Differential Effects of 6-OHDA Lesions of the Frontal Cortex and Caudate Nucleus on the Ability to Acquire an Attentional Set

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Evidence from both human and animal studies indicates that catecholamine (dopamine and noradrenaline) imbalances in the fronto-striatal circuitry are associated with deficits in higher-order cognitive functions. The present study examined how catecholamines within this circuitry modulate attentional function, specifically the ability to develop, maintain, and shift an attentional set. Catecholamine depletions within the frontal cortex of the common marmoset impaired the ability to acquire an attentional set, and increased susceptibility to distraction from task-irrelevant stimuli. Analysis of set-shifting performance with stimulus dimensions of varying salience suggested that frontal catecholamine depletion selectively disrupts 'top-down', but not 'bottom-up' attentional processing. In contrast, the ability to acquire and shift an attentional set remained intact following dopaminergic depletion from the caudate nucleus. However, the reduced susceptibility to distraction from task-irrelevant stimuli displayed by monkeys with dopaminergic depletions of the caudate nucleus suggests that responding was under more rigid control by the currently rewarded stimulus. The results demonstrate opposite behavioural effects of 6-hydroxydopamine (6-OHDA) lesions in the frontal cortex and caudate nucleus in tasks requiring selective attention. Frontal catecholamine depletion caused an increase in distractibility while caudate dopamine loss induced greater focusing of responding.

Introduction

Catecholaminergic projections to the prefrontal cortex (PFC) (Brozoski *et al.*, 1979; Arnsten and Goldman-Rakic, 1985; Roberts *et al.*, 1994; Diamond *et al.*, 1997; Ernst *et al.*, 1999; Mehta *et al.*, 2000) and dopaminergic projections to the striatum (Schneider and Kovelowski, 1990; Taylor *et al.*, 1990a,b; Schneider and Roeltgen, 1993) have both been implicated in the control of higher-order cognitive processes [for reviews see Arnsten and Goldman-Rakic (Arnsten 1998; Goldman-Rakic 1998)]. However, their relative contributions to cognitive processing remain unclear. Previously, we have shown that a loss of catecholamines within the frontal cortex (Roberts *et al.*, 1994) and a loss of dopamine within the caudate nucleus (Collins *et al.*, 2000) induced by intracerebral injections of 6-hydroxydopamine (6-OHDA) produce deficits in performance of the spatial delayed response task in the marmoset, that, superficially at least, are similar to one another, as well as to those seen following ablation of the PFC itself (Dias *et al.*, 1996a). In contrast, such lesions produce a rather different pattern of effects compared, not only to one another, but also to effects of prefrontal excitotoxic lesions, on another test of fronto-executive function, attentional set shifting. The attentional set-shifting task used in these studies was an analogue of the Wisconsin Card Sort Test (Berg, 1948) and required subjects to learn a series of compound visual discriminations composed of two perceptual dimensions, white lines superimposed over blue shapes (see Fig. 1). In each of the discriminations only one of the dimensions was relevant, e.g. shapes, and the subject had to learn to respond to one of the exemplars from the relevant dimension in order to obtain reinforcement. Since novel exemplars from the same dimension were reinforced consistently across discriminations (intra-dimensional shifts), subjects developed an attentional set towards the relevant dimension. Thus, subsequently, when required to learn a discrimination in which an exemplar from the other, previously irrelevant dimension, i.e. lines, was correlated with reinforcement (extra-dimensional shift), subjects made many more errors to learn this discrimination in comparison to the previous discriminations in accordance with the hypothesis of selective responding to a particular dimension (Slamecka 1968).

The ability to shift attentional set from one perceptual dimension to another on this test is impaired not only in humans with damage to PFC (Owen *et al.*, 1991) and disorders of the basal ganglia such as Parkinson's disease (Downes *et al.*, 1989; Owen *et al.*, 1992) and Huntington's disease (Lawrence *et al.*, 1996) but also in marmosets with regionally selective excitotoxic lesions of the lateral PFC (Dias *et al.*, 1996b, 1997). Thus it was originally predicted that 6-OHDA lesions of the frontal cortex and/or striatum would also impair attentional set-shifting ability. However, contrary to these predictions 6-OHDA lesions of the marmoset frontal cortex (Roberts *et al.*, 1994) apparently enhanced attentional set-shifting ability such that lesioned marmosets acquired the discrimination that required a shift of attentional set more rapidly than controls. In contrast, 6-OHDA lesions of the marmoset caudate nucleus were without effect on the first shift of attentional set, but impaired the re-engagement of a previously relevant attentional set (Collins *et al.*, 2000). These somewhat different effects on attentional set shifting, not only between 6-OHDA lesions of the frontal cortex and striatum in marmosets, but also between 6-OHDA lesions in marmosets and Parkinson's disease in humans, led to a re-examination of 6-OHDA lesions of the frontal cortex and striatum on attentional set-shifting ability in the present study.

Detailed analysis of the pattern of impairment in patients with Parkinson's disease on the attentional set-shifting task reveals that these patients not only show a disruption in shifting an attentional set but can also show impaired performance at earlier stages of the test, during the acquisition and maintenance of an attentional set (Owen *et al.*, 1992). Indeed, a failure to maintain an attentional set could have accounted for the apparent improvement in set shifting seen in the 6-OHDA frontal-lesioned monkeys of Roberts *et al.* (Roberts *et al.*, 1994), since monkeys with such an impairment would not be responding to stimuli from the irrelevant dimension at the time of the shift and therefore would not be disadvantaged in their performance. However, while neither 6-OHDA lesions of the frontal cortex nor caudate nucleus in the earlier studies appeared to affect the ability of marmosets to learn discriminations that required maintenance of an attentional set, the effects of such lesions on

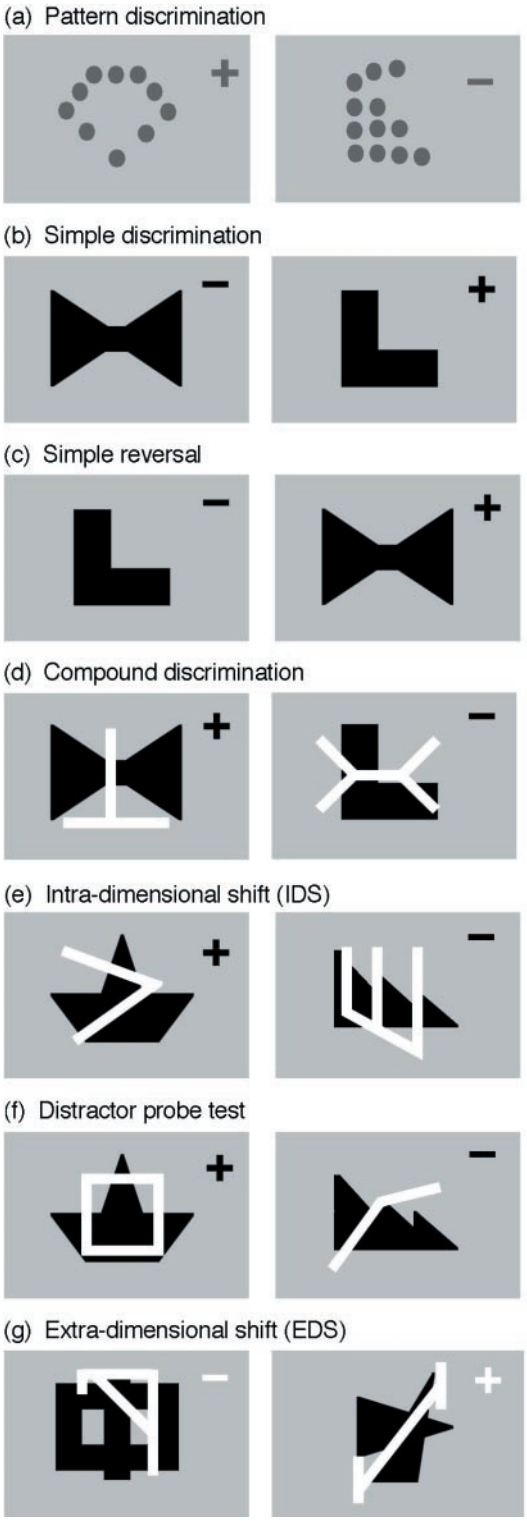

Figure 1. Stimulus exemplars used for the various stages of visual discrimination learning. (*a*) The two 'dot' patterns used for discrimination training prior to surgery. (*b–g*) Examples of discriminations used at the different stages of the attentional set-shifting task. For illustrative purposes the examples presented here are ones in which an exemplar from the 'shapes' dimension is rewarded in all discriminations, except that requiring an EDS in which one of the exemplars from the 'lines' dimension is rewarded. On any one trial of a discrimination, stimulus exemplars from the dimensions of 'shapes' and 'lines' were paired randomly with respect to one another and appeared randomly either on the left or right of the screen. The rewarded and unrewarded stimulus exemplar on each discrimination is indicated by the plus (+) and minus (–), respectively. White symbols indicate that 'lines' is the relevant dimension, black symbols indicate that 'shapes' is the relevant dimension.

acquisition of an attentional set were never examined, as monkeys acquired the attentional set prior to surgery. Consequently, the present study directly compared the effects of 6-OHDA lesions of the frontal cortex and caudate nucleus in the marmoset on the acquisition as well as the maintenance and shifting of an attentional set. The stability of an attentional set and the extent to which performance was affected by extraneous novel stimuli from the irrelevant dimension was also examined by a distractor test.

