery	
	D1	D2	D2 retention	D3 acquisition
Controls	48.25 (13.8)	57.25 (5.59)	7.75 (2.5)	36.5 (7.2)
5-HT lesions	45.75 (8.53)	52.75 (9.0)	4.75 (2.8)	48.0 (6.26)
DA lesions	44.3 (12.6)	48.75 (17.2)	8.75 (4.1)	33.25 (17.33)

Note: Number of errors made before reaching the performance criterion on all prereversal discriminations of Experiment 1 for monkeys with 5-HT lesions, DA lesions, and control lesions. SEM, standard error of the mean.

stage dependent on the attainment of a 90% performance criterion in the previous session (see Fig. 1):

1. Acquisition of a novel discrimination (D1).
2. Acquisition of a second novel discrimination (D2).

Having reached criterion on the second discrimination (D2), 8 monkeys received 5,7-DHT lesions of the OFC and 8 monkeys received sham control procedures. After 2 weeks' recovery, they received the following series of discriminations with performance criteria as before:

3. A retention test of the discrimination learned immediately prior to surgery (D2 retention).
4. Acquisition of a third novel discrimination (D3). As in Experiment 1, all stimuli were fully counterbalanced across the 4 groups from this stage onward.
5. First reversal of the third discrimination, in which the previously rewarded stimulus became unrewarded and vice versa.
6. Second reversal, in which half the monkeys in each group were given a perseveration test and the other half were given a learned avoidance test (see Fig. 1).

To test for perseveration, the monkeys were given a discrimination in which the previously correct stimulus was now incorrect, and the previously incorrect stimulus was replaced with a novel stimulus that was rewarded. To test for learned avoidance, the monkeys were given a discrimination in which the previously incorrect stimulus was now correct, and the previously correct stimulus was replaced with a novel stimulus.

Using this behavioral design, the specific pattern of behavioral performance across the perseveration and learned avoidance conditions in control and lesioned monkeys can provide insight into the behavioral processes that are impaired following 5-HT depletion of the OFC. The predictions are illustrated in Figure 4. Thus, if the impairment in reversal learning induced by 5-HT PFC depletion is due 1) to a difficulty in suppressing the effects of the previously learned reward association on current responding, then at reversal 2, the lesioned monkeys would be expected to perform poorly on the perseveration test (B– C+), as the previously correct stimulus, (B) is still present (lesion errors > control errors). In contrast, they should perform as well as controls on the learned avoidance test (A+ C–), as the previously rewarded stimulus (B) is not present (lesion errors = control errors). The opposite pattern of deficits would be predicted if the deficit is due 2) to enhanced learned avoidance. Thus, lesioned monkeys would perform as well as controls on B– C+, but would perform worse than controls on A+ C– because they would have difficulty approaching the previously incorrect stimulus (A). Alternatively, if the deficit induced by 5-HT depletion is due 3) to proactive interference, the experience of previous discriminations would be expected to impair performance on the second reversal regardless of the particular stimuli presented. Consequently, lesioned monkeys should make more errors than controls in both the perseveration and learned avoidance conditions. Finally, the inclusion of novel stimuli introduces the possibility that enhanced attraction to novelty, or enhanced avoidance of novelty, may contribute to the effects of 5-HT depletions on this task. Thus, if lesioned monkeys are attracted to novel stimuli more than controls, then performance would be predicted to be better than that of controls on B– C+ (when the novel stimulus is the "correct" stimulus) but worse than controls on A+ C– (when the novel stimulus is "incorrect"). Conversely, if lesioned monkeys are more averse to novel stimuli, the opposite pattern of performance would be seen. Lesion performance on B– C+ would be worse than that of controls, whereas lesion performance on A+ C– would be better than that of controls.

