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ORIGINAL INVESTIGATION

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Global 5-HT depletion attenuates the ability of amphetamine to decrease impulsive choice on a delay-discounting task in rats

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Abstract *Rationale:* Psychomotor stimulant drugs such as methylphenidate and amphetamine decrease impulsive behaviour in attention deficit hyperactivity disorder patients by unknown mechanisms. Although most behavioural effects of amphetamine are attributed to the dopaminergic system, some recent evidence suggests a role for serotonin in this paradoxical "calming" effect. *Objectives:* To investigate whether forebrain serotonin depletion affects the action of amphetamine in the rat on a delayed reward task where impulsive choice is measured as the selection of a smaller immediate over a larger delayed reward. *Methods:* Following behavioural training, rats received i.c.v. infusions of either vehicle (n=10) or the serotonergic neurotoxin 5,7-DHT (n=10). Post-operatively, animals received i.p. D-amphetamine (0.3,1.0,1.5, and 2.3 mg/kg/ml), and D-amphetamine co-administered with the dopamine antagonist cis-z-flupenthixol. *Results:* 5,7-DHT (i.c.v.) itself did not affect choice behaviour, despite depleting forebrain serotonin levels by over 85%. Amphetamine increased choice for the large reward, i.e. decreased impulsivity. This effect was attenuated by 5-HT depletion, particularly in animals showing a high level of impulsive choice. Co-administration of cis-z-flupenthixol (0.125 mg/kg) with D-amphetamine abolished the effect of amphetamine in the lesioned group, whereas this was only partially attenuated in the vehicle control group. *Conclusions:* These data suggest that the ability of amphetamine to decrease impulsivity is not solely due to its effects on dopaminergic systems, but may also depend on serotonergic neurotransmission.

Keywords Amphetamine · Serotonin · Delay discounting · ADHD · Impulsivity

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Introduction

Long-term abuse of psychostimulants such as cocaine and amphetamine leads to a number of impairments in cognitive ability including decision making, working memory and impulse control (Rogers et al. 1999; Petry 2002). However, methylphenidate, an amphetamine-like drug, is widely used in the treatment of attention deficit/hyperactivity disorder (ADHD), which is partially characterised by an increase in impulsivity in addition to overactivity and difficulty in maintaining sustained attention (for review see Sagvolden and Sergeant 1998; Solanto 1998). ADHD patients are impaired on behavioural inhibition tasks such as the stop task, where they are unable to inhibit responding once a response has been initiated (Schachar and Logan 1990; Oosterlaan et al. 1998; Nigg 1999), and on delay-discounting tasks, where patients show increased levels of impulsive choice, defined as the selection of a smaller immediate over a larger, delayed reward (Sonuga-Barke and Taylor 1992a; Sonuga-Barke et al. 1992b, 1996, Sonuga-Barke 2002). During delay discounting, the value of the reward alters as a function of time, so that a smaller reward whose delivery is virtually imminent is perceived to be of greater value than a larger reward, the delivery of which is delayed (Ainslie 1975; Logue 1988).

Models of delay discounting and behavioural inhibition have been developed in rodents to investigate the neural and neurochemical basis of these aspects of impulsive behaviour (Thiebot et al. 1985; Mazur 1987; Evenden and Ryan 1996; Ho et al. 1999; Richards et al. 1999). Amphetamine has been shown to improve performance on the stop task in both rodents and humans, but only in those subjects demonstrating relatively poor baseline inhibitory performance (de Wit et al. 2000; Feola et al. 2000). Following amphetamine administration, decreases in impulsive choice have been observed on delay-discounting tasks in humans (de Wit et al. 2002), but both increases and decreases in impulsive responding have been observed in rats (Evenden and Ryan 1996; Richards et al. 1999; Cardinal et al. 2000; Wade et al. 2000).

The behavioural effects of amphetamine have been mainly attributed to its potentiation of the action of dopamine (DA; Maricq and Church 1983; Poncelet et al. 1983; Koob and Bloom 1988; Fletcher et al. 1998; Depoortere et al. 1999), which occurs both through inhibition of the dopamine transporter (DAT; Amara and Kuhar 1993; Giros and Caron 1993; Giros et al. 1996) and through enhanced release of DA from presynaptic nerve terminals (Jones et al. 1998). However, amphetamine also affects other monoamine transporters, increasing extracellular levels of noradrenaline and serotonin (5-HT) (Kuczenski et al. 1987; Kuczenski and Segal 1989, 1995; Seiden and Sabol 1993), and evidence from DAT knockout mice suggests that the paradoxical calming effect seen following amphetamine administration in ADHD patients may be related to the drug's actions on the serotonergic system (Gainetdinov et al. 1999).

Theories implicating the 5-HT system in the regulation of impulsive behaviour have been gathering momentum for over 20 years (Linnoila et al. 1983; Soubrié 1986). Data from studies testing human volunteers indicate that acute tryptophan depletion, which decreases levels of 5-HT in the brain, impaired performance on a probability-based decision-making task which incorporated a reward-discounting component (Rogers et al. 1999; Rogers et al. 2003), yet does not alter performance of a delay-discounting task (Crean et al. 2002). In contrast, previous studies in the rat have found that selective lesions of the serotonergic system lead to an increase in impulsive choice on delay-discounting tasks (Wogar et al. 1993; Mobini et al. 2000).

Global 5-HT depletion also increased impulsive behaviour as measured by the number of premature responses made in the five choice serial reaction time task (5CSRT; Harrison et al. 1997), an effect which is blocked by administration of the D_1 receptor antagonist SCH 23390. Increased premature responding in the 5CSRT is also observed following systemic amphetamine administration (Cole and Robbins 1987). Furthermore, the large increases in premature responding produced by higher doses of amphetamine are diminished in animals following global 5-HT depletion (Harrison et al. 1997). Such evidence implicates interactions between the 5-HT and DA systems in the control of impulsive behaviour, and also suggests that the 5-HT system is involved in aspects of impulse control affected by amphetamine. This experiment aimed to further evaluate the effects of amphetamine administration and global 5-HT depletion in rats on performance of a delay-discounting task, and to investigate whether decreasing forebrain 5-HT levels would alter the behavioural response to amphetamine.