The results provide an explanation for the previously observed facilitation of attentional set-shifting performance in frontal catecholamine lesioned marmosets (Roberts *et al.*, 1994); arising from the failure to form and maintain certain types of attentional set. This cognitive deficit contrasts with that seen following caudate dopamine (DA) depletion and is interpreted within a novel theoretical scheme that encompasses a role for the PFC in certain forms of attention.

Materials and Methods

Subjects

Twenty-two common marmosets (*Callithrix jacchus*) (18 females and 4 males), obtained from Harlan UK Limited, Oxford, UK (n = 4), Porton Down, Salisbury, UK (n = 2) or bred on site at the Medical Research Council colony (n = 16), with a mean age of 23 months, were used in this study. They were housed either in sibling or unisex pairs. All monkeys were fed on 20 g of MP.E1 primate diet [Special Diet Services (SDS), Withams, Essex, UK] and two pieces of carrot and had access to water for 2 h in the afternoon following the daily behavioural testing session. At weekends monkeys had free access to water and the diet was supplemented with fruit, eggs, rusk, and marmoset jelly (SDS). All procedures were performed in accordance with the project and personal licences held by the authors under the UK Animals (Scientific Procedures) Act of 1986.

Apparatus

Testing was conducted within a specially designed automated apparatus situated in a sound attenuated box within a dark room [see Roberts *et al.* for details (Roberts *et al.*, 1988)]. Monkeys sat in front of a colour, high-resolution video display unit (VDU) (model 1440, Microvitec, Bradford, UK) from which they were separated by a vertical array of metal bars, through which they could touch stimuli presented on the VDU. Touches were detected by a touch-sensitive array (Microvitec Touchtec 501) attached to the screen. A reward of ice-cold banana milkshake was delivered via a peristaltic pump to a spout attached to the metal bars, central to the screen. Licking at the spout broke an infrared photocell beam that triggered the delivery of reward. On either side of the VDU were situated loudspeakers (R. S. components, parts 249–429) through which a 4 kHz tone (~60 dB) could be played. The test chamber was lit by a 3 W bulb situated in the centre of the roof. Stimuli to be presented on the VDU were generated on an Acorn Archimedes computer. The dimensions of these stimuli were: 70 mm wide × 58 mm high (abstract green patterns), 32 × 32 (blue filled shapes), 32 × 38 (white lines). The computer controlled the contingencies and recorded both outcome and latency measures using programs written in Arachnid language (CeNeS plc, Histon, Cambridge, UK).

Initial Training

Following reward familiarization the animals were first trained to collect banana milkshake from the delivery spout whenever a 10 s tone was presented and then shaped to touch a stimulus appearing on the VDU in order to obtain the signalled reward. Training continued until animals reliably obtained reward by touching a red square positioned on either the left or right side of the touch sensitive screen. [More extensive details of training can be found in Roberts *et al.* (Roberts *et al.*, 1988)].

Pre-operative Training

All monkeys were trained prior to surgery on a two-choice simultaneous abstract pattern discrimination and reversal. The stimuli used were

composed of small green circles and were visually unlike anything to be used in the subsequent discrimination study both in terms of colour and form (Fig. 1*a*). A response to either stimulus resulted in the stimuli disappearing from the screen. A response to one of the stimuli (positive stimulus) resulted in the sounding of a 5 s tone, which signalled the availability of 5 s of reinforcement. Failure to collect the reward within 5 s following the onset of the tone was scored as a missed reward and ended the trial. A response to the other stimulus (negative stimulus) resulted in a 5 s time-out period during which the house light was extinguished. There was an inter-trial interval of 3 s. Monkeys were presented with 60 trials per day, 5 days a week, until achieving a criterion of 90% correct within a session of 60 trials (54 correct responses in 60 trials). Upon attainment of criterion, on the subsequent day the contingencies were reversed such that a response to the stimulus which had previously been unrewarded became rewarded and vice versa. If subjects showed a significant side bias for two consecutive sessions a correction procedure was employed during the next test session whereby the same trial was presented repeatedly until the monkey had made a correct response.

Monkeys were then divided into three groups: sham-operated control group (line, n = 4, shape, n = 3), 6-OHDA caudate lesion group (line, n = 3, shape, n = 5) and 6-OHDA frontal lesion group (line, n = 3, shape, n = 4).

Surgery

All monkeys were pre-medicated with the monoamine oxidase inhibitor pargyline (Sigma; 50 mg/kg i.p.) to enhance the efficacy of 6-hydroxydopamine hydrobromide (6-OHDA) and were anaesthetized 20 min later with sodium pentobarbitone (3 mg/kg i.p.). Once anaesthetized monkeys were positioned in a stereotaxic frame (David Kopf, Tujunga, CA), which had been modified to be suitable for the marmoset.

Lesions of the dopaminergic innervation to the PFC or caudate nucleus were made by injecting 2 µl of a 6 µg/µl solution of 6-OHDA (Sigma, Poole, UK; in 0.01% ascorbic acid) bilaterally into 15–18 sites within the prefrontal cortex or nine sites within the caudate nucleus using the identical protocol to that described in Roberts *et al*. (Roberts *et al*., 1994) for the PFC and Collins *et al*. (Collins *et al*., 2000) for the caudate nucleus. Sham-operated control monkeys received infusions of the 0.01% ascorbic acid vehicle into either the caudate nucleus (n = 4) or PFC (n = 3). Infusions were made using a 30 gauge cannula attached to a 10 µl Hamilton syringe at a rate of 0.4 µl/20 s.

6-OHDA Lesion of the Frontal Cortex

In order to protect the noradrenergic and serotoninergic innervation of the frontal cortex from the neurotoxic effects of 6-OHDA, monkeys that were to receive a frontal lesion were given an injection of the noradrenaline (NA) uptake blocker talsupram (Lundbeck, Copenhagen, Denmark; 20 mg/kg s.c.) and the 5-hydroxytryptamine (5-HT) uptake blocker citalopram (Lundbeck; 5 mg/kg s.c.) 30 min prior to the injection of 6-OHDA. The stereotaxic co-ordinates used for the frontal lesion were (1) AP + 16.5, LM (i) ± 1.5, (ii) ± 3.0 and (iii) ± 5.0; and (2) AP + 18.5, LM (i) ± 1.0, (ii) ± 2.5 and (iii) ± 4.0 (Stephan *et al*., 1980). Between two and three injections (2 µl/injection) were made at each of the sites, (a) 0.5 mm above the base of the skull, (b) 0.5 mm below the surface of the brain and where there was significant depth, a third (c) equidistant between (a) and (b).

6-OHDA Lesion of the Caudate Nucleus

To protect the serotoninergic innervation of the caudate nucleus from the neurotoxic effects of 6-OHDA, monkeys that were to receive a dopaminergic lesion of the caudate nucleus were given an injection of citalopram (5 mg/kg s.c.). The stereotaxic coordinates used and the volume of 6-OHDA injected for the caudate nucleus lesion were (1) AP + 12.0, (i) LM ± 3.5, DV + 12.5 (2 µl) and (ii) LM ± 2.0, DV + 11.5 (2 µl); (2) AP + 10.5, (i) LM ± 3.0, DV + 13 (2.5 µl) and (ii) LM ± 2.0, DV + 11.8 (2.8 µl); (3) AP + 9.0, (i) LM ± 3.5, DV + 13.5 (2 µl) and (ii) LM ± 2.5, DV + 11.5 (2 µl); (4) AP + 7.5, (i) LM ± 4.0, DV + 13.5 (1.5 µl) and (ii) LM ± 2.5, DV + 12.5 (1.5 µl); and (5) AP + 6.0, LM ± 4.0, DV + 13.5 (1 µl).

Post-operative Testing

Approximately 10 days post-surgery all subjects were re-tested on a training task in which a red square was presented on either side of the touch-sensitive screen, to ensure that they were still motivated to participate in the task. They were then presented with a series of two-choice visual discriminations with stimuli being presented equally to the left or right side of the screen. Progression from one discrimination to the next was dependent on the monkey reaching criterion of 90% correct in a session of 60 trials.

The stages of the test were as follows:

1. **Retention of the abstract pattern discrimination** learned immediately prior to surgery.
2. **A simple discrimination** in which one of two exemplars from a novel perceptual dimension, either blue filled shapes or white lines, was associated with reward (Fig. 1*b*).
3. **A simple discrimination reversal** whereby the reward contingencies of the previous simple discrimination were reversed such that the previously rewarded exemplar became unrewarded and the previously unrewarded exemplar became rewarded (Fig. 1*c*).
4. **A compound discrimination** in which exemplars from the second novel dimension were introduced such that the pair of stimuli were composed of white lines superimposed over blue filled shapes. The exemplar that had previously been rewarded remained rewarded while the exemplars from the newly introduced dimension were not associated with reward and were therefore irrelevant to the discrimination. On any one trial a 'line' exemplar could be paired with one or other of the 'shape exemplars (Fig. 1*d*).
5. **A series of compound discriminations involving intra-dimensional shifts** (IDS1–IDS5) each employing novel exemplars from the two perceptual dimensions. In each of the discriminations, the same dimension that had been relevant in all previous stages remained relevant and one of the exemplars from that dimension was associated with reward (Fig. 1*e*).
6. **A distractor probe test** in which exemplars from the irrelevant dimension in the preceding IDS (IDS5) were replaced with novel exemplars, while the exemplars from the relevant dimension and hence the specific stimulus–reward association remained unaltered (Fig. 1*f*).
7. Re-attainment of criterion on the final IDS (IDS5) for two consecutive sessions.
8. **A compound discrimination involving an extra-dimensional shift** (EDS) in which novel compound stimuli were presented but for the first time, an exemplar from the previously irrelevant perceptual dimension was associated with reward and exemplars from the previously relevant dimension became irrelevant to the discrimination (Fig. 1*g*).