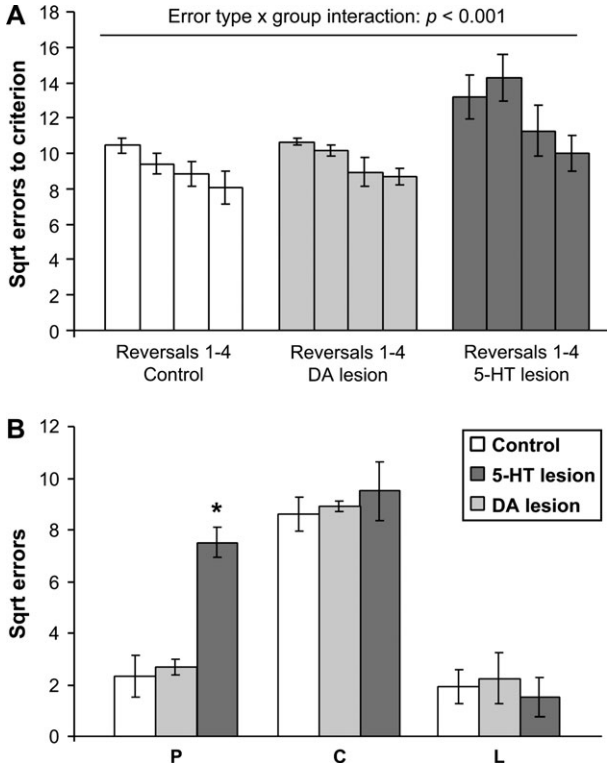

Figure 3. Mean number of errors to criterion (square root ± standard error of the mean) for control, DA-lesioned, and 5-HT-lesioned monkeys. (*A*) Total errors to criterion across all 4 reversals; (*B*) Error type collapsed across reversals (see text for statistical details). P, perseveration stage; C, chance stage; and L, learning stage. *P < 0.001, difference from other groups.

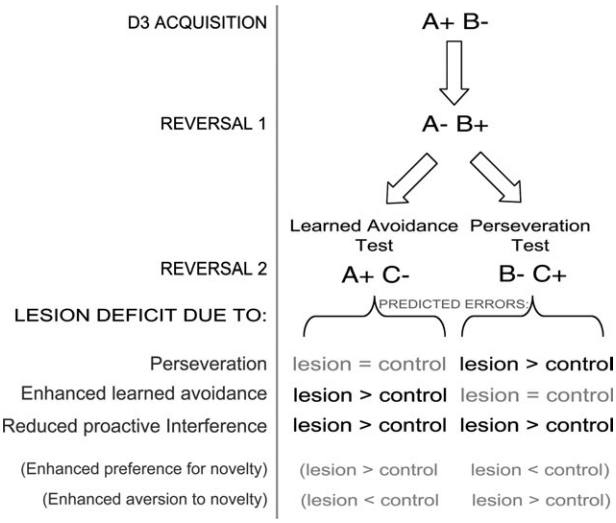

Figure 4. Symbolic representation of stimuli presented at each discrimination, and predictions as to the relative number of errors made by lesioned and control subjects. As before, "+" signifies a correct stimulus and "–" symbolizes an incorrect stimulus; C represents a novel stimulus. Perseveration refers to perseverative responding toward the previously correct stimulus; enhanced learned avoidance means persistent avoidance of the previously incorrect stimulus. Emboldened text indicates where 5-HT-lesioned monkeys would be predicted to perform differently from controls.

Table 3
Experiment 2: post mortem catecholamine tissue levels

Brain region	Serotonin		DA		Noradrenaline	
	Control levels	% depletion	Control levels	% depletion	Control levels	% depletion
OFC	0.90 ± 0.08	38.9 ± 8.21*	0.43 ± 0.07	2.24 ± 14.06	0.90 ± 0.06	0.60 ± 4.39
LPFC	0.98 ± 0.04	42.9 ± 7.3*	0.31 ± 0.02	−12.3 ± 7.16	0.92 ± 0.06	−1.37 ± 8.03
MPFC	1.07 ± 0.06	9.63 ± 8.97	0.33 ± 0.02	−16.7 ± 5.94	1.01 ± 0.06	−0.72 ± 6.49
DPFC	0.74 ± 0.04	7.55 ± 8.86	0.42 ± 0.02	−13.59 ± 8.6	1.09 ± 0.08	−3.52 ± 7.43
M/PM	0.83 ± 0.04	−10.1 ± 10	0.54 ± 0.05	1.48 ± 5.73	1.46 ± 0.09	6.55 ± 6.49
C1	0.99 ± 0.07	−10.8 ± 15.9	0.46 ± 0.05	−16.9 ± 10.7	1.82 ± 0.2	−1.88 ± 11.1
Ant Par	0.94 ± 0.06	−6.63 ± 12.3	0.35 ± 0.04	5.56 ± 10.8	1.57 ± 0.11	3.00 ± 6.27

Note: Mean levels of 5-HT, DA and NA (expressed as pmol/mg wet tissue weight ± standard error of the mean [SEM]) in the cortex of the control group and their percentage depletions (±SEM) in marmosets with 5,7-DHT lesions of the OFC. OFC, orbitofrontal cortex; LPFC, lateral granular PFC; MPFC, pregenual medial PFC; DPFC, dorsal granular PFC; M/PM, primary motor and premotor cortex; C1, anterior cingulate cortex; and Ant Par, anterior parietal cortex. 5-HIAA levels were also analyzed but as no regions showed significant differences from controls, the data are not shown.
*$P < 0.05$.