Materials and methods

Subjects

Subjects were 20 male, Lister Hooded rats (Charles River, UK) weighing 300–320 g at the start of the experiment and were maintained on 14 g of food per day (inclusive of any reward they obtained in the behavioural sessions). Water was available ad libitum. Animals were housed in pairs under a reverse light cycle (lights on from 19.00 hours to 0700 hours) and testing took place between 0900 hours and 1300 hours 6 days per week. All experiments were carried out in strict accordance with the UK Animals (Scientific Procedures) Act 1986.

Behavioural apparatus

The apparatus consisted of eight identical operant conditioning chambers (30×24×30 cm, Med Associates Inc., USA), each enclosed within a sound-attenuating wooden box fitted with a fan for ventilation and masking of extraneous noise. The front aluminium wall of each chamber was fitted with two retractable levers 16 cm apart and 7 cm above the grid floor. Centrally located between the two levers was a food magazine into which an external pellet dispenser could deliver 45-mg sucrose pellets (Noyes dustless pellets, Sandown Scientific, UK). The food magazine was illuminated by a diffused green LED (RS Components Ltd, UK) fitted at the rear of the alcove. Entry to the food magazine could be detected by the breaking of an infrared photobeam located horizontally across the entrance. General illumination was provided by a 2.8-W house light mounted on the rear aluminium wall of the chamber. The apparatus was controlled and monitored by software written in Arachnid (Paul Fray Ltd, UK), a real-time extension to BBC BASIC V running on Acorn Archimedes Series computers (Cambridge, UK).

Behavioural testing

Pretraining

Subjects were first trained under a fixed ratio FR1 schedule to a criterion of 50 presses in 30 min for each lever. They were then trained on a simplified version of the full task. Every 40 s, a trial began with illumination of the house light and the tray light. The subject was required to make a nose-poke response within 10 s to trigger presentation of a single lever. Responding on the lever within 10 s led to illumination of the tray light and delivery of a single food pellet. The left and right levers were presented an equal number of times in the session with not more than two consecutive presentations of the same lever. Rats were trained to a criterion of at least 60 successful trials in 1 h.

Delayed reward task

Each session lasted 100 min and consisted of five blocks of 12 trials, each lasting 100 s. Each block began with a pair of forced choice trials which consisted of one presentation of the left lever and one of the right in a random order. Throughout the task, a response on one lever would produce a reward of one pellet (lever A), whereas a response on the other would produce a reward of four pellets (lever B). The position of these levers (left or right) was kept constant for each rat, but was counterbalanced between rats. The delay between responding on lever A and the concomitant delivery of reward (dA) was always 0 s, whereas the delay between responding on lever B and the delivery of reward (dB) increased within the session in a step-wise manner between blocks from 0 seconds in block 1, to 10 s in block 2, 20 s in block 3, 40 s in block 4 and 60 s in block 5.

Each trial began with the onset of the house light and tray light. As in pretraining, there was a limited hold period of 10 s in which the rat had to nose poke in the magazine to trigger presentation of the two levers, upon which a 10-s response interval was initiated. Failure to respond in either 10-s period resulted in the trial being recorded as an omission and a return to the ITI state until the next trial was due to begin. Once the rat had responded on one of the levers, both levers were retracted, the house light and tray light turned off. Food delivery, signalled by the tray light, occurred either immediately or after a delay. An inter-trial interval of variable length then followed depending on the choice made, so that each trial lasted 100 s. The length of the task was kept constant in this way so that the rate of delivery of reinforcement associated with both behavioural responses was identical, preventing any differences influencing choice.

Surgery

Subjects were matched for baseline performance (see statistical analysis for criteria) and separated into equal sham and lesion groups (*n*=10). All rats were treated 30 min before the start of surgery with 20mg/kg desmethylimipramine HCl (Sigma, UK) dissolved in double distilled water to protect noradrenergic neurons from the neurotoxin. Rats were anaesthetised with Avertin (10 g 2,2,2-tribromoethanol (Fluka, Germany) in 5 g tertiary amyl alcohol, diluted in a solution of 40 ml ethanol and 450 ml PBS) given at a dose of 1 ml/100 g, and secured in a stereotaxic frame fitted with atraumatic ear bars. Rats in the lesion group received bilateral i.c.v. infusions of 80 μg (free base) 5,7-DHT creatinine sulphate (Sigma, UK) dissolved in 10 μl 0.1% ascorbic acid, whilst the vehicle control group received bilateral i.c.v. infusions of 10 μl vehicle. Following each 8-min infusion, the injector was left in place for 2 min before withdrawal to allow the infusate to diffuse. The co-ordinates used were : AP −0.9 mm from bregma, L ±1.5 mm from the midline, DV −3.5 mm from dura. The incisor bar was set at −3.3 mm relative to the interaural line in a flat skull position. After surgery, animals had free access to food for 10 days prior to re-training on the delayed-reward task to allow for the degeneration of 5-HT containing neurons (Bjorkland 1975).

Drugs

All drugs were made up fresh on each test day. Both D-amphetamine sulphate (Sigma, UK) and cis-z-flupenthixol (Sigma, UK) were dissolved in sterile 0.9% saline. All doses were calculated as the salt in keeping with previous reported use. The pH of the cis-z-flupenthixol solution was adjusted with 6.6 μl/ml 0.1 M NaOH and 3.3 μl/ml 0.1M HCl to give a pH of 6.4. All drugs were given in an injection volume of 1 ml/kg and administered i.p.

Experiment 1: effect of D-amphetamine on performance of the delayed reward task in both sham and i.c.v. 5,7-DHT lesioned animals

Injections were given 10 min before the start of the behavioural test session in a different location from the testing room and the home cage. The drug design was based on that used in a previously reported experiment using this task (Cardinal et al. 2000) and began following collection of post-operative baseline data necessary for analysis of the lesion. The lowest three doses were given in sets of six consecutive days following the pattern: saline, 0.3 mg/kg amphetamine, saline, 1.0 mg/kg amphetamine, saline, 1.5 mg/kg amphetamine. This dose regimen was repeated three times, with a minimum of 10 days between each replication. At the end of the regime, the highest dose of D-amphetamine, 2.3 mg/kg, was given, preceded the day before by a vehicle injection. This pair of vehicle-drug injections was repeated three times and at least 5 days separated each cycle. The study took 12 weeks in total. Each rat received the same drug on the same days. Repeated saline injections were included in the drug design so that the effect of each injection could be compared against the immediately preceding vehicle session so as to increase the power for detecting drug effects with gradually shifting baselines. Collecting data for three drug and three vehicle sessions enabled accurate determination of choice by giving 30 choice trials at each delay/dose combination.