Except for the final IDS (IDS5) and the subsequent EDS, all monkeys received the same pair of stimuli at any one stage of the discrimination test, with different pairs being presented at the different stages. However, for the final IDS and the subsequent EDS the compound stimuli were counterbalanced so that approximately half the monkeys from each group received one pair of stimuli at IDS5 and the other pair at the EDS while the other half received the opposite. This counterbalancing prevented any differences between performance on IDS5 and the subsequent EDS being an artefact due to differences in the discriminability of the actual compound stimuli presented.

Behavioural Measures

The main measure of a monkey's ability to learn visual discriminations was the total number of errors made before achieving criterion (excluding criterion day of 90% correct) for each discrimination. For the simple reversal, errors were divided into perseverative and non-perseverative. Perseverative errors were defined as those errors made until the monkey's performance was no longer significantly below chance for two consecutive, non-overlapping 20 trial blocks. All subsequent errors including those made during the two consecutive, 20 trial blocks of chance performance were scored as non-perseverative.

Additional measures were recorded for each trial including (i) the latency (to the nearest 0.01 s) to respond to the stimuli presented on the VDU (response latency); (ii) the latency to collect the reward from the spout (lick latency); (iii) the number of licks made during the tone; (iv) the side of the screen on which a response was made, either left or

right; and (v) the specific compound stimulus (shape and line combination) that was responded to.

In Vivo Assessment of the Dopaminergic Lesion of the Caudate Nucleus

Extracellular levels of DA were measured in the caudate nucleus of anaesthetized control (n = 6) and 6-OHDA caudate-lesioned (n = 8) monkeys using *in vivo* microdialysis. Concentric design dialysis probes were constructed as described previously (Dalley *et al*., 1998) except that the shaft of the outer tubing was extended in length to 40 mm and the active length of dialysing surface was 1.5 mm. Under Saffan anaesthesia (Alphaxalone, 0.9% w/v, Alphadolone acetate, 0.3% w/v; Pitman-Moore; 0.4 ml i.m., every 45–60 min) dialysis probes were implanted vertically in the dorsolateral caudate nucleus so that the tip of the dialysis membrane was situated at the following coordinate (mm): AP +11.25, LM –3.5, DV 11.05, according to the atlas of Stephan *et al*. (Stephan *et al*., 1980). A microsyringe pump (Harvard, Edenbridge, UK) set at 1 µl/min was used to perfuse the probes with artificial cerebrospinal fluid (pH 7.4) containing (mM): NaCl (147), KCl (3.0), $CaCl_2$ (1.3), $MgCl_2$ (1.0), $NaH_2PO_4.2H_2O$ (0.2), Na_2HPO_4 (1.3). Three hours after probe implantation, three 30 min baseline samples were collected into 2 µl aliquots of 0.2 M perchloric acid. At the start of the fourth sample a local depolarizing challenge of 75 mM potassium was given over 5 min. The osmolarity of the high potassium perfusate was kept constant by lowering the concentration of sodium ions by 75 mM to 72 mM. A further four, 30 min samples were collected before D-amphetamine sulphate (Sigma) was administered subcutaneously (1 mg/kg, free base). Sampling continued until a total of 13 samples had been collected. Throughout the experiment core body temperature was monitored by a rectal probe and maintained between 36 and 37°C.

Dialysate samples were analysed for their DA content on the same day as collection using reversed-phase HPLC and electrochemical detection. DA was separated at room temperature (20–22C) on a C18 analytical column (100 × 4.6 mm Hypersil ODS3; HPLC Technology, Welwyn Garden City, UK) using a mobile phase consisting of $NaH_2PO_4.H_2O$ (10.35 g/l), 1-octanesulphonic acid (320 mg/l), EDTA (20 mg/l), triethylamine (100 µl/l) and acetonitrile (10%). The mobile phase was adjusted to pH 3.0 with orthophosphoric acid and vacuum degassed across a 0.2 µm filter prior to being delivered at 1 ml/min (ESA 580 pump). DA was detected by oxidation with working potentials of –150 mV (E_1) and 180 mV (E_2) and a gain of 20 nA. (Coulochem II, 5041 analytical cell, ESA). The HPLC system was routinely calibrated with DA-spiked standards to determine the linearity and reproducibility of the DA signal (detection limit 5 fmol/20 µl). The data were integrated and processed using computer software (Gyncosoft, version 5.42).

Post-mortem Lesion Assessment

The extent and specificity of the 6-OHDA lesion of the caudate nucleus on monoamine function in cortical and subcortical regions has been extensively characterized in a previous study (Collins *et al*., 2000). In this earlier study DA levels were shown to be significantly depleted in antero-ventromedial and antero-dorsolateral regions of the head of the caudate nucleus but remained unaffected in all other striatal regions including the caudal sectors of the caudate nucleus, the putamen, the nucleus accumbens and cortical regions within the frontal lobes. Over time, however, monkeys that had received lesions of the caudate nucleus showed a substantial recovery of DA levels within the striatum. Given that the monkeys in the present study remained alive up to 21 months after the behavioural testing reported here was completed, post-mortem tissue analysis would not accurately reflect the extent of DA depletion at the time of testing. However, DA function during testing could be assessed using *in vivo* microdialysis, which was considered to be the more informative measure of striatal DA neurotransmission.

DA depletion from the PFC apparently does not show such marked recovery over time as from the striatum (Roberts *et al*., 1994). Thus due to the difficulty of measuring extracellular DA effectively *in vivo* from the PFC, post-mortem tissue analysis is the only effective way of assessing prefrontal DA levels. The extent and specificity of the PFC lesion was assessed 9–24 months after the administration of 6-OHDA in both cortical [defined according to the cytoarchitectonic map of Brodmann (Brodmann 1909) and our own cytoarchitectonic observations] and subcortical regions, as previously described (Roberts *et al*., 1994). Tissue levels of NA, DA and serotonin (5-HT) were determined using HPLC and electrochemical detection. Tissue aliquots (10–35 mg) were homogenized in 200 µl 0.2 M perchloric acid for 1 min and centrifuged at 6000 revolutions per minute for 15 min at 4°C. The supernatant (20 µl) was injected via a peltier-cooled autosampler (Gilson 233 XL) directly onto the HPLC system, which comprised a PM-80 pump set at 1.2 ml/min (BAS Technicol, Congleton, UK), a C18 ODS5 analytical column (Hypersil 4.6 × 150 mm; HPLC Technology) and a BAS LC-4B cell fitted with a 3 mm glassy carbon electrode held at a potential of 750 mV relative to a Ag/AgCl reference electrode. The mobile phase contained citric acid (31.9 g/l), sodium acetate (2 g/l), 1-octanesulphonic acid (460 mg/l), EDTA (30 mg/l), 15% HPLC grade methanol adjusted to pH 3.60 with saturated potassium hydroxide. Under these conditions the retention time of the end marker 5-HT was ~12 min.

Statistics

The behavioural results were subjected to ANOVA using the Genstat 5 statistical package (Rothamstead, UK). Where data did not conform to the assumptions of normality and homogeneity of variance appropriate transformations were employed. *Post hoc* comparisons were made using both simple main effects and the Newman–Keuls test. Tissue data were analysed using a Student's *t*-test.

Results

Extracellular Levels of DA in the Caudate Nucleus of Controls and Caudate-lesioned Monkeys Using in Vivo Microdialysis

Due to the marked, long-term recovery of tissue levels of DA in the caudate nucleus (Collins *et al*., 2000), extracellular DA levels were measured using *in vivo* microdialysis at a time point comparable to when the behavioural assessments were made. Apart from the data from one control animal that was excluded due to a technical problem, data was collected and analysed from all other controls and 6-OHDA caudate-lesioned monkeys. Baseline levels of DA across the first three samples were significantly lower in the 6-OHDA caudate-lesioned group than in controls (see insert of Fig. 2). ANOVA of the first three baseline samples (1–3) revealed a main effect of Group [$F(1,12) = 4.93$, $P = 0.046$]. Subsequent administration of a 5 min pulse of potassium (75 mM) induced a comparable rise in extracellular DA in both lesioned and control groups. ANOVA of DA levels before (mean of samples 1–3) and after (sample 4) the potassium pulse revealed a main effect of Sample [$F(1,12) = 14.53$, $P = 0.002$] but no main effect of Group, nor a Group × Sample interaction. In contrast, while amphetamine induced a rise in extracellular DA in both groups, this was significantly reduced in the 6-OHDA lesioned group. ANOVA of the mean baseline levels of DA prior to amphetamine (samples 5–7) and those immediately after amphetamine administration revealed a main effect of Group [$F(1,12) = 170.43$, $P = 0.001$] and Sample [$F(1,12) = 51.09$, $P < 0.001$] as well as a Group × Sample interaction [$F(1,12) = 16.62$, $P = 0.002$]. *Post hoc* tests showed that the increase in DA levels in response to amphetamine in the control group were significantly higher than mean baseline DA levels (samples 5–7) as well as significantly higher than DA levels following amphetamine in the 6-OHDA caudate-lesioned group (all $P < 0.01$). ANOVA of all samples following amphetamine administration showed a main effect of Group [$F(1,12) = 13.54$, $P = 0.003$] and Sample [$F(5,59) = 2.53$, $P = 0.039$].