Results

Post mortem Depletions of Serotonin Within Selected Regions of the PFC following 5,7-DHT Lesions of the OFC

As in Experiment 1, 5,7-DHT injections into the OFC produced significant depletions of 5-HT in both the OFC and lateral regions of PFC 8–14 months postoperatively (Table 3). Pretreatment with the NA and DA reuptake blockers nisoxetine and GBR 12909 successfully protected NA and DA, respectively, with their levels remaining the same as controls. As before, no significant depletions of 5-HT, DA, or NA were seen in any other frontal or striatal regions, including the primary motor and premotor cortex, the pre- and postgenual cingulate cortices, and the caudate nucleus.

Levels of 5-HT, DA, NA, and 5-HIAA were first square root transformed to eliminate the heterogeneity of variance between groups (demonstrated using Levene's test) and then compared across groups (5-HT lesion and sham-operated control) using the model $\text{group}_2 \times (\text{region}_{12} \times \text{S})$. This revealed a significant region × group interaction for 5-HT ($F_{3.2,45.4} = 4.509$, $\tilde{\varepsilon} = 0.295$, $P < 0.006$) but not DA or NA (Pvalues >0.05). As it has already been demonstrated that subcortical regions are unaffected by this lesion, post hoc analysis focused on only the 6 prefrontal regions to maximize statistical power. Thus, independent sample t-tests using the Šidák correction for multiple comparisons revealed significant 5-HT depletions in the OFC (38.9 ± 8.21% depletion; $t_{14} = 3.161$, $P_{\text{corrected}} = 0.04$) and lateral PFC (42.87 ± 7.3%; $t_{14} = 4.881$, $P_{\text{corrected}} < 0.005$) only.

Although statistically significant, these depletions are much lower than those reported in Experiment 1 and in previous studies (Clarke and others 2004, 2005). This is almost certainly because these monkeys continued to be tested experimentally (data not reported) after the completion of the reversal study reported here, resulting in a marked delay prior to the post mortem neurochemical assessment. This is supported by unpublished findings illustrated in Figure 5, in which the levels of 5-HT can be seen to recover slowly across time. Because all the behavioral testing in the present study was completed within the first 10 weeks postoperatively, the extent of the depletion during this time period is expected to have been equal to, or slightly larger, than that seen in Experiment 1.

Behavioral Assessment

Preoperative performance. Preoperatively, there were no differences between the groups on either D1 or D2. ANOVA using the model $\text{lesion}_2 \times \text{test}_2 \times (\text{discrimination}_2 \times \text{S})$ where "lesion" and "test" are between-subjects factors with 2 levels (lesion: destined to receive a 5-HT lesion or sham control procedure; test: destined to receive perseveration or learned avoidance tests), and "discrimination" is a within-subjects factor with 2 levels (D1 and D2), revealed no significant effects (all Fvalues <1; see Table 4).

Postoperative performance. Retention and acquisition. Postoperatively, there was no significant difference between the groups on their ability to remember a previously acquired discrimination, or their ability to acquire a new discrimination (using the same model as before, all terms involving lesion: F values <1), with both control and lesioned groups making fewer errors to reattain the criterion on the previously acquired discrimination compared with the acquisition of the novel discrimination (main effect of discrimination: $F_{1,12} = 8.288$, $P = 0.014$; see Table 4). Again, these findings are indicative of no lesion-induced motoric or motivational disruption.