Experiment 2: effect of combined administration of amphetamine and the D_1/D_2 receptor antagonist cis-z-flupenthixol on performance of the delayed reward task in sham and i.c.v. 5,7-DHT lesioned rats

Two doses of amphetamine (i.p. 0, 1.0, 1.5 mg/kg) plus vehicle were administered 10 min before the start of the task according to a Latin square drug design. On each test day, 10 min before the injection of amphetamine or saline was given, an injection of 0.125 mg/kg cis-z-flupenthixol was administered. This dose was selected on the basis of pilot data indicating that, although this dose alone did not severely disrupt locomotor activity, it did attenuate the ability of amphetamine to elevate locomotor activity. Injections were given on a 3-day cycle, starting initially with a baseline session, so that the study took just under 2 weeks. The following day, subjects received drug prior to testing on the delayed reward task. On the third day, animals were not tested and remained in their home cages. Two weeks passed between the end of the amphetamine study and the first administration of cis-z-flupenthixol during which time animals were tested every other day.

Experiment 3: effects of amphetamine on spontaneous locomotor activity in both sham and i.c.v. 5,7-DHT lesioned animals

Locomotor activity was assessed in individual activity cages over 2 h at approximately the same time each day. Eleven activity cages (25×40×18 cm) were used, each with two photocell beams located 1 cm above the floor and spaced equally along the length of the cage. A "run" was scored if the two beams were broken within 0.2 s. The data were collated over 5-min bins using software running on an Acorn Archimedes series computer (Cambridge, UK). Animals were habituated to the boxes over two sessions before receiving systemic injections of saline, 0.3 mg/kg and 2.3 mg/kg amphetamine. All animals received the same dose of drug on each day.

Ex vivo lesion analysis

At the end of the experiment, animals were sacrificed through exposure to increasing concentrations of carbon dioxide. The brains were then rapidly removed and frozen on dry ice. Thereafter, coronal sections were cut (150-μm thickness) on a cryostat (−18°) from the frontal pole and mounted onto pre-chilled microscope slides. A stainless-steel micropunch (0.75-mm diameter) was used to remove 0.6- to 1.0-mg aliquots of tissue from the following (left and right) brain regions: nucleus accumbens (NAC), prelimbic cortex (PRL), anterior cingulate cortex (Acx), dorsomedial striatum (DMS), dorsolateral striatum (DLS), amygdala (AMYG), ventral hippocampus (VHPC), dorsal hippocampus (DHPC), septum (SEP) and hypothalamus (HYP). Samples were homogenised in 75 μl 0.2 M perchloric acid to precipitate protein material. Following centrifugation at 6000 rpm for 20 min at 4°C, 50 μl of the supernatant was decanted and placed into autoinjector microvials ready for analysis. Levels of DA, 5-HT and their metabolites dihydroxyphenylacetic acid (DOPAC) and 5-hydroxyindoleacetic acid (5-HIAA), and noradrenaline (NA) were determined in brain samples by reversed-phase, high-performance liquid chromatography (HPLC), as described previously (Palkovits 1973).

Data analyses

All analyses were conducted using SPSS for Windows (version 9.0; SPSS, Chicago, IL) apart from curve fitting, which was done using Microsoft Excel (Microsoft, Seattle, WA, USA). The total number of choices of the large reward during each delay per session was used to analyse choice behaviour. The number of omissions made did not affect this choice measure. These data were subjected to an arcsine transformation in order to limit the effect of an artificially imposed ceiling (ten responses per delay was the maximum possible per session). In order to judge whether an animal had successfully acquired the task and reached stable baseline performance, data from ten sessions were analysed by repeated-measures ANOVA with two within-subjects factors, day and delay. In order to satisfy performance criteria, the effect of delay had to be significant at the $P<0.05$ level and the effect of day non-significant, i.e. performance had to be delay dependent and stable over ten sessions, regardless of the pattern of choice shown.

Once stable behaviour had been attained following 35 training sessions, the individual variation within the subject group was analysed through fitting an exponential curve to data from individual subjects of the form:

$y = e^{-(kd)}$ where y = number of choices of the large rewardd

= delay to the large reward

The co-efficient k determined the rate of exponential decay of choice of the larger delayed reward with time. The larger the k value, the steeper the exponential delay-discounting function (i.e. as the delay to the large reward is increased, the animals choose the small immediate reward to a greater extent), and the more impulsive the animal's behaviour becomes. When the values of the k co-efficient were plotted, a group of highly impulsive individuals were identified (n=6) whose k values were significantly greater than the rest of the group (impulsive group: mean 0.127, 95% CI: 0.113–0.140; less impulsive group: mean 0.039, 95% CI: 0.011–0.067; independent samples t-test: t=−10.020, df=18, $P<0.0001$). Subjects were matched for baseline performance using the k values so that the same range of behavioural variation was present in both sham and lesioned animals.

The effects of the lesion were assessed through comparison of data collected over the final ten pre-operative sessions and the first ten post-operative sessions. Data were analysed using a repeated-measures ANOVA with surgery (two levels, pre-op and post-op), day and delay as within-subjects factors. The post-op data were also subjected to a repeated-measures ANOVA with day and delay as within-subjects factors and lesion as a between-subjects factor. In addition to the number of choices of the large reward made per delay, the total number of omissions made per session and the average time taken to respond on either lever (response latency) per session were also analysed.

In keeping with previous drug studies (Cardinal et al. 2000; Wade et al. 2000), data obtained using the same drug dose over three sessions was averaged and analysed by repeated-measures ANOVA, with drug (five levels: vehicle plus four doses of amphetamine) and delay (five levels: 0, 10, 20, 40 and 60 s) as within-subjects factors and baseline (two levels: impulsive and non-impulsive) and lesion (two levels: sham and lesion) as between-subjects factors. Due to repeated administration of amphetamine, it was possible that the animals could have developed a sensitised response to the drug; therefore a further ANOVA was performed on data from the first and final rounds of administration, with replication, drug and delay as within-subjects factors and lesion as a between-subjects factor.