Neurochemical Analysis of Post-mortem Brain Tissue of Controls and 6-OHDA Frontal-lesioned monkeys

6-OHDA injections into the PFC produced substantial depletions of DA and NA in several regions within the frontal lobes

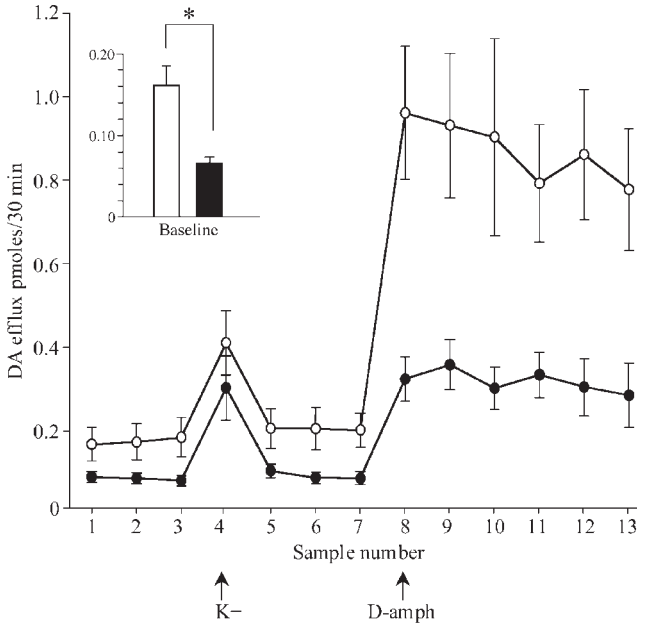

Figure 2. Mean extracellular DA content (± SEM) in the dorsolateral head of the caudate nucleus in control (○; $n = 6$) and 6-OHDA caudate (●; $n = 8$) lesioned monkeys. Values given are the levels of DA for each successive 30 min dialysis sample, expressed in picomoles. The arrows indicate the local administration of potassium (K^+, 75 mM for 5 min) and the systemic administration of D-amphetamine (1 mg/kg s.c.). The inset graph shows the mean levels of DA in the sham-operated and 6-OHDA caudate-lesioned animals averaged over the first three basal samples. *Significant difference between control and 6-OHDA caudate-lesioned monkeys, $P < 0.05$.

(Table 1). Eighteen months post-surgery the greatest reductions in DA were seen in lateral PFC (83.3%; $P < 0.05$), dorsal granular and premotor cortices (72.2%; $P < 0.05$), primary motor cortex (48.6%; $P < 0.05$) and anterior cingulate cortex (59.1%; $P < 0.05$). There was also a trend for a reduction in DA in the orbitofrontal cortex (52.1%) although this just failed to attain significance ($P = 0.062$).

Pre-treatment with talsupram did not apparently protect the noradrenergic projections to the frontal cortex from the neurotoxic effects of 6-OHDA. Large NA depletions were seen in the lateral PFC (89.5%; $P < 0.05$), dorsal granular and premotor cortices (78.8%; $P < 0.05$) and anterior cingulate cortex (60.1%; $P < 0.05$). There were also non-significant trends for depletion in the medial PFC (72.5%; $P = 0.053$), orbitofrontal cortex (75.9%; $P = 0.094$) and primary motor cortex (78.8%; $P = 0.054$).

Pre-treatment with citalopram did successfully protect the serotoninergic system from the effects of 6-OHDA, tissue levels of 5-HT being comparable to control values in all regions.

Behavioural Results

Pre-operative Performance

Acquisition and Reversal of an Abstract Pattern Discrimination. While all monkeys made fewer errors on the abstract pattern discrimination than on the subsequent reversal in which the reward contingencies were reversed, there was no difference between the groups (see Table 2). ANOVA revealed a significant main effect of Reversal [$F(1,16) = 77.82$, $P < 0.001$] but no main effect of Group ($F < 1$) or Group by Reversal interaction ($F < 1$).

Table 1
Tissue levels of biogenic amines throughout the cerebral cortex and striatum of 6-OHDA frontal-lesioned marmosets

	Dopamine		Noradrenaline		Serotonin	
	Control level (ng/mg)	% depletion (SEM)	Control level (ng/mg)	% depletion (SEM)	Control level (ng/mg)	% depletion (SEM)
LAT	0.062	83.3 (5.8)*	0.153	89.5 (1.1)*	0.221	25.6 (6.4)
ORB	0.045	52.1 (15.1)	0.129	75.9 (6.9)	0.239	35.9 (7.8)
MED	0.049	57.4 (13.1)	0.149	72.5 (4.3)	0.303	24.8 (6.5)
DORSAL	0.074	72.2 (7.5)*	0.192	78.8 (2.6)*	0.159	12.4 (6.6)
MOTOR	0.062	48.6 (11.6)*	0.147	62.0 (4.1)	0.147	20.4 (6.5)
C1	0.109	59.1 (12.5)*	0.253	60.1 (9.9)*	0.218	24.1 (11.0)
C2	0.051	34.2 (12.7)	0.252	52.9 (7.2)	0.288	35.2 (7.0)
C3	0.024	28.2 (12.9)	0.199	49.6 (8.1)	0.256	16.5 (4.9)
F2	0.068	27.6 (13.7)	0.259	59.1 (5.9)	0.271	22.7 (5.7)
F3	0.034	21.9 (11.4)	0.177	48.3 (8.0)	0.205	9.2 (5.4)
dlcaud	7.879	0.1 (0.1)	nd	nd	0.263	9.4 (6.5)
vmcaud	14.44	24.2 (7.1)	nd	nd	0.366	6.6 (4.4)
NA	5.156	6.5 (3.3)	0.471	39.0 (15.4)	1.027	30.7 (11.4)
caud2	13.95	2.2 (2.2)	nd	nd	0.377	7.5 (5.1)
caud3	5.931	0.0 (0.0)	nd	nd	0.374	38.1 (12.8)
put1	8.675	6.7 (4.5)	nd	nd	0.306	6.4 (3.4)
put2	7.324	1.5 (1.5)	nd	nd	0.286	0.0 (0.0)

Mean levels of dopamine, noradrenaline and serotonin (expressed as ng/mg wet weight tissue) in cortex and basal ganglia of the control group and the percentage depletion (± SEM) in marmosets with 6-OHDA lesions of the frontal cortex. LAT, lateral granular PFC; ORB, orbitofrontal cortex; MED, medial PFC; DORSAL, dorsal granular and premotor cortex; MOTOR, primary motor cortex; C1, anterior cingulate cortex; C2, mid-cingulate cortex; C3, posterior cingulate cortex; F2, posterior frontal and anterior parietal cortex; F3, posterior parietal cortex; dlcaud, antero-dorsolateral head of the caudate; vmcaud, antero-ventromedial head of the caudate; NA, nucleus accumbens; caud2, posterior head of the caudate; caud3, body of the caudate; put1, anterior putamen; put2, mid-putamen. nd, not detected.

*Mean scores of lesioned animals differ significantly from those of the control group ($P < 0.05$).

Table 2
Mean number of errors $\sqrt{(x + 1)}$ (± SEM) to reach criterion on unidimensional visual discriminations and reversals

	Control	6-OHDA caudate	6-OHDA frontal
Pre-operative performance			
Abstract discrimination	13.83 ± 2.6	10.98 ± 1.14	10.08 ± 1.42
Abstract reversal	26.22 ± 4.9	22.73 ± 1.78	22.33 ± 2.68
Post-operative performance			
Retention test	1.31 ± 0.3	4.81 ± 0.89*	5.85 ± 1.01**
Simple discrimination	7.74 ± 0.58	10.77 ± 2.75	9.46 ± 1.24
Simple reversal	11.96 ± 1.58	17.54 ± 2.3	14.30 ± 1.47

*$P < 0.05$, **$P < 0.01$.

Post-operative Performance

Retention Test. Control monkeys rapidly re-attained criterion on the abstract discrimination that they had learned immediately prior to surgery. However, both the 6-OHDA caudate and 6-OHDA frontal-lesioned monkeys made more errors before re-acquiring this discrimination (see Table 2). ANOVA of the square-root transformed errors to re-attain criterion revealed that there was a main effect of Group [$F(2,16) = 7.60$, $P = 0.005$]. Newman–Keuls *post hoc* analysis revealed that both 6-OHDA caudate ($P < 0.05$) and 6-OHDA frontal ($P < 0.01$) lesioned monkeys made significantly more errors than controls.

Acquisition and Reversal of a Simple Visual Discrimination. All monkeys, irrespective of group, made more errors on the reversal than on the original discrimination. There were, however, no differences in the performance of the groups in acquisition or reversal (see Table 2). ANOVA of the square-root transformed

errors to criterion on the discrimination and reversal showed that there was a main effect of Discrimination [$F(1,16) = 66.08$, $P < 0.001$] but no effect of Group [$F(2,16) = 1.07$, $P = 0.367$] or a Group by Discrimination interaction ($F < 1$).