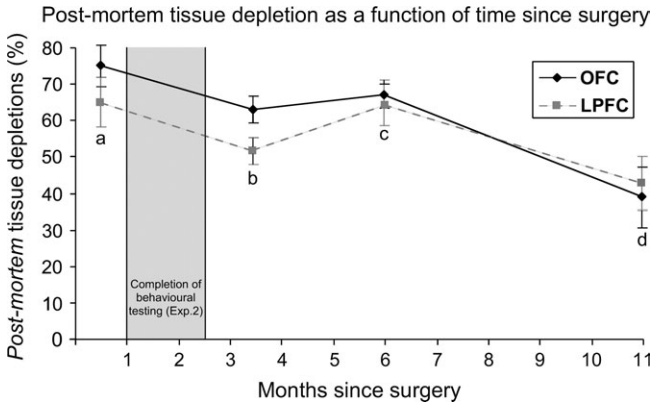

Figure 5. Post mortem tissue depletions in the OFC and lateral PFC at a range of time points after selective serotonergic lesions within the PFC: a, 2 unilaterally lesioned marmosets assessed at 2 weeks postoperatively; b, 4 bilaterally lesioned marmosets (reported in Experiment 1) assessed an average of 3.4 months postoperatively; c, 4 bilaterally lesioned marmosets assessed at 6 months postoperatively (Walker S. C., Mikheenho Y. P., Argyle L. D., Robbins T. W., and Roberts A. C. unpublished data); d, 8 bilaterally lesioned marmosets assessed an average of 11 months postoperatively (current experiment). All lesions used the same methods (as described in the present study). At all time points, the OFC and lateral PFC were the only regions showing significant depletion ($P < 0.05$). The gray region indicates the range of times in which behavioral testing was completed, postoperatively, in the current study (mean completion time, 6 weeks postoperatively).

Table 4
Experiment 2: prereversal discrimination performance

	Before surgery		After surgery	
	D1	D2	D2 Retention	D3 Acquisition
A. Subjects due to receive the perseveration test				
Controls (SEM)	41.8 (±10)	51 (±14.7)	9.8 (±4.8)	33 (±6.5)
Lesions (SEM)	41 (±11.3)	62 (±16.6)	8.8 (±5.4)	21.8 (±5.1)
B. Subjects due to receive the learned avoidance test				
Controls (SEM)	35.8 (±10)	41.3 (±8.3)	4.8 (±4.8)	23 (±11.3)
Lesions (SEM)	32.8 (±8.6)	48.8 (±6.7)	10.5 (±4.1)	47.3 (±28)

Note: Total number of errors incurred at the prereversal stages for both control and lesioned monkeys. There were no significant differences between groups. SEM, standard error of the mean.

Serial reversals. The 5-HT-lesioned monkeys differed from control monkeys across the series of reversals in a test-dependent manner. Control monkeys showed a decline in the number of errors to reach criterion from reversal 1 to reversal 2 in both the perseveration and learned avoidance tests. However, although 5-HT-lesioned monkeys performing the learned avoidance test showed a similar decline to controls in errors across reversal 1 to reversal 2, those performing the perseveration test did not, and overall, performed significantly worse than the control monkeys (Fig. 6).

ANOVA using the model $\text{lesion}_2 \times \text{test}_2 \times (\text{reversal}_2 \times \text{S})$, where "reversal" has the levels "reversal 1" and "reversal 2," revealed a significant main effect of reversal ($F_{1,12} = 38.83$, $P < 0.001$), a near-significant reversal × test interaction ($F_{1,12} = 4.718$, $P = 0.051$), and a 3-way reversal × test × lesion interaction ($F_{1,12} = 8.965$, $P = 0.011$). Subsequent analysis of the simple interactions revealed that a difference between control and lesioned subjects was not present on reversal 1 (all terms involving lesion: F values <1) but emerged on reversal 2 (lesion: $F_{1,12} = 6.709$, $P = 0.024$; lesion × test: $F_{1,12} = 6.819$, $P = 0.023$). Simple main effects revealed that in reversal 2, lesioned subjects did not differ from controls in the "learned avoidance" test ($F < 1$), but performed worse than controls in the perseveration test ($F_{1,6} = 15.687$, $P = 0.007$).

To determine whether the effects of the lesion were present on the 1st day of the reversal, errors performed on day 1 of both reversal 1 and 2 were subjected to ANOVA. This revealed a significant main effect of reversal ($F_{1,6} = 13.035$, $P = 0.011$) and a reversal × group interaction ($F_{1,6} = 11.179$, $P = 0.016$) with the main effect of group just failing to attain significance ($F_{1,6} = 5.831$, $P = 0.052$). Post hoc analysis revealed that whereas controls showed an improvement in their performance on the 1st day of reversal 2 compared with reversal 1 ($t_3 = 4.486$, $P = 0.021$), 5-HT-lesioned monkeys did not ($t_3 = 0.211$, $P = 0.846$).

