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ORIGINAL INVESTIGATION

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Differential involvement of serotonin and dopamine systems in cost-benefit decisions about delay or effort

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Abstract *Rationale:* Although tasks assessing the role of dopamine in effort-reward decisions are similar to those concerned with the role of serotonin in impulsive choice in that both require analysis of the costs and benefits of possible actions, they have never been directly compared. *Objectives:* This study investigated the involvement of serotonin and dopamine in two cost-benefit paradigms, one in which the cost was delay and the other in which it was physical effort. *Methods:* Sixteen rats were trained on a T-maze task in which they chose between high and low reward arms. In one version, the high reward arm was obstructed by a barrier, in the other, delivery of the high reward was delayed by 15 s. Serotonin and dopamine function were manipulated using systemic pCPA and haloperidol injections, respectively. *Results:* Haloperidol-treated rats were less inclined either to exert more effort or to countenance a delay for a higher reward. pCPA had no effect on the performance of the rats on the effortful task, but significantly increased the rats' preference for an immediate but smaller reward. All animals (drug treated and controls) chose the high reward arm on the majority of trials when the delay or effort costs were matched in both high and low reward arms. *Conclusion:* A dissociation was found between the neurotransmitter systems involved in different types of cost-benefit decision making. While dopaminergic systems were required for decisions about both effort and delay, serotonergic systems were only needed for the latter.

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Introduction

Many neurological patients have difficulties with decision making, particularly in situations in which they have to evaluate different behavioural options on the basis of their respective costs and benefits (Rahman et al. 2001). This is true not only of patients with lesions to parts of prefrontal cortex (Bechara et al. 1994; Rogers et al. 1999; Manes et al. 2002), but also of patients who suffer from neuropsychiatric disorders such as the frontal-variant of frontotemporal dementia (Rahman et al. 1999), unipolar and bipolar depression (Murphy et al. 2001) and substance abuse (Rogers et al. 1999; London et al. 2000). Animal models may help produce a better understanding of the neurobiological causes underlying these decision-making problems. In the rat, cost-benefit evaluation can be studied with paradigms that offer the animal a choice between a high reward obtainable at high cost and a low reward obtainable at low cost. The type of cost involved could be, for example, either increased physical effort or delay of reinforcement.

Mesolimbic dopamine fibres projecting to the nucleus accumbens (NAc) have been implicated in effort-based cost-benefit decision making. Blocking dopamine transmission using either systemic injections of the D_2 antagonist, haloperidol, or following 6-hydroxydopamine (6-OHDA) lesions of the NAc induced rats to shift their behaviour towards choosing freely available lab chow over preferred food which was only obtainable by lever pressing (Salamone et al. 1991; Cousins and Salamone 1994; Sokolowski et al. 1998). Moreover, on operant tasks using fixed ratio schedules, differences between 6-OHDA lesioned animals and control animals were only found for higher fixed ratio schedules (e.g. FR5, FR16, FR64, but not FR1: Aberman and Salamone 1999; Ishiwari et al. 2004). The lesioned animals were significantly less inclined to

press the lever for reward when the ratio of required lever presses to rewards was increased. The shift in preference towards lower ratio schedules was also observed when differences in the frequency of reinforcement on high and low ratio schedules were reduced, using a paradigm on which for both schedules the delivery of reward was intermittent and of approximately the same reinforcement density (Salamone et al. 2001; Correa et al. 2002).

Evidence for the involvement of dopamine in effort-based cost-benefit evaluations has also been obtained using a T-maze task. Rats were given the choice between a small number of food pellets in one arm and a larger number of food pellets in the other arm. Access to the high reward arm, however, could only be obtained after climbing a barrier. Blocking dopamine function using either systemic haloperidol or following 6-OHDA depletions of NAc led to rats choosing the low effort/low reward arm substantially more often than controls (Salamone et al. 1994; Cousins et al. 1996).

Similar T-maze paradigms to those used for studying effort-based decisions have also been employed in studies of impulsivity. The rat is again given a choice between a larger and a smaller reward, but this time, the cost associated with the former is in terms of a delay before reward delivery. Serotonin has been implicated in delay-based cost-benefit decisions of this kind. Several studies have reported that drugs which directly or indirectly reduce serotonin function increase the frequency with which animals choose an immediate small reward over a larger delayed reward (e.g. Thiebot et al. 1985; Bizot et al. 1999). Conversely, administration of serotonin re-uptake inhibitors causes rats to choose the arm with the larger delayed reward more often than vehicle-injected controls (Bizot et al. 1988). Analogous studies using operant paradigms have also shown that manipulations of serotonin function affect rats' choices between small immediate and larger delayed rewards (Evenden and Ryan 1996, 1999). In addition, rats with lesions of the dorsal and medial raphé nuclei, which represent the origins of the serotonergic projections to the frontal cortex, were found to be less inclined than sham lesioned animals to choose a larger but delayed reward over a smaller, immediate reward (e.g. Wogar et al. 1993; Mobini et al. 2000b).