In order to assess any interactions between flupenthixol and amphetamine, the effect of amphetamine alone was compared with the effect of amphetamine plus flupenthixol. Data were analysed by repeated-measures ANOVA as before with antagonist (present or absent), drug (three levels: vehicle, 1.0 mg/kg amphetamine and 1.5 mg/kg amphetamine) and delay as within-subjects factors, and lesion as a between-subjects factor. Significant drug × delay and drug × delay × lesion effects were followed up using either further ANOVA examining responses to single drug doses over delay, or paired-sample t-tests comparing either sham and lesion data or vehicle and drug data at different delays.

Locomotor activity data were analysed by repeated-measures ANOVA with bin as a within-subjects factor, and lesion and baseline as between-subjects factors. The effect of amphetamine was also determined by repeated-measures ANOVA, with drug and bin as within-subjects factors and baseline and lesion as between-subjects factors.

Results

Lesion assessment

Post-mortem analyses of 5-HT concentrations throughout the forebrain revealed a statistically significant reduction in levels of 5-HT and 5-HIAA in all areas tested of over 85% (Table 1). Levels of DA, DOPAC and NA were not significantly affected.

Effect of 5-HT depletion on performance of the delayed reward task

Serotonin depletion had no effect on impulsive choice (Fig. 1). Performance after surgery did not differ significantly from performance before surgery as indicated by non-significant effects of surgery in both sham and lesioned animals nor was there a significant difference between sham and lesion groups during post-operative testing as indicated both by a non-significant effect of lesion and by a non-significant lesion × delay interaction. Furthermore, 5-HT depletion did not differentially affect the patterns of choice behaviour in more impulsive compared with less impulsive animals. The number of trials omitted per session also remained constant in both groups of subjects (omissions: shams pre-op 0.03±0.02, post-op: 0.07±0.02, lesions pre-op 0.07±0.04, post-op 0.28±0.18) as did the response latency (shams pre-op 0.90±0.08 s, post-op: 0.92±0.09 s; lesions pre-op 0.87±0.06 s, post-op 0.85±0.07 s).

Effects of systemic D-amphetamine administration

In general, systemic D-amphetamine increased choice for the large reward over delay (drug: $F_{4,64}$=2.873, $P<0.03$; drug × delay: $F_{16,256}$=4.921, $P<0.001$). However, as shown in Fig. 2, a significant difference emerged between the choice behaviour of sham and lesioned groups following administration of amphetamine (lesion × delay: $F_{6,16}$=4.017, $P<0.006$), and there was a trend for the different doses of amphetamine to have different effects in sham and lesioned animals (drug × delay × lesion: $F_{16,256}$=1.600). When data from the final replication of replication administration was compared with that from the first, there was no significant effect of replication, indicating these effects are unlikely to be due to the development of a sensitised response to amphetamine.

To isolate the source of these lesion differences, data from each drug dose were analysed separately. Whilst there were no significant differences between the sham and lesion groups following saline, 1.0 mg/kg or 1.5 mg/kg D-amphetamine, at 2.3 mg/kg, choice of the large reward was significantly increased at all delays in sham animals, yet lesioned animals were unaffected at any delay (delay × lesion: $F_{4,64}$=6.853, $P<0.001$). Furthermore, after 0.3 mg/kg D-amphetamine sham animals showed an increase in their choice of the large reward at

Table 1 Tissue concentrations of serotonin (5-HT), 5-hydroxyindoleacetic acid (5-HIAA), dopamine (DA), dihydroxyphenylacetic acid (DOPAC) and noradrenaline (NA) in cortical, striatal and limbic areas of i.c.v. 5,7-DHT lesioned and sham-operated rats. The data are averaged levels (±SEM) expressed as picomoles per milligram to two decimal places. *PrL* prelimbic cortex, *ACx* anterior cingulate, *NAC* nucleus accumbens, *DMS* dorsomedial striatum, *DLS* dorsolateral striatum, *Amyg* amygdala, *VHPC* ventral hippocampus, *DHPC* dorsal hippocampus, *SEP* septum, *HYP* hypothalamus

Region	5-HT		5-HIAA		DA		DOPAC		NA	
	Sham	Lesion	Sham	Lesion	Sham	Lesion	Sham	Lesion	Sham	Lesion
PrL	0.22 (0.07)	0.00* (0.00)	9.87 (1.10)	0.28* (0.09)	3.34 (0.67)	3.53 (0.99)	1.67 (0.30)	1.50 (0.26)	3.61 (0.82)	2.72 (0.60)
ACx	0.16 (0.05)	0.03* (0.03)	8.73 (0.83)	0.16* (0.08)	2.20 (0.60)	1.62 (0.43)	1.04 (0.41)	0.93 (0.18)	2.81 (0.53)	2.47 (0.60)
NAC	0.30 (0.14)	0.02* (0.01)	10.04 (1.03)	1.06* (0.25)	32.13 (9.29)	28.28 (6.88)	24.78 (11.23)	28.04 (8.55)	7.81 (3.27)	8.06 (4.16)
DMS	0.21 (0.07)	0.00* (0.00)	6.53 (0.46)	0.36* (0.11)	34.08 (9.72)	38.00 (10.24)	40.85 (10.49)	33.33 (7.46)	0.59 (0.29)	0.22 (0.12)
DLS	0.17 (0.05)	0.00* (0.00)	7.44 (0.45)	0.51* (0.16)	12.65 (4.35)	9.77 (2.56)	40.60 (11.61)	35.86 (7.22)	0.84 (0.47)	0.36 (0.24)
Amyg	0.26 (0.06)	0.11* (0.08)	10.41 (1.37)	0.51* (0.24)	1.65 (0.53)	1.21 (0.23)	4.42 (1.57)	5.54 (1.93)	4.87 (0.94)	5.18 (1.22)
VHPC	0.20 (0.06)	0.00* (0.00)	10.95 (1.59)	0.21* (0.09)	0.82 (0.18)	0.57 (0.11)	0.18 (0.14)	0.39 (0.20)	6.35 (1.81)	4.44 (1.03)
DHPC	0.18 (0.09)	0.00* (0.00)	7.74 (1.41)	0.06* (0.04)	1.07 (0.14)	0.66 (0.17)	0.59 (0.22)	0.66 (0.25)	4.15 (0.58)	3.17 (0.70)
SEP	0.24 (0.06)	0.02* (0.02)	7.96 (0.89)	0.55* (0.12)	1.27 (0.36)	0.69 (0.18)	5.94 (1.92)	4.34 (1.03)	7.85 (1.73)	8.74 (1.68)
HYP	0.26 (0.08)	0.06* (0.03)	8.96 (0.83)	1.82* (0.47)	32.14 (10.09)	31.25 (9.39)	0.76 (0.28)	0.94 (0.21)	12.18 (2.41)	10.42 (2.74)