There was also no difference in the nature of the errors made between the groups when learning the reversal. ANOVA of the number of perseverative and non-perseverative errors made before reaching criterion showed that there was a main effect of Error type [$F(1,13) = 12.73$, $P = 0.003$] such that all monkeys made more non-perseverative errors compared with perseverative errors. However, there was no Group [$F(2,13) = 1.29$, $P = 0.308$] or Group × Error type ($F < 1$) interaction.

6-OHDA lesions of the frontal cortex or caudate nucleus did not affect response latencies or the propensity to develop a side bias. ANOVA showed no effect of lesion on response latency either on the retention test [$F(2,19) = 1.25$, $P = 0.309$] or on discrimination and reversal learning pre- and post-surgery [Group: $F(2,19) = 1.04$, $P = 0.373$; Group × Surgery: $F < 1$] and no differences in side bias [retention test, $F < 1$; discrimination and reversal learning pre- and post-surgery, Group: $F(2,19) = 1.96$, $P = 0.168$, Group × Surgery: $F(2,19) = 1.47$, $P = 0.256$].

Acquisition of a Series of Compound Discriminations and the Development of an Attentional Set. Across the subsequent series of five compound discriminations it was apparent that those monkeys discriminating between exemplars from the 'shapes' dimension made fewer errors overall than those monkeys discriminating between exemplars from the 'lines' dimension (Fig. 3*a*). ANOVA of the square root transformed errors to criterion across all five discriminations (IDS1–IDS5) revealed that there was a main effect of Dimension ('shapes' versus 'lines') [$F(1,16) = 12.86$, $P < 0.002$]. There was also a main effect of Discrimination [$F(4,64) = 10.59$, $P < 0.001$], whereby the performance of monkeys improved across discriminations. Newman–Keuls *post hoc* analysis showed that fewer errors were made on IDS2 through to IDS5 (Ps < 0.05) compared to IDS1, thus demonstrating the development of an attentional set to the reinforced dimension.

While this pattern of improved performance across discriminations was seen in the controls and 6-OHDA caudate-lesioned monkeys, the performance of 6-OHDA frontal-lesioned monkeys across discriminations was inconsistent (Fig. 3*b*). ANOVA revealed a Group by Discrimination interaction [$F(8,64) = 2.09$, $P = 0.049$], which subsequent analysis of the simple main effects showed was due to highly significant main effects of Group on IDS3 [$F(8,64) = 3.996$, $P = 0.0007$] and IDS5 [$F(8,64) = 5.96$, $P < 0.0001$]. Newman–Keuls *post hoc* analysis revealed that the 6-OHDA frontal-lesioned monkeys made significantly more errors relative to controls ($P < 0.05$) on IDS3 and relative to both controls ($P < 0.01$) and 6-OHDA caudate-lesioned monkeys ($P < 0.05$) on IDS5. Detailed analysis of the individual error scores of monkeys in control and 6-OHDA caudate-lesioned groups on IDS3 and IDS5 compared to IDS2 and IDS4 did not however reveal any obvious differences in difficulty between these different discriminations.

Thus, overall, the controls and 6-OHDA caudate-lesioned monkeys showed consistently better performance over IDS2–5, compared to IDS1, quite likely as a result of the development of dimensional control over their performance, i.e. acquisition of an attentional set. In contrast, the variable performance of 6-OHDA frontal-lesioned monkeys across these discriminations is consistent with a failure to develop an attentional set and thus an impairment in dimensional control over behaviour.

Distractor Probe Test. Having reached criterion on the final compound discrimination (IDS5), in the following session the exemplars from the irrelevant perceptual dimension were replaced with novel exemplars, while the exemplars from the relevant dimension and the reward contingencies remained the same (see Fig. 1*f*). In this first distractor session the introduction

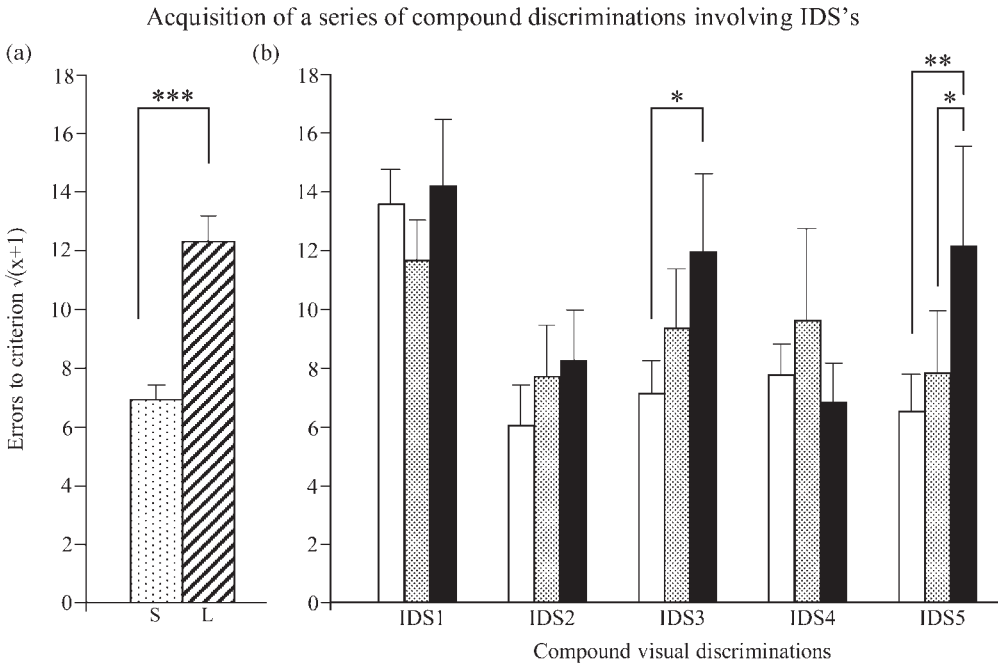

Figure 3. (*a*) Mean number of errors (± SEM) made by monkeys responding to exemplars from the shape (stippled box; $n = 12$) or line (hatched box; $n = 10$) dimensions across the series of five compound visual discriminations. (*b*) Mean number of errors (± SEM) made by control (open box; $n = 7$), 6-OHDA caudate (stippled box; $n = 8$) and 6-OHDA frontal (filled box; $n = 7$) lesioned monkeys on each of the five compound visual discriminations (IDS1–IDS5). The groups differ significantly from one another: $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.005$.

of novel exemplars resulted in a small increase in the number of errors made by control monkeys and hence a small decrement in their overall performance. While 6-OHDA frontal-lesioned monkeys showed an equivalent decrement in performance to that of controls, the performance of the 6-OHDA caudate-lesioned monkeys was far less disrupted (Fig. 4*a*). ANOVA of the square-root transformed errors made on the criterion day of IDS5 and the first session of the distractor test revealed main effects of Discrimination [$F(1,16) = 17.68$, $P < 0.001$] and of Group [$F(2,16) = 4.37$, $P = 0.031$] as well as a Discrimination × Group interaction [$F(2,16) = 4.56$, $P = 0.027$]. Analysis of the simple main effects showed that there was a main effect of Group on the first session of the distractor test [$F(2,16) = 12.69$, $P < 0.0005$] but not on the preceding criterion day ($F < 1$). *Post hoc* Newman–Keuls analysis showed that the 6-OHDA caudate-lesioned monkeys made significantly fewer errors than both the 6-OHDA frontal-lesioned ($P < 0.01$) and control-lesioned ($P < 0.01$) monkeys.

Regardless of surgery, the performance of monkeys discriminating between two 'lines' exemplars was more disrupted by the introduction of novel, irrelevant 'shapes' than that of the monkeys experiencing the converse, i.e. discriminating between two 'shape' exemplars when two novel, irrelevant 'line' exemplars were introduced. ANOVA revealed a significant interaction between Discrimination and Dimension [$F(1,16) = 8.42$, $P < 0.01$], which was shown by *post hoc* analysis of the simple main effects to be due to a significant effect of dimension on the first session of the probe [$F(2,16) = 20.22$, $P < 0.0001$] but not on the preceding criterion session ($F < 1$).

After the first session on the distractor test monkeys were then given repeated sessions on this test until they had re-attained criterion performance. While there was a trend for 6-OHDA caudate-lesioned monkeys to re-attain criterion more rapidly than controls, in keeping with their better performance on the first day of the distractor test (see Fig. 4*b*), this did not reach statistical significance. However, in contrast to both controls and 6-OHDA caudate-lesioned monkeys, monkeys with 6-OHDA frontal lesions made many more errors before re-attaining criterion. ANOVA of the square-root transformed errors to re-attain criterion (not including errors on day 1) revealed a main effect of Group [$F(2,16) = 7.46$, $P = 0.005$]. Newman–Keuls *post hoc* analysis showed that the 6-OHDA frontal lesion group made significantly many more errors in comparison to both control ($P < 0.05$) and 6-OHDA caudate-lesioned ($P < 0.01$) monkeys. Thus, the introduction of distracting stimuli disrupted the discrimination performance of 6-OHDA frontal-lesioned monkeys for a longer period of testing compared to controls whereas the discrimination performance of 6-OHDA caudate-lesioned monkeys was unaffected.