Taken together, these studies suggest a role for both dopamine and serotonin in decision making. It remains to be established, however, whether both neurotransmitter systems are equally implicated in effort-based and delay-based cost-benefit decision making tasks using these T-maze paradigms. The first aim of the present study therefore was to determine whether serotonin, in addition to its involvement in decisions where the cost is in terms of delay of reinforcement, is also important for decisions about whether to exert increased effort for greater reward. Conversely, the second aim was to establish whether dopamine, in addition to its role in effort-based decision making, is equally important for delay-based cost-benefit decision making using the T-maze task. There is evidence consistent with a role for dopamine in aspects of impulsivity, and, more specifically, in delay discounting (Cole and Robbins 1989; Wade et al. 2000), though various tests of impulsivity may assess diverse cognitive processes (Evenden 1999).

The present study compared the effects of blocking either dopamine or serotonin function on two different versions of the T-maze task, both of which have been used previously for studying decision making where the cost is in terms of either increased effort or delayed reward (Thiebot et al. 1985; Bizot et al. 1999; Salamone et al. 1994; Walton et al. 2002, 2003). The rat was given the choice between a high reward arm and a low reward arm. Depending on the task, it either had to exert physical effort by climbing a barrier to obtain the high reward or wait until a delay period of 15 s had elapsed. The two versions of the T-maze task thus allowed decision making with both kinds of cost (effort versus delay of reinforcement) to be compared using very similar experimental paradigms. Serotonin levels were manipulated using systemic injections of *para*-chlorophenyl-alanine methyl ester (pCPA), a serotonin synthesis blocker. Dopamine function was blocked by the D_2 receptor antagonist haloperidol.

Materials and methods

Animals

Sixteen male Lister hooded rats served as subjects throughout the main series of experiments (1A, 1B, 2A and 2B). They were approximately 7 months old at the beginning of testing. All of the rats were experimentally naive prior to training on the cost-benefit T-maze task. They were extensively familiarised with the barrier task (Experiment 1A) having served as the unoperated control group in another experiment (see Walton et al., in press). The animals were housed in pairs under standard conditions (12 h light/dark cycle, lights on between 7 a.m. and 7 p.m.). They were kept at about 85% of their free-feeding weight throughout the study. Water was available ad libitum. Treatment and care of the animals was in accordance with the Principles of laboratory animal care and the United Kingdom Animals Scientific Procedures Act (1986).

An additional group of 12 male Lister hooded rats served as subjects in a biochemical assay to determine the extent of the serotonin depletion following the pCPA treatment schedule used in the behavioural studies.

Apparatus

The T-maze consisted of three wooden arms (a start arm and two goal arms) which were 60 cm long, 10 cm wide and 40 cm high. Metal food wells (3 cm in diameter, 1 cm high) were placed at each end of the two goal arms, 3 cm from the wall. The maze was elevated 80 cm above floor level and painted in a uniform grey colour. A video camera was mounted on the ceiling above the maze to allow recording of the rats' performance on certain days of testing in order to obtain latency measurements. On forced

trials a wooden block (30 cm high and 10 cm wide) was used to stop the animal from entering a particular goal arm.

Two different versions of the T-maze task were used (see Fig. 1). Experiment 1 was concerned with cost-benefit decision making where the cost was in terms of increased effort (Fig. 1a). A triangular wire mesh barrier was placed in the high reward goal arm so that the rat first had to overcome a vertical side of 30 cm, before then descending down the slanted side towards the food (45 mg Noyes food pellets; Formula A/I; P.J. Noyes and Co., Lancaster, N.H., USA). Performance was also assessed under conditions in which a second barrier with the same attributes was placed in the low reward goal arm.

In experiment 2 the cost was in terms of delayed reinforcement (see Fig. 1b). Four wooden guillotine doors were built into the maze. In each goal arm there was one door just in front of the food well (10 cm from the end wall of each goal arm) and one near the entrance of the goal arm (10 cm from the junction of the start arm and the goal arms). They were painted the same grey colour as the rest of the maze.

Drugs

Based on previous findings (Walton et al., in press), haloperidol was administered at a dose of 0.2 mg/kg. Ampoules of Haldol (haloperidol dissolved in lactic acid and water at a concentration of 5 mg/ml; Janssen-Cilag Ltd, High Wycombe, UK) were further diluted in 0.9% saline to give a final concentration of 0.2 mg/ml. The drug was then injected IP at a volume of 1 ml/kg 50 min before the start of testing. Saline (0.9%; 1 ml/kg) was injected as a vehicle control.

pCPA (Sigma-Aldrich; Poole, UK) was injected IP at a dose of 300 mg/kg (dissolved in 0.9% saline at a volume of 10 ml/kg). Again, saline (0.9%; 10 ml/kg) served as the vehicle control. Each rat received two injections, 48 h and 24 h before the start of testing. This regimen has been repeatedly shown to reduce levels of serotonin and its metabolite 5-hydroxyindoleacetic acid (5-HIAA) by more than 85% in frontal cortex and hippocampus (Castro et al. 2003; Hajos et al. 1998), and for up to 7 days (Jakala et al. 1992). To verify this, an additional group of six animals similarly received two injections of pCPA (300 mg/kg) 24 h apart. A further six rats received saline vehicle injections. Twenty-four hours after the second injection (corresponding to the start of behavioural testing) the animals were killed and tissue samples from frontal cortex, striatum and hippocampus were removed and frozen for subsequent measurement of serotonin and 5-hydroxyindoleacetic acid (5-HIAA) levels (for methods, see Hajos and Sharp 1996; McQuade and Sharp 1995).