* Significant difference (P<0.05) between sham and lesioned groups

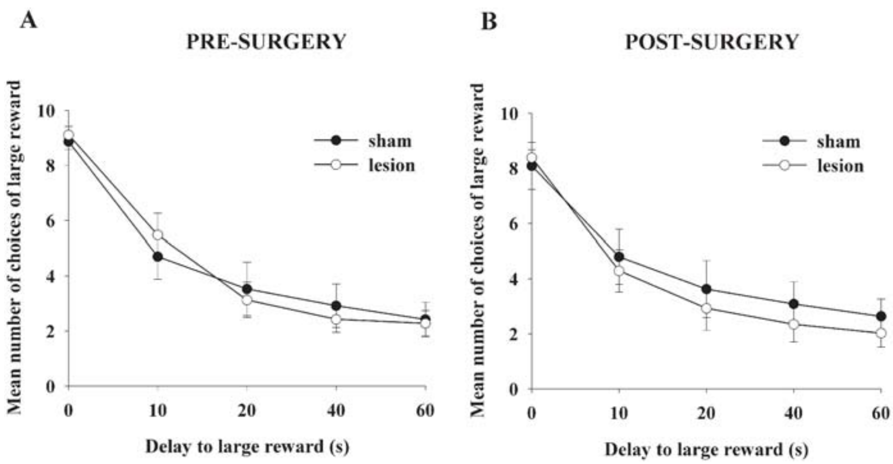

Fig. 1A, B Effects of i.c.v. 5,7-DHT lesions on choice of the delayed reward. **A** Performance averaged over the last 7 days prior to surgery. **B** Choice in the first seven sessions after surgery. The lesion had no effect on choice behaviour. Values shown are mean and SEM

the 10-s delay, which tended to be absent in lesioned animals (delay × lesion: $F_{4,64}$=2.521, P<0.058).

A moderate increase in omissions was also observed following administration of the highest dose of amphetamine (drug $F_{4,64}$=12.688, P<0.0001), and the two highest doses also increased the latency to respond (drug $F_{4,64}$=9.658, P<0.001) (Table 2). However, no significant differences between sham-operated and lesioned animals were detected through analysis of these performance measures.

In summary, amphetamine decreased impulsive choice, but this effect was blunted in lesioned relative to sham animals, particularly at the highest dose.

Interactions between baseline levels of impulsivity and D-amphetamine administration in sham and 5,7-DHT lesioned animals

The effect of D-amphetamine also depended on the basal level of impulsivity displayed by the subjects (drug × delay × baseline: $F_{16,256}$=1.790, P<0.003; drug × delay ×

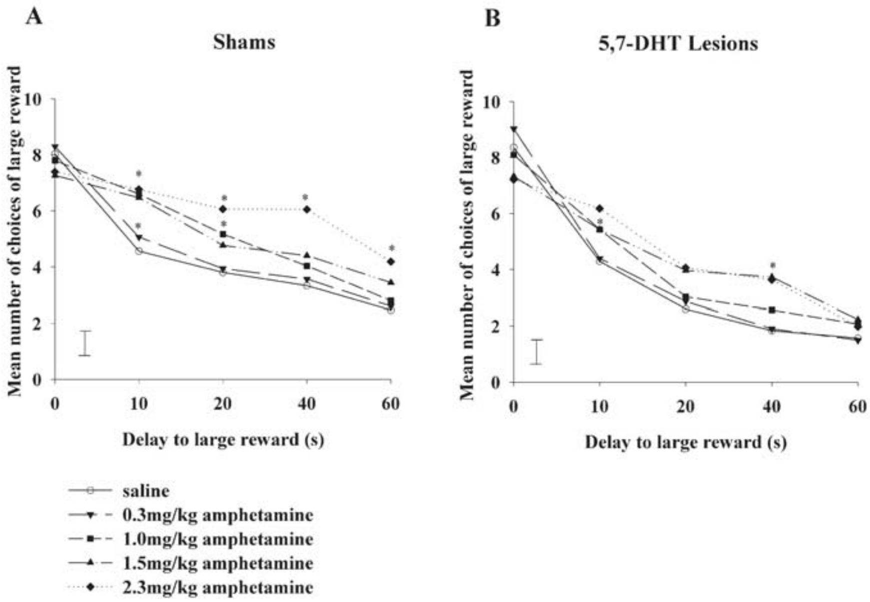

Fig. 2 Effects of amphetamine (i.p. 0, 0.3, 1.0, 1.5 and 2.3 mg/kg) on choice of the large delayed reward in sham-operated (**A**) and i.c.v. 5,7-DHT-lesioned (**B**) rats. The *vertical bar* depicts one SED (standard error of the difference between the means) for the drug × delay interaction. This is the appropriate index of variability for many pair-wise comparisons of means post hoc, and is calculated according to the formulae provided by (Cochran and Cox 1957), $^{*}P<0.05$ vs vehicle

Table 2 The effect of amphetamine on numbers of omissions and response latency per session in sham and lesioned rats. The data are averaged levels (±SEM) to two decimal places

		Dose of amphetamine (mg/kg)				
		0.0	0.3	1.0	1.5	2.3
Omissions	Sham	0.11 (0.08)	0.00 (0.00)	0.07 (0.07)	0.70 (0.32)	8.70* (3.14)
	Lesion	0.51 (0.30)	0.07 (0.05)	0.13 (0.11)	3.27 (2.02)	6.17* (2.19)
Response latency (s)	Sham	0.91 (0.08)	0.88 (0.09)	0.93 (0.13)	1.10* (0.11)	1.23* (0.13)
	Lesion	0.84 (0.05)	0.81 (0.06)	0.89 (0.05)	1.09* (0.08)	1.10* (0.09)

* Significant difference ($P<0.05$) when compared with performance after vehicle administration. No significant differences were observed between sham and lesioned groups

lesion × baseline: $F_{16,256}=2.404$, $P<0.004$). Within the group of animals showing the highest baseline levels of impulsivity, sham-operated and lesioned animals responded very differently to the D-amphetamine challenge (Fig. 3A, B). Whereas sham-operated controls continued to show a dose-dependent increase in the choice of the large reward across delay, the lesioned animals did not significantly change their behaviour in response to D-amphetamine (drug × delay × lesion: $F_{16,64}=2.643$, $P<0.003$). This difference in response was most pronounced at the highest dose of amphetamine (delay × lesion interaction: $F_{4,16}=5.363$, $P<0.006$).