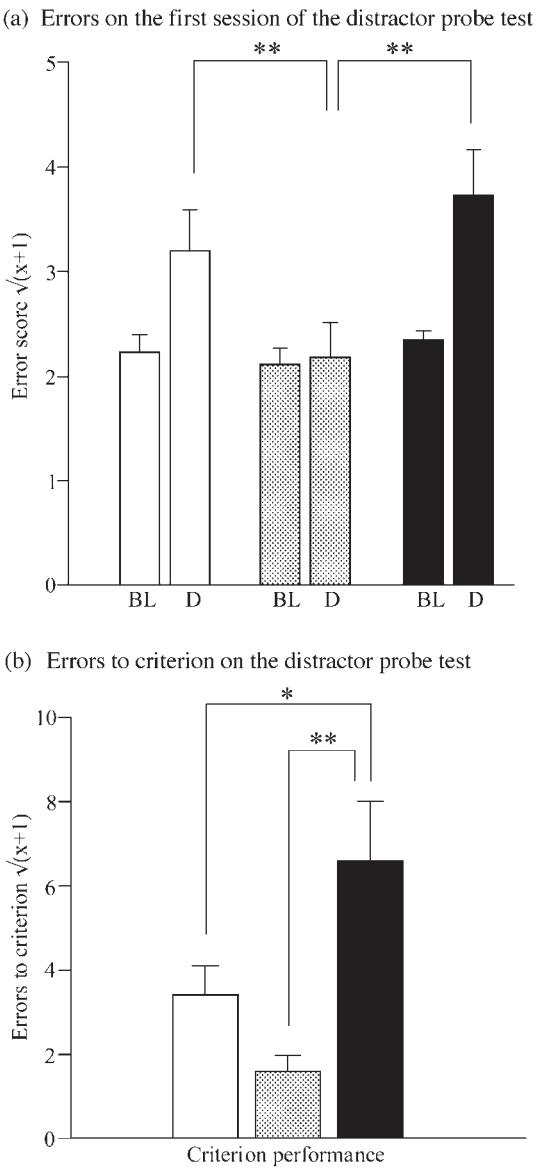

Figure 4. Mean number of errors (± SEM) made by control operated (open box; $n = 7$), 6-OHDA caudate-lesioned (stippled box; $n = 8$) and 6-OHDA frontal-lesioned (filled box; $n = 7$) marmosets on (*a*) the criterion session of IDS5 (BL) and the first session of the distractor probe test (D) and (*b*) before attaining criterion on the distractor probe test. The groups differ significantly from one another: $*P < 0.05$, $**P < 0.01$.

Shifting of Attentional Set from One Perceptual Dimension to Another. Shifting attentional set from one dimension to another differed depending on the particular dimensions to which, and from which, monkeys were shifted (compare Fig. 5*a* and *c*). Specifically, when learning a new discrimination that required a shift of attentional set from 'shapes' to 'lines' all control monkeys made more errors relative to their performance on the preceding IDS. This pattern of performance suggests that control monkeys had developed an attentional set for the 'shapes' dimension across the preceding series of IDSs and thus at the EDS stage of the task (requiring a shift to 'lines') were continuing to maintain an attentional set toward this previously relevant dimension. A similar pattern of performance was seen in 6-OHDA caudate and 6-OHDA frontal-lesioned monkeys, both lesioned groups making more errors before reaching criterion on the EDS compared to the preceding IDS (see Fig. 5*b*).

In contrast, when required to shift attentional set in the opposite direction, i.e. from 'lines' to 'shapes', there was no difference between performance of control monkeys on the IDS and subsequent EDS (see Fig. 5*d*). Equivalent performance at these two stages suggests that these monkeys had not learned to attend selectively to the 'lines' dimension prior to the EDS. While 6-OHDA caudate-lesioned monkeys also displayed equivalent performance on the two types of shift, this pattern was not seen in the 6-OHDA frontal-lesioned monkeys. Instead the 6-OHDA frontal-lesioned monkeys made many more errors on the preceding IDS in comparison to controls and also notably, in comparison to their own subsequent EDS performance (see Fig. 5*d*).

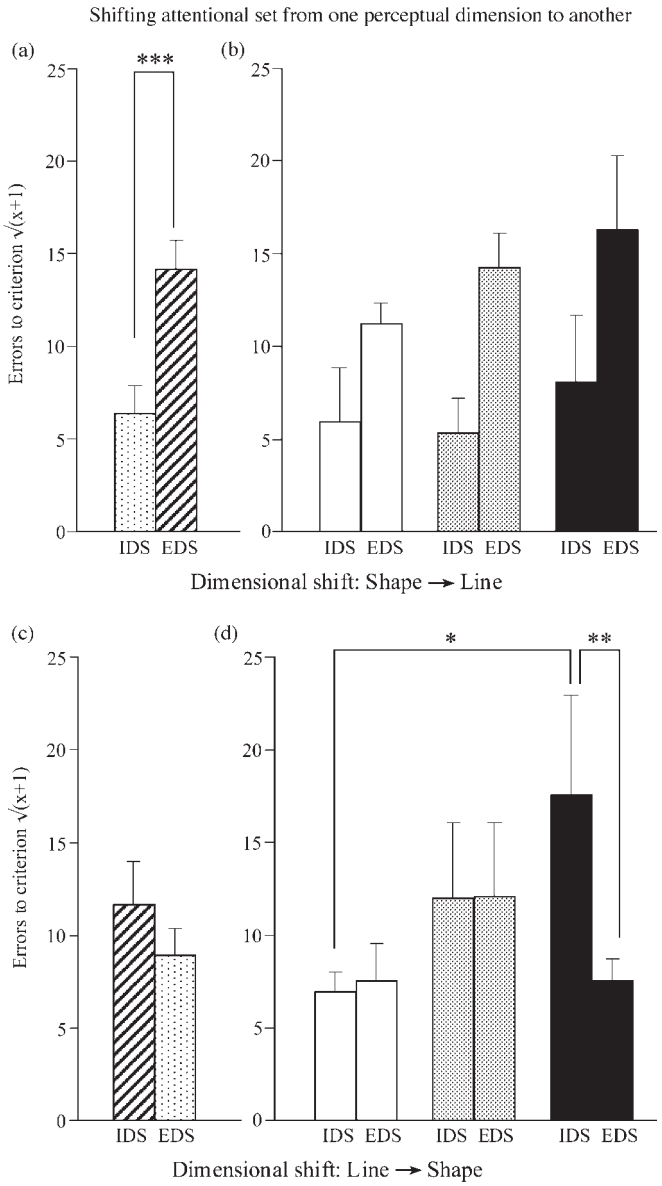

Figure 5. Mean number of errors (± SEM) made on the final IDS (IDS5) and subsequent EDS. (*a* and *c*) Overall performance for monkeys shifting an attentional set from 'shapes' (stippled box) to 'lines' (hatched box; $n = 12$) and 'lines' to 'shapes' ($n = 10$), respectively. (*b*) Performance of control (open box; $n = 3$), 6-OHDA caudate (stippled box; $n = 5$) and 6-OHDA frontal (filled box; $n = 4$) lesioned groups shifting an attentional set from 'shapes' to 'lines'. (*d*) Performance of control ($n = 4$), 6-OHDA caudate ($n = 3$) and 6-OHDA frontal ($n = 3$) lesioned groups shifting an attentional set from 'lines' to 'shapes'. The groups differ significantly from one another: $^*P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.0001$.

Statistical analysis supported these qualitative differences. Thus, ANOVA of the square-root transformed errors to criterion on the final IDS and subsequent EDS showed a significant main effect of Shift (IDS versus EDS) [$F(1,16) = 8.80$, $P = 0.009$], and a significant Shift × Dimension [$F(1,16) = 26.16$, $P < 0.001$] interaction. Subsequent analysis of the simple main effects revealed a significant effect of shift for those monkeys shifting attentional set from 'shapes' to 'lines' [$F(1,16) = 32.29$, $P = 0.0001$] such that all monkeys made more errors on the EDS compared to the preceding IDS. In contrast, there was no such difference for those monkeys shifting attentional set from 'lines' to 'shapes', if anything, there being a trend in the opposite direction [$F(1,16) = 3.33$, $P = 0.087$] (see Fig. 5*c*). Figure 5*d* shows that this trend was due to the marked impairment of the 6-OHDA frontal-lesioned group on the IDS in comparison to their intact performance on the EDS; i.e. EDS performance was actually superior compared with IDS performance. The statistical significance of this effect in the 6-OHDA frontal-lesioned group was confirmed by ANOVA, which revealed a significant Shift × Group × Dimension interaction [$F(2,16) = 3.64$, $P = 0.05$]. Subsequent analysis of the simple interaction effect showed a significant Shift × Group interaction for those monkeys shifting from 'lines' to 'shapes' [$F(2,16) = 5.50$, $P = 0.0152$], but not for those monkeys shifting in the opposite direction from 'shapes' to 'lines' ($F < 1$). Newman–Keuls *post hoc* analysis of the Shift × Group interaction revealed that the 6-OHDA frontal-lesioned monkeys made significantly more errors on the IDS relative to control monkeys ($P < 0.05$), as well as relative to their own subsequent performance on the EDS ($P < 0.01$).