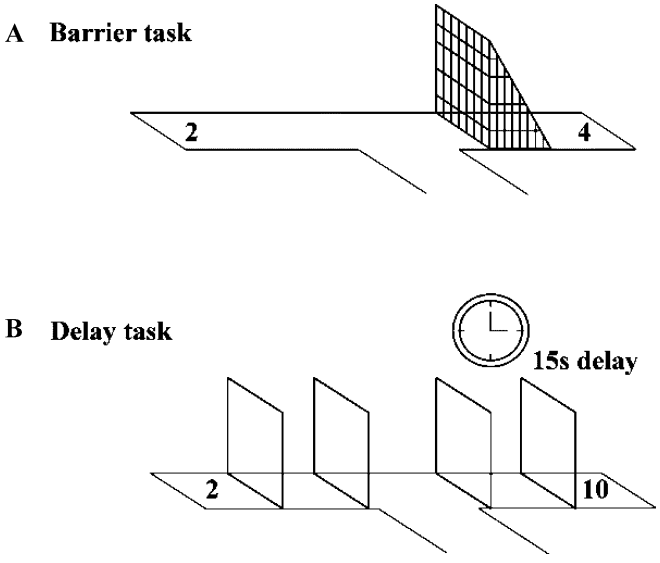

Fig. 1 Diagram illustrating the experimental set-ups for both the barrier (experiment 1) and delay (experiment 2) versions of the T-maze cost-benefit decision-making task. **a** On the barrier task the rat had to choose between climbing a barrier for a four pellet reward or no barrier for a two pellet reward. **b** On the delay task, the rat had to choose between an immediate reward of two pellets or a larger ten pellet reward which was delayed by 15 s

Procedure

In all experiments, the rats were tested in batches of four with an inter-trial interval of approximately 5 min. The location of the high reward arm was counterbalanced with respect to treatment groups, being always on the left for half of the animals and always on the right for the other half. The results were analysed with ANOVAs using Huynh-Feldt corrections where appropriate.

Experiment 1A: haloperidol on the barrier task

The rats were first trained on the barrier task. The animals were given the choice between either climbing the barrier for four food pellets in the high effort/high reward goal arm, or receiving two food pellets in the low effort/low reward arm in which no barrier was present (Salamone et al. 1994; Walton et al. 2002, 2003). As the rats had been trained on this task 2 months previously as part of a separate experiment, no lengthy habituation period was required. Instead they were simply reminded of the procedure by running them for several days on a series of forced trials, during which they had no choice of which arm to enter because one of the goal arms was blocked. The rats were pseudorandomly forced into either the high or low reward arm (five trials to each per day). Pre-drug testing on the task proper then began. On each day of testing the rats first received two forced trials (one to each side). They then received ten choice trials during which the number of times the rat chose the high reward arm was recorded. This procedure in which two forced trials preceded ten choice trials was used throughout the entire study unless otherwise specified.

Drug manipulations began as soon as all animals consistently chose the high reward on at least 75% of trials. The effects of haloperidol on decision making were assessed using a within-subjects design. On test day 1, eight rats received haloperidol and eight received saline. The assignment of animals to injection conditions was counterbalanced with respect to pre-drug performance and the left/right orientation of the high/low reward arms. Twenty-four hours after each injection day, the rats were retrained on the task. They received ten forced trials (five to both the high and low reward arms) and ten choice trials: at this point all animals were once again choosing the high reward arm on at least 75% of the trials. On the following day, a second test session was conducted but with the allocation of animals to the drug and vehicle conditions now reversed.

For the barrier control task, a second barrier was then added to the low reward arm. The rats could still choose between two food pellets in the low reward arm and four food pellets in the high reward arm, but now there was a 30 cm barrier in each arm (Walton et al. 2002). The rats were run for 2 days on this two barrier task prior to receiving any drug treatments. The rats were again divided into two groups, counterbalanced according to performance and left/right orientation of the high/low reward arms. Haloperidol and vehicle were again administered according to a within-subjects design. Performance of the rats was videotaped in order to obtain latency measurements. The times taken to get (i) from the starting position to the bifurcation of the maze (phase I), (ii) from there to the top of the barrier (phase II), and (iii) from the top of the barrier to the food (phase III) were recorded.

Experiment 1B: pCPA on the barrier task

The animals were then re-trained on the single barrier task until they were again choosing the high reward arm on at least 75% of trials. The effects of pCPA on decision making were assessed using a between subjects design. The rats were newly assigned to groups according to pre-drug performance and the left/right orientation of the high/low reward arms. Half of the animals received two injections of pCPA 24 h apart, the other half received saline. Testing on the single barrier task then began 24 h after the second injection. The rats were tested for 2 days on the single barrier task (days 1–2 post-pCPA; ten choice trials per day).