Response latencies and lick latencies. ANOVA of response latencies [using the model $\text{lesion}_2 \times \text{test}_2 \times (\text{response type}_2 \times \text{discrimination}_2 \times \text{S})$, where "response type" = correct or incorrect] revealed no significant preoperative or postoperative differences between 5-HT lesioned monkeys and controls on correct or incorrect response latencies (largest F: $F_{1,12} = 3.742$, $P = 0.108$).

As before, ANOVA of lick latencies revealed no significant prereversal differences between 5-HT-lesioned and control monkeys in their latencies to respond to the licker (all terms involving lesion: F values <1). However, ANOVA of lick latencies for the 2 reversal stages using the model $\text{lesion}_2 \times \text{test}_2 \times (\text{discrimination}_2 \times \text{S})$ showed a test × discrimination interaction ($F_{1,12} = 6.594$, $P = 0.025$), and a lesion × discrimination interaction ($F_{1,12} = 6.225$, $P = 0.028$). However, the lesion effect did not depend on the test type (terms involving lesion × test: F values ≤1.14). Simple main effects showed that whereas the lesioned animals on the leaned avoidance test showed the same lick latencies across reversals 1 and 2 ($F < 1$), controls showed a longer latency on reversal 2 ($F_{1,7} = 16.727$, $P = 0.005$).

Discussion

The primary results of these studies are that selective depletion of 5-HT from the marmoset OFC and lateral PFC produced deficits in visual discrimination reversal learning, whereas selective OFC DA depletion was without effect (Experiment 1). As previously observed, the deficit induced by 5-HT depletion was due to persistent responding to the previously rewarded stimulus (Clarke and others 2004, 2005). Further examination of the nature of the behavioral deficit (Experiment 2) revealed that the failure of 5-HT-lesioned monkeys to cease responding to the previously correct stimulus was due to an inability to disengage from that stimulus and was not due to a failure to reengage with the stimulus previously learned to be incorrect (learned avoidance) or to an attenuation of proactive interference.

In Experiment 1, the behavioral deficits in the 5-HT-lesioned monkeys were accompanied by selective 5-HT depletions within the OFC and lateral regions of the PFC (OFC: depletion by 63.2 ± 3.8%; lateral: 51.6 ± 5.7%), 4–11 months postoperatively. There were no DA or NA depletions within these regions and, as shown before (Clarke and others 2004), other prefrontal, striatal, and subcortical regions were unaffected. In the DA-lesioned monkeys, selective DA depletion was restricted to the OFC (depletion by 75 ± 11.7%), with no other monoaminergic depletions seen, confirming the neurochemical and neuroanatomical selectivity of the dopaminergic lesion. The same regional specificity of the serotonergic lesion was seen in Experiment 2.

The finding that 5-HT depletion restricted to ventral regions of marmoset PFC impairs reversal learning extends and refines our previous findings in which global depletions of 5-HT throughout the frontal lobes disrupted reversal learning (Park and others 1994; Rogers and others 1999; Clarke and others 2004, 2005). Although the 5-HT depletion in Experiment 1 was not restricted to the OFC but extended into the lateral PFC (probably due to the infusions affecting serotonergic axons in the OFC en route to the lateral PFC), it is most likely that the loss of OFC 5-HT is responsible for the observed deficit. This is consistent with our previous findings that excitotoxic lesions of the OFC, and not the lateral PFC, impair reversal learning in marmosets (Dias and others 1996a, 1996b).

The lack of effect of selective OFC DA depletion on the serial reversal paradigm is consistent with the findings of previous PFC catecholaminergic depletion studies (Roberts and others 1994; Crofts and others 2001). However, as described above, these previous results were open to alternative explanations. Thus, the current findings extend these earlier results by demonstrating that substantial OFC DA depletions (of approximately 75%), with no significant loss of NA, are without effect on serial reversal learning. Although it may still be possible that a mean 75 ± 11% loss in DA was insufficient to cause a behavioral deficit in the current study, we feel this is unlikely given that