Examining responding across trials can identify significant response runs (5 consecutive responses, $P < 0.05$) to a specific exemplar indicating whether a monkey is selecting exemplars primarily from one particular dimension. ANOVA of the first session of the final IDS and subsequent EDS showed a significant Exemplar Type (relevant versus irrelevant dimension) × Shift × Dimension [$F(1,32) = 19.38$, $P < 0.001$] interaction. Simple interaction effects revealed an Exemplar Type ×Shift interaction for monkeys shifting from 'shapes' to 'lines' [$F(1,32) = 25.21$, $P < 0.0001$] but not 'lines' to 'shapes' [$F(1,32) = 1.74$, $P = 0.2$]. Newman–Keuls *post hoc* analysis showed that, irrespective of lesion, monkeys trained on 'shapes' not only made more responses towards exemplars from the 'shape' as opposed to the 'line' dimension on the final IDS ($P < 0.01$; shape: 26.7 ± 6.6, line 6.3 ± 2.1) but also on the subsequent EDS ($P < 0.01$; shape: 23.3 ± 5.1, line: 6.5 ± 1.9) supporting the hypothesis that their responding was under the control of the 'shape' dimension. In contrast, monkeys trained on 'lines' did not preferentially select exemplars from the 'line' dimension and thus their responding was not under dimensional control. If anything these monkeys tended to select exemplars from the 'shape' dimension regardless of which dimension was relevant (final IDS – shape: 15.7 ± 3.8, line: 10.6 ± 3.3; EDS – shape: 14.2 ± 3.7, line: 8.6 ± 2.7). Although there were no significant effects for lesion there was a trend for the 6-OHDA frontal-lesioned monkeys to display less responding to exemplars from the previously relevant, now irrelevant dimension, on the EDS (shams: 18.4 ± 6.3, caudates: 19.6 ± 6.7, frontals: 11.3 ± 4.5).

Discussion

Monkeys with 6-OHDA lesions of either the frontal cortex or caudate nucleus exhibited very different patterns of performance on the attentional set formation and set-shifting task. Frontal-lesioned monkeys showed marked deficits in acquiring a series of compound visual discriminations and a sustained decrement in performance on a distractor test. These deficits in acquiring and maintaining an attentional set towards a specific perceptual dimension contrasted with facilitated shifting of attentional set from one perceptual dimension to another. On the other hand, 6-OHDA caudate-lesioned monkeys, whose performance was relatively preserved across the entire set-shifting task, displayed a completely opposite effect to that of 6-OHDA frontal-lesioned monkeys on the distractor test, being less, rather than more distractible. These results support opposing functional effects of cortical and subcortical DA depletion and help to explain our previous behavioural findings. They also provide

a new perspective on the functions of frontal catecholamines, possibly consistent with novel theoretical proposals (Usher *et al*., 1999; Braver and Cohen, 2000; Durstewitz *et al*., 2000) that link these neurochemical systems to processes of 'executive attention' and to theories suggesting deficits in the mesocortical DA systems in schizophrenia (Weinberger *et al*., 1988; Lewis *et al*., 1992) and attention deficit hyperactivity disorder (ADHD) (Ernst *et al*., 1998).

Neurochemical Effects of 6-OHDA Lesions of the Frontal Cortex and Caudate Nucleus

Multiple injections of 6-OHDA into the PFC produced substantial depletions of NA and DA restricted to the frontal lobes, including the lateral granular, dorsal granular and premotor, primary motor and anterior cingulate cortices. There were no catecholamine depletions in other regions such as the parietal cortex or striatum and citalopram successfully protected the 5-HT innervation of the frontal cortex (Roberts *et al*., 1994). Percentage depletions of DA and NA in frontal lobe areas, measured 9–24 months post-surgery, were in the range of 48.6–83.3 and 60.1–89.5%, respectively. Reductions of DA and NA in orbitofrontal (52.1 and 72.5%, respectively) and medial PFC (52.9 and 75.9%, respectively) did not reach significance. However, at the time of behavioural testing (2 weeks through to 10 months post-surgery) these depletions may have been considerably greater as tissue DA and NA levels evaluated just 3 weeks post-surgery were shown to have been depleted by between 75% and 95% in lateral, medial and orbital PFC in comparison with controls (Roberts *et al*., 1994).

Multiple injections of 6-OHDA into the caudate nucleus caused a profound reduction in extracellular DA levels in the dorsolateral head of the caudate, as measured by *in vivo* microdialysis. Immediately after completion of the attentional set shifting task, ~10 months post-surgery, basal levels of DA were significantly lower than in controls and elevations of extracellular DA induced by the administration of systemic amphetamine were significantly attenuated. Thus, DA function in the dorsolateral caudate nucleus was significantly impaired throughout the period of behavioural testing. While the extent of DA depletion elsewhere in the caudate nucleus was not measured in the present study, the same lesioning protocol was used as previously (Collins *et al*., 2000) when a comparable reduction of evoked extracellular DA release in the dorsolateral head of the caudate nucleus 5–11 months post-surgery was associated with post-mortem depletions of DA throughout the head and body of caudate in the range of 81–99% 3 weeks post-surgery, with levels recovering to 32–62% of control within 18–24 months.

Frontal Cortical Catecholamines and Set Formation and Set Shifting

The impairments of 6-OHDA frontal-lesioned monkeys in compound visual discrimination learning were not due to general deficits in the ability to solve discriminations as they acquired earlier unidimensional discriminations (i.e. simple discrimination and reversal), normally after initial minor retention decrements. The absence of the normal consistent improvement in performance over the series of compound discriminations did not depend on which dimension was relevant, but there was a tendency for those 6-OHDA frontal-lesioned monkeys for which 'lines' was the relevant dimension to be most affected. This was particularly evident on the final discrimination requiring an IDS for 'line' stimuli in which 6-OHDA frontal-lesioned monkeys made significantly many more errors. This did not simply reflect a general overall difference between the discriminability of the particular 'shape' and 'line' exemplars used for the final IDS (IDS5), as two different pairs of compound stimuli were counterbalanced across the final IDS and the subsequent EDS (see Materials and Methods for details). Since performance, regardless of lesion, was poorer across compound discriminations in which 'lines' was the relevant dimension, the deficit in frontal catecholamine-depleted monkeys on the final IDS reflects special difficulty in solving 'line' discriminations.

The greater disruption caused in 6-OHDA frontal-lesioned monkeys when exemplars from the irrelevant dimension were replaced with novel exemplars in the distractor probe test indicates their responding to be less strongly controlled by the rewarded exemplar from the relevant dimension. This distractibility is also consistent with their pattern of EDS performance when required to shift attentional set from the previously relevant to the previously irrelevant dimension. Like controls and monkeys with 6-OHDA caudate lesions, they made more errors to reach criterion on the EDS compared with the preceding IDS when required to shift attentional set from 'shapes' to 'lines'. This pattern is consistent with the hypothesis that the responding of all monkeys had come under the control of the 'shapes' dimension, hence being disadvantaged at the EDS stage when exemplars from the 'lines' dimension became associated with reward. However, the performance of the frontal-lesioned monkeys was not equivalent to controls and caudate-lesioned monkeys when required to shift attentional set from 'lines' to 'shapes'. Their performance on the EDS was *superior* to their performance on the preceding IDS, unlike the control and 6-OHDA caudate-lesioned monkeys, which displayed *equivalent* performance across the two types of shift.

Any explanation of this altered performance pattern of 6-OHDA frontal-lesioned monkeys in terms of a generally enhanced ability to shift attentional sets, (Roberts *et al*., 1994) can be ruled out. First these monkeys only showed an enhanced ability to shift attentional set from 'lines' to 'shapes' and not 'shapes' to 'lines'. Secondly, any superior performance they showed on the EDS was due to their impaired performance on the preceding IDS, rather than truly enhanced performance on the EDS (see Fig. 5). The most plausible explanation is that 6-OHDA frontal-lesioned monkeys had an impairment in developing an attentional set. Acquiring attentional sets recruits 'top down' attentional mechanisms dependent upon prior knowledge, intentions and goals (Bacon and Egeth, 1994) and it is hypothesized that 6-OHDA lesions of the frontal lobes disrupt these mechanisms. However, can such a hypothesis explain (i) why the performance of monkeys trained on 'shapes' as the relevant dimension was less affected by 6-OHDA lesions of the frontal cortex as compared with those trained on 'lines'?; and (ii) why the 6-OHDA frontal-lesioned monkeys, despite being trained on 'lines', actually learned a discrimination requiring a shift of attentional set to 'shapes' more rapidly than one requiring maintenance of an attentional set to 'lines'?