On the following day (day 3 post-pCPA), the barrier control task was run. A second identical barrier was now placed in the low reward arm. After two forced trials (one to each of the high and low reward arm), the rats received 20 choice trials with barriers in both goal arms during which preference for the high reward arm was recorded. Latency measurements were obtained as in experiment 1A.

Experiment 2A: haloperidol on the delay task

For the second set of experiments which examined decision making when the cost was in terms of delayed reinforcement, the animals could now choose between an immediate smaller reward and a delayed larger reward. The spatial location of the high and low reward arms remained unchanged, although the high reward arm now contained ten pellets and the low reward arm two pellets (Thiebot et al. 1985; Bizot et al. 1999). When the rat chose the high reward arm, it was locked in the goal arm by means of the pair of sliding doors. After 15 s the sliding door adjacent to the food well was opened and the rat was allowed to consume the reward. In contrast, when the rat chose the low reward arm, the door adjacent to the food was opened as soon as the door at the entrance of the goal arm was closed (i.e. as soon as the animal was fully inside the arm).

Several days were required to train the rats to this new procedure so that they were choosing the delayed high reward option on the majority of trials. As in experiment 1, the effects of haloperidol on the delay task were assessed using a within-subjects design. After 2 days of drug free testing on the task, half the animals were injected with haloperidol and half with saline. On the second day of drug testing the assignment of animals to drug and vehicle groups was reversed. All rats received 1 day of drug free testing in between the 2 injection days, consisting of ten forced and ten choice trials interleaved. Testing with haloperidol on the delay task began 2 weeks after the previous pCPA treatment. The assignment of animals to drug and vehicle groups on the first day of drug testing was counterbalanced as before and with respect to previous pCPA or vehicle treatment.

A 15 s delay was then also introduced in the low reward arm (delay control task). The rats could still choose between two food pellets in the low reward arm and ten food pellets in the high reward arm, but now there was an equal delay in reinforcement in each arm. The rats received 2 days of drug-free testing prior to further drug manipulations. As before, on the first day of drug testing half the animals were injected with haloperidol and half with saline. On day 2 of drug testing, the assignment of animals to drug and vehicle groups was reversed.

Experiment 2B: pCPA on the delay task

The rats then underwent 3 days of drug-free testing with a delay of 15 s in the high reward arm and immediate reinforcement in the low reward arm. As before, the effects of pCPA on decision making were assessed using a between-subjects design. Half of the animals received two injections of pCPA 24 h apart, the other half received two injections of saline. The assignment of animals to pCPA and vehicle groups was identical to experiment 1B. Testing on the single delay task then began 24 h after the

second injection and the rats were tested for 3 consecutive days (days 1–3 post-pCPA; ten choice trials per day).

Several weeks later the rats were retrained as drug free animals on the single delay version of the task. Further injections of pCPA or saline were then administered, after which the rats then received 3 days testing on the delay control task (days 1–3 post-pCPA injection) with a 15 s delay now introduced in the low reward arm as well as the high reward arm. Animals were re-assigned to vehicle and pCPA groups according to a fully counterbalanced design on the basis of both prior drug history (previously pCPA or vehicle) and performance during the drug-free testing immediately prior to injections.

Results

Experiment 1A: haloperidol on the barrier task

The mean percentage of high effort/high reward arm choices obtained for haloperidol and saline groups on the barrier tasks is displayed in Fig. 2 (experiment 1A). When tested with just a single barrier in the high reward arm, haloperidol injected animals chose the high effort/high reward arm significantly less often than saline treated animals. When a second barrier was then also placed in the low reward arm, the haloperidol treated rats now showed a much stronger preference for the high reward arm (more than 80% high reward arm choices), although still slightly less so than the saline-injected controls. One animal stopped running on the task during the pre-drug training phase. In addition, two rats failed to run on the task after haloperidol treatment. This analysis therefore included data from 13 subjects. An ANOVA revealed a main effect of task [single barrier versus double barrier control; $F(1,12)=28.96$; $P<0.001$], a main effect of drug [$F(1,12)=31.27$; $P<0.001$], and a task×drug interaction [$F(1,12)=8.06$; $P<0.05$]. From Fig. 2 it is clear that this is explained by a greater impairment on the barrier task as opposed to the double barrier control task. Nevertheless subsequent analyses of simple main effects confirmed that there were significant impairments with haloperidol for both versions of the barrier task [$F(1,12)>9.72$; $P<0.01$]. Analysis of simple main effects also revealed an effect of task (single barrier versus double barrier) for haloperidol treatment [$F(1,12)=18.99$; $P<0.005$], although this did not quite reach statistical significance for vehicle injection [$F(1,12)=4.46$; $0.10>P>0.05$].

Analysis of the latency to complete trials revealed an interaction between drug treatment and the three phases of trials [$F(2, 24)=7.88$, $P<0.005$]. Although haloperidol caused a slight increase in time taken to climb the barrier (phase II), from Fig. 3 (left panel) it is clear that haloperidol particularly increased latencies in the first and last phases of trials.