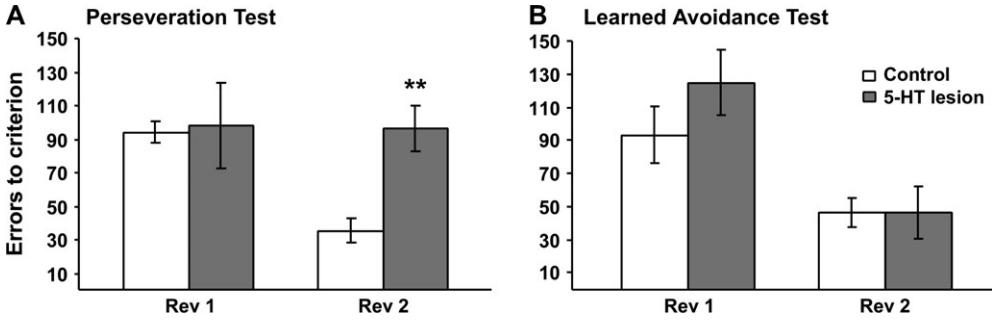

Figure 6. Number of errors made before attaining the performance criterion for monkeys performing reversal 1 and either (*A*) perseveration or (*B*) learned avoidance tests in reversal 2 of Experiment 2. $^{**}P < 0.01$, difference from controls.

two of the 4 DA-lesioned monkeys had OFC DA depletions in excess of 90%, but despite this still displayed identical reversal performance to that of controls (with minimal perseveration). In addition, our previous findings and that of other groups have reported significant behavioral effects with prefrontal DA depletions ranging from 77% to 84% in a variety of tasks (Roberts and others 1994; Crofts and others 2001; Kheramin and others 2004).

Implications for the Role of DA in Reversal Learning and the Functional Modulation of the OFC

The lack of effect of DA depletion of the OFC on reversal learning is of particular significance given that DA per se has been implicated in the reversal learning deficits apparent in Parkinson's Disease (PD). PD is caused by degeneration of the dopaminergic neurons within the substantia nigra pars compacta, and the primary treatment is to increase levels of DA with the dopaminergic precursor L-dopa. However, although administration of L-dopa to PD patients improves certain aspects of learning and performance, such as spatial working memory and the acquisition and maintenance of an attentional set (Lange and others 1992), it impairs probabilistic reversal learning (Swainson and others 2000; Cools and others 2001) although, unlike the present study, the deficit is not perseverative in nature. The "overdose" account of this behavioral dissociation suggests that L-dopa reverses the effects of DA loss in the dorsal striatum and ameliorates dorsal striatal motor symptoms and set-shifting impairments (Swainson and others 2000; Cools and others 2001) but "overdoses" the relatively unaffected ventral striatum (Kish and others 1988; Agid and others 1993), thereby disrupting functions associated with the OFC and its associated striatal loop (Alexander and others 1986; Gotham and others 1988; Swainson and others 2000; Cools and others 2001). If this is the case, the current findings of intact reversal learning following OFC DA depletion would suggest that any reversal impairment seen in L-dopa–treated PD patients is most likely due to a disruption of function at the level of the striatum, and not the OFC, a result supported by a recent functional magnetic resonance imaging finding of PD patients on and off L-dopa (Cools 2005). Similarly, dopaminergic effects at the level of the striatum may account for the impairments in probabilistic reversal learning that occurs following low-dose treatment with the D2 DA agonist bromocriptine (Mehta and others 2001), which also induces a deficit that is not perseverative in nature. Thus, it may be speculated that the perseverative reversal learning impairments seen after repeated peripheral administration of cocaine in vervet monkeys may be due to cocaine-induced modulation of 5-HT, and not DA, within the OFC (Jentsch and others 2002).

Despite the failure of OFC DA depletion to disrupt reversal learning, DA has been implicated in other aspects of OFC-mediated reward processing. Behavioral evidence suggests that DA has an important influence on the OFC's contribution to the evaluation of both reinforcer magnitude and delay discounting (Kheramin and others 2004; Winstanley and others 2005). Electrophysiological studies have also implicated OFC DA in reward processing (Schultz 2002), and intra-OFC administration of DA D1 and D2 receptor antagonists decrease the break point on a progressive ratio schedule, consistent with a role for OFC DA in translating motivation into action (Cetin and others 2004). Thus, future studies should directly compare the effects of OFC 5-HT and DA manipulations on these different aspects of reward processing to refine further our understanding of their differential contribution to orbitofrontal functioning. The use of in vivo microdialysis to assess compensatory changes in catecholamine levels following indoleamine lesions (or vice versa) may also reveal any secondary alterations in monoamine function that could impinge upon behavior.