'Top-down' Versus 'Bottom-up' Attentional Control

Closer examination of the individual performance of monkeys revealed that there was a tendency for animals to show a general bias towards responding to 'shape' exemplars (possibly as a consequence of their overall greater surface area) as compared to 'line' exemplars. Thus, while all control and 6-OHDA caudate-lesioned monkeys showed the expected increase in errors when required to shift attentional set from 'shapes' to 'lines' at the EDS stage of the task – confirming development of an attentional set for 'shapes' – only two of the four control monkeys and one of

the three 6-OHDA caudate-lesioned monkeys trained on 'lines' showed the expected increase in errors when required to shift from 'lines' to 'shapes', that would indicate a prior attentional set to 'lines'. The remaining monkeys not only failed to develop an attentional set for 'lines' but instead continued to respond to exemplars from the 'shape' dimension even though 'lines' was the relevant dimension. Similar difficulties in learning which 'line' exemplar is associated with reward have been reported in previous studies in marmosets (Roberts *et al*., 1988, 1994) as well as in humans (Lawrence *et al*., 1999). Such a tendency to be biased towards a particular perceptual dimension has been described as a form of stimulus-driven attentional capture (Bacon and Egeth, 1994) and probably depends more on bottom-up as opposed to top-down influences. Thus, while development of an attentional set to 'lines' depends almost entirely on top-down influences, development of an attentional set to 'shapes' is greatly enhanced by bottom-up effects. Consequently, the most plausible explanation of the effects of frontal catecholamine depletion on set formation and set shifting is that they disrupt top-down, but not bottom-up, attentional processes.

The results of the present study confirm and extend our previous findings described in Roberts *et al*. (Roberts *et al*., 1994), although they differ in one important respect. In the Roberts *et al*. study the effect of the 6-OHDA frontal lesion on performance of an EDS was not limited to one that involved a shift of attentional set from 'lines' to 'shapes'. However, consideration of the individual lesioned monkeys' performance from this earlier study reveals that those monkeys actually showing *superior* performance on the EDS compared to the IDS were primarily those monkeys required to shift from 'lines' to 'shapes' (5 out of 5) as compared with 'shapes' to 'lines' (1 out of 6) ($\chi^2 = 7.64$, $P < 0.01$).

Comparison of Excitotoxic and Catecholaminergic Lesions of the PFC on Attentional Function

The PFC has long been implicated in top-down attentional processing (Norman and Shallice, 1986; Corbetta *et al*., 1993; Knight *et al*., 1995; Desimone, 1996; Corbetta 1998) and of particular relevance to the present study are the rather different computational models of Cohen and Durstewitz (Cohen and Servan-Schreiber, 1993; Braver and Cohen, 2000; Durstewitz *et al*., 2000) in which DA plays a critical role in the gating of relevant and irrelevant information within PFC. The finding that a loss of frontal catecholamines in monkeys impairs the development of an attentional set provides empirical evidence in support of these models. However, this effect of frontal catecholamine depletion apparently contrasts with effects of excitotoxic PFC lesions which disrupt the ability to shift attentional sets (Dias *et al*., 1996a,b), but not the ability to develop them (Dias *et al*., 1997). One explanation for these differential effects is that distinct regions of the frontal cortex may be involved in developing and shifting attentional sets and the catecholamines may be more or less important in modulating these regions. In the present study catecholamines were significantly depleted not only in lateral granular PFC, the region that, if lesioned, impairs attentional set shifting (Dias *et al*., 1996b) but also the dorsal granular, medial PFC and premotor and supplementary motor regions, any of which may play a role in developing an attentional set. Alternatively, the distinct, but complementary effects of catecholaminergic and excitotoxic lesions of the frontal cortex may reflect the difference between functional effects of removing a structure, as occurs following excitotoxic lesions, as distinct from a loss of its neuromodulatory input [cf. the differential effects of excitotoxic or DA depleting lesions of the ventral striatum on locomotor activity (Parkinson *et al*., 2000, 2001)].

Conceivably, however, the differential effects may simply have been an artefact of the different apparatus used to test excitotoxic or catecholaminergic lesioned marmosets. Excitotoxic lesioned marmosets were tested by hand in a non-automated apparatus in which the monkey's response and the location of the food reward were spatially contiguous (Dias *et al*., 1996b), while catecholaminergic lesioned marmosets were tested in an automated apparatus in which the response and reward location were spatially separate, as shown by Roberts *et al*. (Roberts *et al*., 1994) and the present study. The relative ease with which monkeys in the hand-operated apparatus were able to acquire attentional sets in comparison to the greater difficulty experienced by monkeys in the computerized version may simply have rendered IDS performance insensitive to prefrontal lesions. This can eventually be addressed by specifically examining the effects of excitotoxic prefrontal lesions on the acquisition of attentional sets in the computerized apparatus.

The Contribution of Caudate Dopamine to Set Formation and Set Shifting

Monkeys with dopaminergic depletions within the caudate nucleus, unlike those with frontal catecholamine depletions, showed relatively spared performance on the attentional set shifting task. These animals could develop and subsequently shift attentional sets, consistent with previous findings of largely intact performance of monkeys with 6-OHDA caudate lesions when required to maintain and shift a pre-operatively acquired attentional set (Collins *et al*., 2000). In the current study the performance of 6-OHDA caudate-lesioned monkeys was only distinguishable from both controls and 6-OHDA frontal-lesioned monkeys on the first session of the probe test when their performance was significantly less disrupted than controls following the introduction of novel stimulus exemplars on the irrelevant dimension. This was completely opposite to the marked disruption of performance induced by 6-OHDA lesions of the frontal cortex under these same conditions. Thus, overall, 6-OHDA caudate-lesioned monkeys were less distractible than controls to changes in task irrelevant cues while 6-OHDA frontal-lesioned monkeys were more distracted. However, since the performance of 6-OHDA caudate-lesioned monkeys did not differ at all from controls on attentional set-shifting *per se*, any differences seen in their performance at the distractor stage is unlikely to have been due to changes at the level of dimensional selection. Instead, their responding, which appeared to be under greater control by the currently rewarded individual exemplars than that of the control groups, could be described as more 'stimulus bound' in nature.

A 6-OHDA lesion of DA terminals in the caudate nucleus does not lead to a complete loss of caudate dopaminergic activity (Collins *et al*., 2000). However, at the time of behavioural testing, extracellular DA levels in the present study were reduced to an extent similar to, if not greater than, that seen in the previous study in which widespread reductions in tissue dopamine throughout the head and body of the caudate nucleus resulted in impaired spatial delayed response performance and an impaired ability to re-engage a previously established attentional set. Thus, while a failure to observe differences in set formation and set shifting to novel stimulus dimensions following only partial 6-OHDA caudate lesions cannot rule out the hypothesis that these processes are dependent upon caudate DA, present findings suggest that cognitive processes other than set

formation and set shifting may well be more sensitive to changes in dopaminergic modulation within the caudate nucleus.

This analysis is consistent with results from a functional neuroimaging study in humans using essentially the same test as used in the present study (Rogers *et al*., 2000) in which shifting an attentional set activated the dorsolateral PFC and putamen, but not the caudate nucleus. Only reversal learning (which involved switching responding between two exemplars within the same dimension) differentially activated the caudate nucleus/ventral striatum, Thus, at present, there is no direct evidence to support a role for the caudate nucleus and its DA input in set formation and set shifting to novel dimensions; disruption of these functions in patients with Parkinson's (Downes *et al*., 1989) and Huntington's (Lawrence *et al*., 1999) diseases may be due to disruption of circuits outside the caudate nucleus.

The opposing effects of striatal and frontal 6-OHDA lesions on performance of the distractor test provides insight into the nature of the functional interactions between the PFC and striatum. Changes in the activity of the PFC and its DA input are well documented to alter the activity of the striatal DA system (Iversen *et al*., 1971; Pycock *et al*., 1980; Roberts *et al*., 1994; Wilkinson *et al*., 1998). Moreover, under certain circumstances, behavioural impairments induced by frontal ablations can be reversed by systemically administered DA receptor blockers (Ridley *et al*., 1993) supporting the hypothesis that the observed changes in behaviour are, in part, a consequence of an up-regulated subcortical DA system. However, the observation in this study that 6-OHDA lesions of the frontal cortex and striatum produce opposing effects on the same cognitive task, further emphasizes possible competition, as well as co-ordination, between prefrontal and striatal mechanisms for control over behaviour. Indeed, reductions in prefrontal control and resulting enhancements of subcortical control, mediated by excessive levels of catecholamines in the PFC as a consequence of stress, has been proposed to impair cognitive function (Arnsten, 1998).

Clinical Implications

Altered catecholamine function within the PFC and striatum is associated with a variety of neurodegenerative and neuropsychiatric disorders including Parkinson's disease (Agid *et al*., 1987), schizophrenia (Weinberger *et al*., 1988; Lewis *et al*., 1992) and ADHD (Ernst *et al*., 1998). In all of these disorders the disturbance in fronto-striatal circuitry is accompanied by alterations in attentional control (Lees and Smith, 1983; Canavan *et al*., 1989), although the precise nature of the impairments may vary not only between disorders but also with different putative stages and clinical syndromes of conditions such as schizophrenia (Elliott *et al*., 1995; Hutton *et al*., 1998; Pantelis *et al*., 1999). Of particular relevance to the present study is the finding that Parkinson's disease patients, while tending to have particular difficulties in shifting attentional sets (Downes *et al*., 1989) also display impairments in developing and maintaining attentional sets (Flowers and Robertson, 1985; Owen *et al*., 1992). Moreover, it is performance at those stages of the task that require development and maintenance of an attentional set that is improved following treatment with L-dopa, a precursor of both DA and NA (Lange *et al*., 1992). Thus, while the precise relationship between different types of attentional impairment and catecholamine dysregulation of fronto-striatal circuits in these various disorders is still unknown, the present study emphasizes the importance of catecholamine modulation within the frontal cortex on executive attentional mechanisms in conjunction with effects of the dopaminergic modulation of fronto-striatal mechanisms of response control.

Notes

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