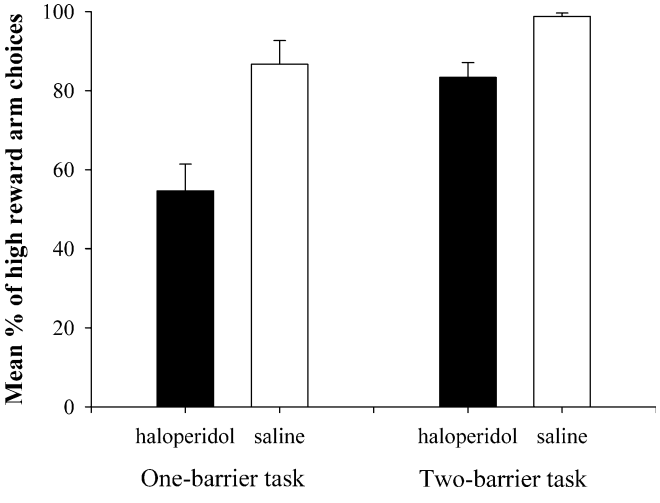

Fig. 2 Mean percentage of high reward arm choices (+SEM) for haloperidol (*black bars*) and saline (*white bars*) injected animals on the barrier task (*left-hand side*) and the barrier control task (*right-hand side*) (experiment 1A). Data were collapsed across days

Experiment 1B: pCPA on the barrier task

Tissue levels of serotonin (pmol/mg tissue; mean±SEM) in frontal cortex, hippocampus and striatum (2.81±0.59, 1.42±0.06 and 1.90±0.24, respectively) were reduced by 85–95% following pCPA treatment (0.18±0.01, 0.09±0.01 and 0.28±0.02, respectively). Levels of 5-HIAA (pmol/mg tissue; mean±SEM) were similarly depleted in pCPA treated animals (0.06±0.01, 0.06±0.01 and 0.10±0.01 for frontal cortex, hippocampus and striatum, respectively) relative to rats that had received saline injections (1.64±0.35, 1.68±0.11 and 1.79±0.21, respectively).

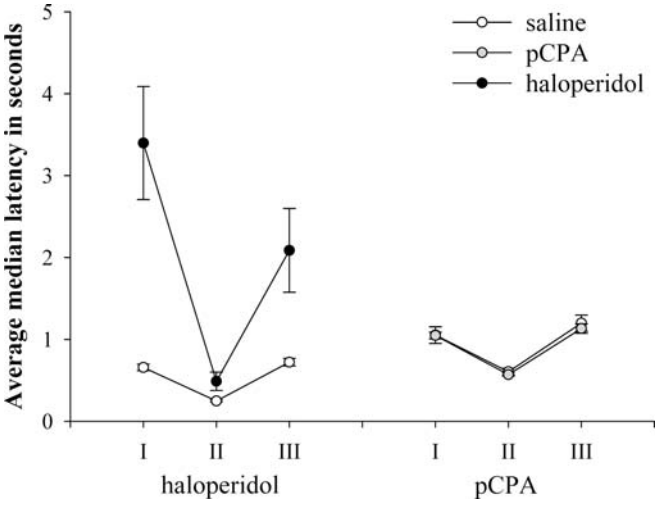

Fig. 3 Mean latency (±SEM) on the barrier control task after haloperidol (*left panel*; experiment 1A) and pCPA (*right panel*; experiment 1B) injections. Only data from high reward trials are displayed. In the case of haloperidol, data from 2 days has been combined. I=phase I (time it took the animal from the start to the choice point); II=phase II (time it took the animal from the choice point to the top of the barrier); III=phase III (time it took the animal from the top of the barrier to the food)

Figure 4 shows the mean percentage of trials on which the rats chose the high effort/high reward arm, before and after pCPA injection, on the barrier task. Serotonin depletion did not affect the frequency with which rats chose the high effort/high reward arm in preference over the low effort/low reward arm. An ANOVA confirmed the absence of any main effect of group or interactions involving group ($P>0.20$). The pCPA and saline groups also did not differ when a second barrier was placed in the low reward arm ($P>0.05$). Furthermore, pCPA treatment had no effect on mean trial latencies during performance of the two-barrier version of the task ($P>0.20$; Fig. 3, right panel).

Experiment 2A: haloperidol on the delay task

The effect of haloperidol on the delay task is displayed in Fig. 5. Following injection of haloperidol, rats were less likely to choose the delayed/high reward arm than controls. When reinforcement in the low reward arm was also delayed by 15 s, the frequency with which haloperidol treated rats chose the high reward arm was now much higher (greater than 80%), although as with the barrier task the drug treated animals still chose the high reward arm less often than the controls. One haloperidol treated animal failed to run during this stage of testing: the analysis therefore consists of data from 15 subjects. The ANOVA revealed a main effect of task [single delay versus double delay control; $F(1,14)=19.19$; $P<0.005$], a main effect of drug [$F(1,14)=23.75$; $P<0.001$], and a task×drug interaction [$F(1,14)=6.43$; $P<0.05$]. From Fig. 5 it is clear that the interaction is explained by a greater impairment on the single delay task than on the double delay control task. Nevertheless, analysis of simple main effects confirmed that there were significant effects of haloperidol for both versions of the delay task [$F(1,14)>6.29$; $P<0.05$]. Analysis of simple main effects also revealed an effect of task (single delay versus double delay control) for both vehicle [$F(1,14)=9.33$; $P<0.01$] and haloperidol treatment [$F(1,14)=18.06$; $P<0.005$].