Both sham and 5,7-DHT lesioned animals in the less-impulsive subgroup demonstrated decreased levels of impulsive choice in response to D-amphetamine (drug × delay: $F_{16,192}=3.808$, $P<0.0001$). The blunted response to high doses of D-amphetamine in the lesioned group was therefore attributable to animals in the impulsive subgroup. However, at 0.3 mg/kg D-amphetamine, lesioned animals did not change their behaviour in response to amphetamine, whereas sham-operated rats increased their choice for the large reward over delay (data from all doses of D-amphetamine: delay × lesion: $F_{4,48}=2.775$, $P<0.037$; 0.3 mg/kg: delay × lesion: $F_{4,48}=3.356$, $P<0.017$).

In summary, 5,7-DHT lesioned animals were less susceptible to the effects of amphetamine, particularly at the lowest and highest doses tested. This latter effect was most pronounced in subgroup of animals showing a high baseline level of impulsive behaviour.

Effect of co-administration of D-amphetamine and flupenthixol on impulsive choice in sham and 5,7-DHT lesioned animals

As significant effects of D-amphetamine were only obtained in both sham and lesion animals at 1.0 mg/kg and 1.5 mg/kg, these doses were tested in combination with a dose of 0.125 mg/kg flupenthixol. This dose alone had no effect on impulsive choice compared with vehicle but did have different effects in sham-operated and lesioned animals when co-administered with D-amphetamine (antagonist × lesion: $F_{1,6}=6.101$, $P<0.048$; Fig. 4). Flupenthixol did not significantly affect the ability of D-amphetamine to decrease impulsive choice in sham animals but did block the ability of D-amphetamine to promote choice of the large reward in lesioned animals (antagonist: $F_{1,4}=11.845$, $P<0.026$).

Effect of D-amphetamine on locomotor activity in sham and 5,7-DHT lesioned animals

5,7-DHT lesions did not affect levels of spontaneous locomotor activity, nor were there any significant effects of baseline level of impulsivity (Fig. 5). As expected, D-

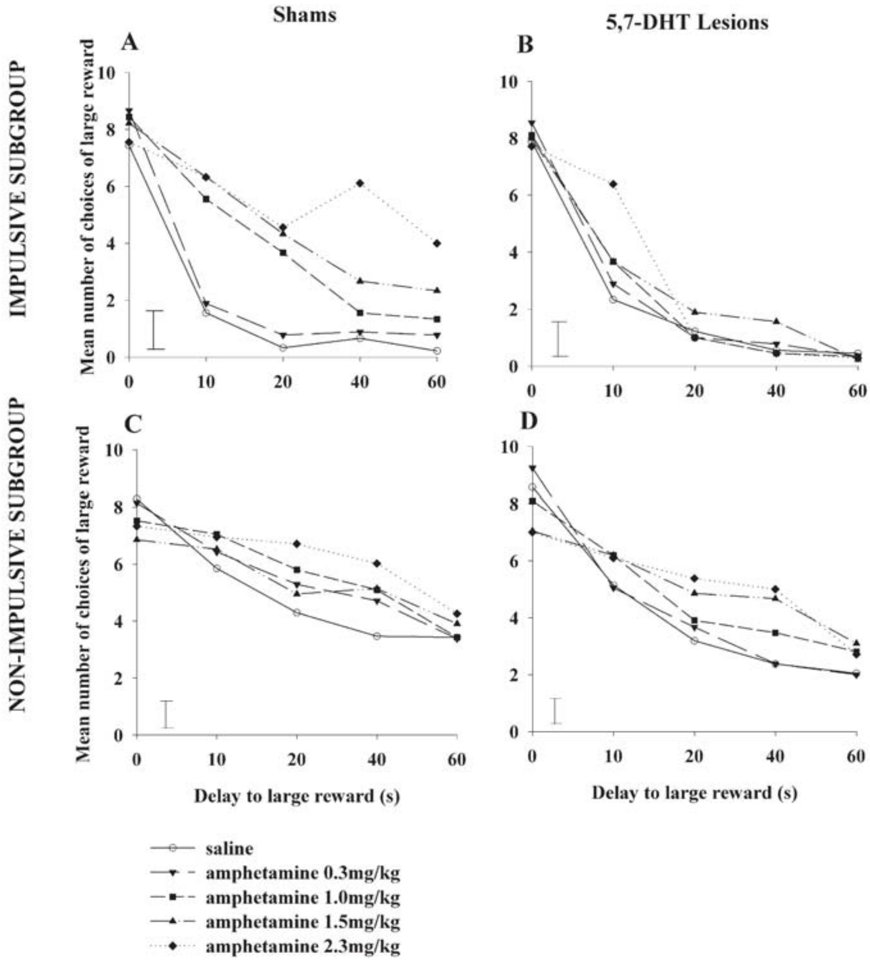

Fig. 3 Effects of amphetamine (i.p. 0, 0.3, 1.0, 1.5 and 2.3 mg/kg) on choice of the large delayed reward in the impulsive subgroup (sham-operated, **A**; and i.c.v. 5,7-DHT, **B**) and in the non-impulsive subgroup (sham-operated, **C**; and i.c.v. 5,7-DHT, **D**). Values shown are mean and SED