Behavioral Processes Underlying the Perseverative Reversal Deficit Induced by Regional PFC 5-HT Depletion

Experiment 2 of the present study showed that the inability to cease responding to the previously correct stimulus in a visual discrimination task is due to the continued presence of the previously rewarded stimulus, and not learned avoidance or proactive interference. However, a number of mechanisms could be responsible for such apparently stimulus-bound behavior including 1) failure to detect an error or punishment or a failure to respond appropriately to such punishment, 2) failure to inhibit the previously rewarded response, or 3) failure to inhibit a previously relevant stimulus-reward association. The latter is unlikely, as it has been shown that following a change in contingencies, the original stimulus-reward association remains intact and can continue to motivate behaviors distinct from those expressed at the time of the contingency change (Rescorla 2001). A failure in error detection has classically been associated with damage to the medial PFC and in particular the dorsal cingulate regions (for review, see Cardinal and others 2002), and 5-HT depletion in humans (induced by a low tryptophan diet) has been shown to modulate activity in this region during receipt of negative feedback, suggesting a role for prefrontal 5-HT in the processing of aversive signals (Evers and others 2005). However, 5-HT was not depleted in the medial prefrontal and cingulate cortices in the present study, and thus primary dysfunction in this region is unlikely to have contributed to the reversal effects.

Alternatively, an altered sense of punishment or aversiveness may have contributed to the failure to inhibit a prepotent response. Consistent with this, functional neuroimaging studies have identified a region of lateral OFC that is sensitive to aversive rather than rewarding situations (O'Doherty and others 2001; Small and others 2001). This region has also been implicated in the ability to withhold a previously correct response (Butter 1969; Iversen and Mishkin 1970; Elliott and others 2000; O'Doherty and others 2001; Small and others 2001), which may be an alternative explanation for the reversal deficit seen in the current study. For example, serotonergic drugs have been shown to decrease the hyperactivity of the lateral OFC associated with OCD symptomatology (see Saxena and others 1998, 1999), difficulty in inhibiting responding in the stop-signal reaction time task correlates with decreased platelet 5-HT transporter affinity for paroxetine in children with attention-deficit hyperactivity disorder (Oades and others 2002), and increases in impulsive action have been seen after tryptophan depletion in humans (LeMarquand and others 1998, 1999; Crean and others 2002; but see Clark and others 2005), although the neural locus of these latter effects is uncertain. Thus, overall, the precise mechanism underlying the failure to cease responding to the previously rewarded stimulus remains to be determined.

The determination of such a mechanism may have profound implications for our understanding of the psychobiology of disease states such as schizophrenia and obsessive-compulsive

disorder, disorders in which both ventromedial PFC dysfunction and compulsive and impulsive behaviors are seen (Abbruzzese and others 1995; Freedman and others 1998; Pantelis and others 1999; Yogev and others 2003). Although serotonergic dysfunction has been implicated in impulsivity (see Cardinal and others 2004; Winstanley and others 2004), the reversal learning deficit in the present study is probably a better model of compulsive (i.e., repetitive and perseverative) behavior rather than impulsive behavior (such as action without foresight). Nevertheless, 5-HT may well be implicated in both types of behavior, and serotonergic drugs (i.e., atypical neuroleptics and selective 5-HT reuptake blockers) are used effectively in the symptomatic treatment of various compulsive and perseverative disorders (Saxena and others 1999; Meltzer and others 2003). It remains to be seen whether similar treatments will ameliorate the perseverative deficits in reversal learning seen in the current studies.

In conclusion, these studies suggest that the discrimination reversal deficits induced by ventral prefrontal 5-HT depletion are due specifically to a failure to cease responding to the previously rewarded stimulus. They also highlight the neurochemical specificity of the effects, in that DA depletions of the OFC are without effect. Taken together with our previous findings of a lack of an effect of prefrontal 5-HT depletion on attentional set shifting (Clarke and others 2005), but a marked disruption of attentional selection by prefrontal catecholaminergic depletion (Roberts and others 1994; Crofts and others 2001), these results demonstrate the highly specific and dissociable contribution of 5-HT and DA in the modulation of prefrontal processing.

Notes

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