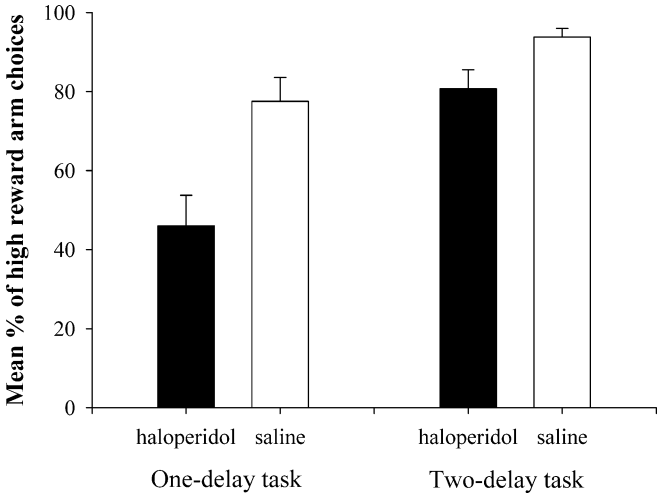

Fig. 5 Mean percentage of high reward arm choices (+SEM) for haloperidol (*black bars*) and saline (*white bars*) injected animals on the delay task (*left-hand side*) and the delay control task (*right-hand side*) (experiment 2A). Data were collapsed across days

Experiment 2B: pCPA on the delay task

The effects of serotonin depletion on the delay task can be seen in Fig. 6. pCPA treated rats chose the delayed/high reward arm less often than the saline controls. An ANOVA revealed a significant drug group×block interaction [$F(1,14)=4.64$; $P<0.05$], as well as significant main effect of block [pre-injection versus post-injection; $F(1,14)=31.36$; $P<0.001$], reflecting a small change in performance across both groups after injection. Analysis of simple main effects confirmed that the pCPA and saline treated animals differed significantly post-injection [$F(1,19)=4.46$; $P< 0.05$]. When a delay was also introduced in the low reward arm (Fig. 7), both pCPA and saline groups showed an increased and equivalent preference for the high reward arm ($P>0.10$; saline versus pCPA for double delay control task).

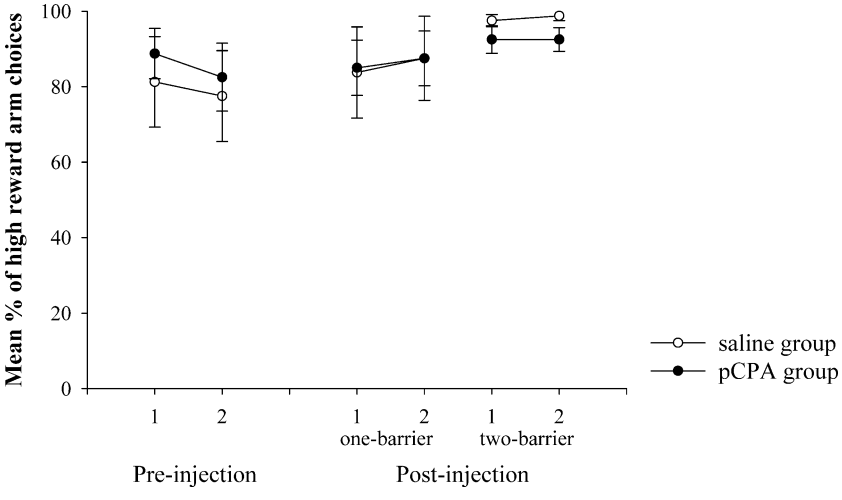

Fig. 4 Mean percentage of high reward arm choices (±SEM) for serotonin manipulations on the barrier task (experiment 1B). Depicted are 2 days of data collected before pCPA injections and data collected after pCPA injections (two blocks of ten trials on the barrier task and two blocks of ten trials on the barrier control task)

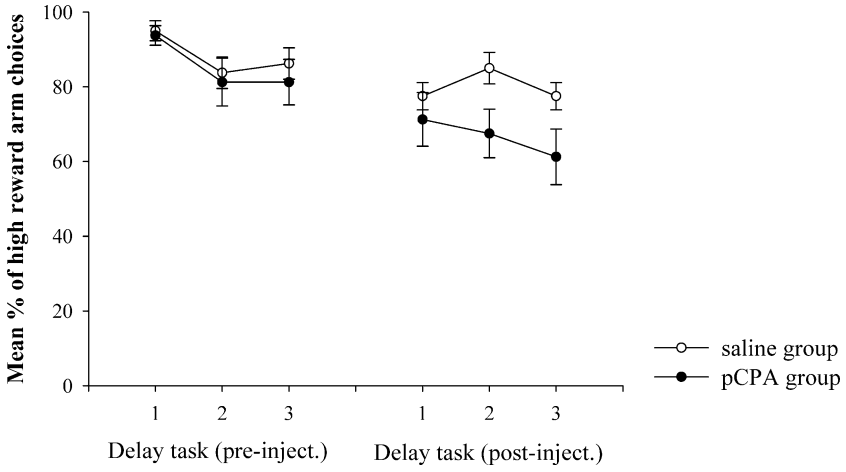

Fig. 6 Mean percentage of high reward arm choices (±SEM) for serotonin manipulations on the delay task (experiment 2B). Depicted are 3 days before pCPA injections (pre-injection) and 3 days after pCPA injections (post-injection, pCPA: *filled circles*, vehicle: *empty circles*)