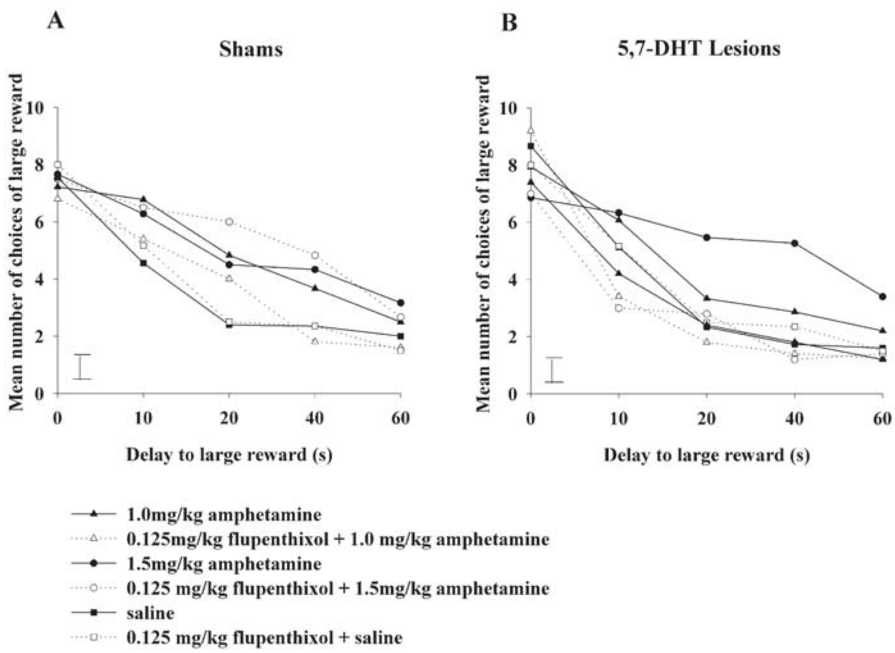

Fig. 4A, B Effects of amphetamine (i.p. 0, 1.0, 1.5 mg/kg) and the combined administration of amphetamine (1.0, 1.5 mg/kg) and cis-z-flupenthixol (i.p. 0.125 mg/kg) on choice of the large delayed reward. Values shown are mean and SED

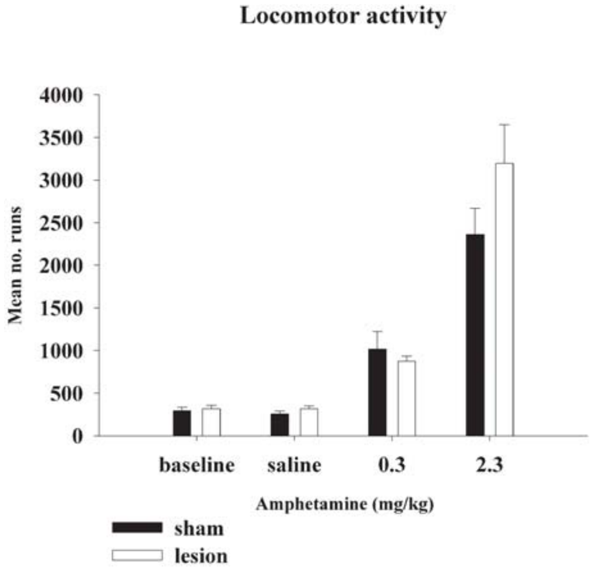

Fig. 5 Effects of amphetamine (i.p. 0, 0.3 and 2.3 mg/kg) on locomotor activity in sham-operated and i.c.v. 5,7-DHT lesioned rats. Baseline levels of locomotor activity are also represented for comparison. Values shown are the mean and SEM of the total number of runs made per session

amphetamine increased locomotor activity in rats relative to saline administration (drug: $F_{1,16}$=111.250, P<0.0001). Although 2.3 mg/kg D-amphetamine did not affect impulsive choice in lesioned animals, this dose of the drug nevertheless increased locomotor activity to the same level as sham-operated rats irrespective of baseline levels of impulsivity. A subset of animals was also tested with the lowest dose (0.3 mg/kg) of D-amphetamine used (0.3 mg/kg). Again, the drug increased locomotor activity relative to saline to the same extent in both sham and lesioned animals independent of baseline levels of impulsivity.

Discussion

The results of this study support and extend previous findings that amphetamine can decrease impulsive choice in a rodent model of delay discounting (Cardinal et al. 2000; Richards et al. 1999; Wade et al. 2000). The ability of amphetamine to reduce impulsive behaviour in this task was diminished by i.c.v. 5,7-DHT lesions leading to chronic depletion (~85–90%) of forebrain 5-HT. This reduced response to amphetamine was most evident in animals showing high baseline levels of impulsive choice. Co-administration of the dopamine receptor antagonist cis-z-flupenthixol also blocked the effects of amphetamine on choice behaviour in 5-HT-depleted but not in sham-operated rats. Overall, these data indicate that the ability of amphetamine to decrease impulsivity may depend on both serotonergic and dopaminergic neurotransmission. In contrast, the locomotor stimulant effects of amphetamine were not significantly affected by i.c.v. 5,7-DHT lesions. Thus, there is some specificity in the involvement of 5-HT in mediating the ameliorative effects of amphetamine on impulsive choice.

In keeping with data obtained following tryptophan depletion in human volunteers (Crean et al. 2002), global 5-HT depletion alone had no effect on delay discounting. This contrasts with previous studies reporting increased choice of the small, immediate reward following serotonergic lesions of the dorsal and median raphé nuclei (Wogar et al. 1993; Mobini et al. 2000). Although the reasons for this discrepancy are unclear, there are a number of obvious differences between these studies, not least the use of different behavioural tasks and methodology. For example, in contrast to previous work, this study tested the effect of 5-HT depletion on performance rather than during the acquisition of delay discounting, which could contribute to the differing results. However, other data from this laboratory indicate that i.c.v. 5,7-DHT lesions do not alter acquisition of a delay-discounting task either (Winstanley and Robbins 2002).

Different lesion co-ordinates were also used [i.c.v. (this study) vs intra-raphé infusions of 5,7-DHT (Wogar et al. 1993; Mobini et al. 2000)]. Although both intra-raphé and i.c.v. infusions of 5,7-DHT cause similar levels of long-lasting 5-HT depletion, it may be pertinent to note that, unlike in the current experiment, NA-containing neurons in the studies by Wogar et al. and Mobini et al. were not protected by pre-treatment with desipramine. Although no alteration in NA levels was observed in cortical regions, damage to noradrenergic neurons in the local vicinity of the infusion cannot be excluded due to the substantial volume of toxin administered (2 μl). Furthermore, intra-raphé infusions of 5,7-DHT preceded by administration of desipramine result in only a small and transient increase in impulsive choice (Bizot et al. 1999).