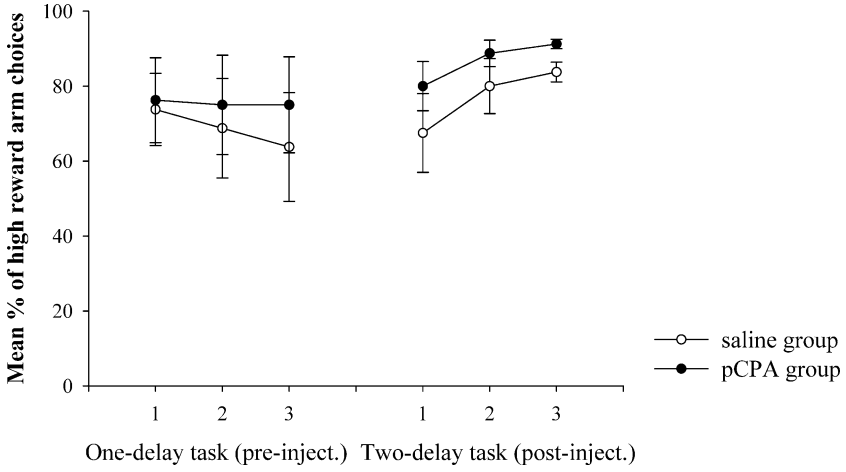

Fig. 7 Mean percentage of high reward arm choices (±SEM) for serotonin manipulations on the delay control task (experiment 2B). Depicted are 3 days before pCPA injections (pre-injection) and 3 days after pCPA injections

Discussion

The present study examined the roles of dopamine and serotonin in both effort-based and delay-based cost-benefit decision making. The effects of manipulating the two neurotransmitter systems were tested on two cost-benefit decision making tasks using the T-maze, one in which the cost was effort (Salamone et al. 1994) and one in which the cost was delay (Thiebot et al. 1985). In agreement with the previous report of Bizot et al. (1999), serotonin depletion (in excess of 85% depletion) resulted in animals being more likely to choose the smaller but immediate reward, and less likely to choose the larger but delayed reward. In contrast, serotonin-depleted rats were as inclined as controls to put in increased effort (climbing a 30 cm barrier) for a larger reward (Table 1). Both the effort-based and delay-based decision making tasks were sensitive to dopamine receptor blockade. Animals that had received the D_2 receptor antagonist haloperidol chose the high effort/high reward arm significantly less often than vehicle injected controls, in agreement with the previous report of Salamone et al. (1994). In addition, they also chose the smaller but immediate reward more often than controls in agreement with Wade et al. (2000). These results therefore demonstrate a partial dissociation of the roles of serotonin and dopamine in cost-benefit decision making. While serotonin is implicated when the cost is in terms of delay but not when it is in terms of effort, dopamine is implicated in deciding about both effort and delay costs.

Table 1 Overview of the findings from all the drug and task manipulations. *Ticks* indicate significant effect of drug administration

	Haloperidol		PCPA	
	Decision	Control	Decision	Control
Effort	✓	✓	✗	✗
Delay	✓	✓	✓	✗

A role for serotonin in delay-based but not effort-based decision making

The results of the present series of experiments therefore suggest a selective role for serotonin in decision making tasks where the animal has to choose between a smaller but immediate reward and a larger but delayed reward. Importantly, when a 15 s delay was also introduced in the low reward arm, pCPA-treated rats increased their preference for the high reward arm and were indistinguishable

from the controls. This result argues strongly that the effect of serotonin depletion is in terms of reducing animals' tolerance of a delay for increased reward, and against the possibility that it is due to an effect of pCPA on some other aspect of task performance such as memory for the location of the high reward or appetite for reward pellets. Furthermore, the normal performance of the pCPA treated rats on the barrier task also argues against an effect of the drug on some non-specific aspect of performance such as memory or appetite. Indeed, the dissociation between the effect of pCPA on the delay task and the lack of an effect on the barrier task suggests that serotonin is selectively involved in the ability of animals to tolerate a delay in order to obtain a larger reward. This implies that serotonin is involved in a specific aspect of decision making associated with a specific kind of cost, namely delay of reinforcement.

We cannot completely rule out the possibility that the barrier task was simply less sensitive to serotonin depletion than the delay task. Nevertheless, a number of points argue against this possibility. First, there is absolutely no sign of even any marginal effect of pCPA treatment on the barrier task; the performances of both groups were almost identical. It therefore seems extremely unlikely that the lack of an effect is due to insufficient power in the experiment. Second, the absence of an effect of pCPA on the barrier task is not because the dosing regimen used was ineffective. This treatment schedule produced a greater than 85% reduction in serotonin levels in frontal cortex, striatum and hippocampus, and was sufficient to disrupt performance on the delay task. Third, the absence of an effect of pCPA on the barrier task is not because the barrier task itself is insufficiently sensitive. In addition to the clear effects of haloperidol in the present study (see also Salamone et al. 1994), we have also shown dramatic effects after anterior cingulate cortex lesions, using exactly the same apparatus and testing parameters (Walton et al. 2002, 2003). It seems, therefore, that the crucial factor in terms of a role for serotonin is the nature of the cost associated with the task.

A selective role for serotonin specifically in delay-related cost-benefit evaluations has been reported previously. Mobini et al. (2000b) demonstrated that lesions of the ascending serotonergic pathways affected choice behaviour between a small but immediate reward and a larger but delayed reinforcement but not between small certain rewards and large uncertain rewards. Thus, like effort-based cost-benefit decision making, serotonin does not seem to be necessary for choices concerned with the probability of reward delivery. There is, however, some evidence that, under some circumstances, serotonin depletion may also impair the perception and discrimination of reward magnitudes (Rogers et al. 2003). However, it seems unlikely that the deficit following serotonin depletion on the delay task in the present study (experiment 2B) is due to impaired perception and discrimination of reward magnitudes. The fact that pCPA treated animals behaved like controls and successfully selected the high reward arm on the majority of trials during both (i) the barrier tasks, and (ii) the double delay task, suggests that these animals are perfectly capable of perceiving and discriminating different reward magnitudes.

A more general role for dopamine in decision making tasks

Rats that received haloperidol were more inclined to choose the low cost/low reward option on both versions of the task, irrespective of whether the cost was in terms of effort or delay of reinforcement. These results are in agreement with several previous studies which have implicated dopamine both in the ability to put in more effort to obtain a greater reward (Salamone et al. 1994; Salamone and Correa 2002), and also the ability to withhold impulsive responding (Cole and Robbins 1989; Wade et al. 2000; Peterson et al. 2003). The effect of haloperidol on the barrier task is unlikely to be due to the delay imposed by climbing the barrier, with latency data showing that its duration is negligible even in haloperidol injected rats. This also argues against a simple motor account. Furthermore, the performance of haloperidol treated rats on the two barrier task, during which they demonstrated that they had retained the ability to climb the barrier, also argues against such an account.

The role of dopamine in decision making tasks is not, however, entirely independent of the nature of the cost. For example, it has recently been shown that dopamine might be differentially involved in calculating the cost of physical work when it is concerned with the number of lever presses that have to be performed, but not when it is concerned with how much force is required in order to press the lever (Ishiwari et al. 2004). This raises the possibility that accumbens dopamine might be required for putting in increased effort for increased reward but only in terms of sustained effort and not in terms of more forceful responding.

It is also worth noting that although the frequency with which haloperidol treated animals chose the high reward arm increased dramatically when the cost (either in terms of effort or delay) was subsequently equated in both the high and low reward arms, the level of responding to the high reward arm was still significantly lower than that displayed by the controls. The reason for this is not immediately obvious. One possibility is that haloperidol might have an effect on processing of reward value. It has been demonstrated that orbitofrontal cortex lesions, for instance, can affect both the evaluation of a delay-based cost and the sensitivity to the ratio of available rewards (Kheramin et al. 2002). Unfortunately, the nature of the T-maze paradigm used here means that it is difficult to establish whether haloperidol contributed to changes in the perception of the relevant costs and benefits. Furthermore, it could be that the effects of haloperidol on task performance may extend beyond decision making. A large body of evidence indicates that haloperidol, along with other anti-psychotics, may influence the reinforcing nature of stimuli (Wise 1982; Wise and Bozarth 1987; Mobini et al. 2000a) and impact on various motor processes (Horvitz

and Ettenberg 1988; Liao and Fowler 1990). Consistent with this possibility, it is also worth noting that the haloperidol injected rats were slower to complete running a trial on the two barrier version of the task than vehicle injected controls (see also Cousins and Salamone 1994; Salamone et al. 1994). This is consistent with a number of demonstrations of the involvement of dopamine in wide ranging aspects of motivation and response initiation. Importantly, however, the highly significant interaction between drug treatment and task for both the effort and delay control versions (i.e. one barrier versus two barrier and one delay versus two delays) suggests that at least part of the effect of disrupting dopamine transmission is in terms of a change in decision making.

Conclusions

In conclusion, the present study demonstrates a clear dissociation between the neurotransmitter systems involved in two different types of cost-benefit decision making. While dopamine is important for decisions concerned with both effort and delay, serotonin is only crucial for evaluations concerned with delay. It is also possible that these different decision making processes depend on partially dissociable neuroanatomical circuits (Cardinal et al. 2001; Mobini et al. 2002; Walton et al. 2002, 2003).

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