Although i.c.v. 5,7-DHT-induced 5-HT depletion had no effect in this delay-discounting paradigm, the same serotonergic lesions increased impulsivity in the 5CSRT, an effect that can be ameliorated by administration of the D_1 receptor antagonist SCH 23390. These two forms of impulsive behaviour can therefore be dissociated, at least with regard to the role of the serotonergic system, supporting the suggestion that impulsivity is not a unitary construct. However, serotonergic neurotransmission was necessary for expression of the full effect of amphetamine to decrease impulsive choice, particularly in very impulsive responders. The non-selective dopamine antagonist cis-z-flupenthixol also completely abolished the effect of amphetamine in 5,7-DHT lesioned animals, but not in sham controls. Both forms of impulsive behaviour are therefore open to modulation by 5-HT-DA interactions.

The finding that amphetamine increases choice of the larger, delayed reward agrees with some previous findings (Richards et al. 1999; Wade et al. 2000), but not with others (Evenden 1998; Cardinal et al. 2000). There are essentially two processes governing the process of delay discounting: the perceived value of the reward and the perceived length and aversive nature of the delay (Mazur

1987; Logue 1988; Ho et al. 1999), and amphetamine may have modulated these variables in a number of ways. First, amphetamine has been shown to affect perception of the duration of time (Maricq et al. 1981; Maricq and Church 1983; Chiang et al. 2000), theoretically by speeding up an internal clock or pacemaker (Meck 1983; Gibbon et al. 1997). However, such impairments in temporal judgement would be expected to increase rather than decrease impulsivity and, therefore, cannot easily explain the results obtained here.

Previously, it has been reported that amphetamine decreased impulsive choice using this paradigm if a conditioned reinforcer (CRf) was used to signal the large delayed reinforcer (Cardinal et al. 2000), and it is well-established that amphetamine promotes the control of responding by CRfs (Robbins et al. 1983). Although the opposite effect of amphetamine was observed by Cardinal et al. in the absence of the CRf, the more extensive training schedule used here in comparison to previous studies might have promoted the development of the instrumental response itself as a possible CRf (Mackintosh and Dickinson 1979; Garrud et al. 1981) through strengthening the association between response on the lever with its concomitant feedback, and delivery of the reward.

Alternatively, amphetamine administration could have induced perseveration on the large reward lever due to the development of stereotyped behaviour, particularly at the higher doses used. It has previously been suggested that the stereotypy produced by psychostimulant drug involves the repetition of actions associated with goal or reward (Robbins 1976), and it has been argued that it is precisely this focusing of behaviour which results in improvements in the symptoms of ADHD (Sahakian and Robbins 1977). It is unlikely that any changes in impulsive choice were due to non-specific changes in behavioural output, such as increased response latency and trials omitted, as even when such increases were observed, they were moderate and did not result in a break-down of task performance.

Amphetamine administration has also been shown to increase reinforcer efficacy (Poncelet et al. 1983; Martin-Iverson et al. 1987; Depoortere et al. 1999; Mayorga et al. 2000), which provides an alternative explanation for the drug-induced increase in the choice of the large reward. The ability of amphetamine to enhance the value of reinforcers has been attributed to its facilitation of dopaminergic systems which are heavily implicated in mediating the rewarding value of reinforcement and conditioned reinforcers (Wise 1978; Cador and Robbins 1991; Wilson et al. 1995), and in goal-directed behaviour (Wise and Rompre 1989; Schultz and Romo 1990; Robinson and Berridge 1993). However, there is evidence to suggest that serotonergic neurons are also implicated in modulating reward processes (Wogar et al. 1991; Fletcher et al. 1993; Rogers et al. 2003), possibly through complex interactions with the dopamine system. Amphetamine increases extracellular concentrations of 5-HT at higher doses (Kuczenzski et al. 1989) and so the effect of 5-HT depletion observed in this study may operate by blocking these actions of the drug during delay discounting.

A critical role for an intact serotonergic system in the action of amphetamine appears to be restricted to reinforcement-maintained behaviours. While 5-HT depletion appears to reduce the reinforcing effectiveness of amphetamine in self-administration studies (Lyness et al. 1980; Leccesse and Lyness 1984; but see Fletcher et al. 1999), the ability of amphetamine to increase locomotor activity is not blocked by selective 5-HT lesions (present study, Sills et al. 1999) and may even be enhanced (Breese et al. 1974). However, serotonergic agents co-administered with amphetamine do modulate amphetamine-induced increases in locomotor activity and dopamine release (Hollister et al. 1976; Ickikawa et al. 1995; Gainetdinov et al. 1999; Kuroki et al. 2000; Frantz et al. 2002), perhaps indicating that, whilst 5-HT release can modulate the actions of amphetamine on these responses, it is not essential for these drug effects.

The ability of 5,7-DHT lesions to attenuate the effect of amphetamine was much more pronounced in animals with a high baseline level of impulsive choice, which was more susceptible to reduction by amphetamine in sham controls analogous to rate-dependent (Wenger and Dews 1976) or "probability" dependent (Robbins and Evenden 1985) effects. There is a growing body of evidence implicating dysregulation of the serotonergic system in impulsive individuals, both in terms of overall levels of 5-HT and in 5-HT receptor distribution (Dalley et al. 2002; Preece, Dalley, Theobald, Robbins and Reynolds unpublished observations). It has also been suggested that individual variation in response to amphetamine is related to levels of tonic 5-HT release (Segal and Kuczenski 1987; Kuczenski and Segal 1989). Global 5-HT depletion in impulsive individuals may have interacted with an already compromised 5-HT system, thus more effectively blocking the effect of amphetamine. Further studies investigating whether animals showing high levels of impulsive choice demonstrate altered neurotransmitter levels or patterns of receptor expression may reveal more information regarding the neurobiological systems underpinning this kind of impulsive behaviour.

In conclusion, the data presented here suggest an important role for the serotonergic system in the action of amphetamine to decrease impulsive choice, most likely via interactions with the dopaminergic system. Neuroimaging studies of patients with ADHD have revealed abnormalities in the dopaminergic system (Ernst et al. 1998; Dougherty et al. 1999; Krause et al. 2000), which could be related to suggestions that the behavioural symptoms of ADHD are caused by an elevated reward threshold (Haenlein and Caul 1987; Barkley 1989; see Solanto 1998 for review). The beneficial effects of amphetamine in treatment of these symptoms may be related to its ability to potentiate the importance of reward and reward-related stimuli in the control of behaviour. Improved understanding of the interactions between the 5-HT and DA systems in the control of impulsivity could lead to further insight into the nature and remediation of disorders such as ADHD.

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