

Noradrenergic versus dopaminergic modulation of impulsivity, attention and monitoring behaviour in rats performing the stop-signal task

Possible relevance to ADHD

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Abstract

Rationale Deficient response inhibition is a prominent feature of many pathological conditions characterised by impulsive and compulsive behaviour. Clinically effective doses of catecholamine reuptake inhibitors are able to improve such inhibitory deficits as measured by the stop-signal task (SST) in humans and other animals. However, the precise therapeutic mode of action of these compounds in terms of their relative effects on dopamine (DA) and noradrenaline (NA) systems in prefrontal cortical and striatal regions mediating attention and cognitive control remains unclear.

Objectives We sought to fractionate the effects of global catecholaminergic manipulations on SST performance by using receptor-specific compounds for NA or DA. The results are described in terms of the effects of modulating specific receptor subtypes on various behavioural measures such as response inhibition, perseveration, sustained attention, error monitoring and motivation.

Results Blockade of $\alpha 2$ -adrenoceptors improved sustained attention and response inhibition, whereas $\alpha 1$ and $\beta 1/2$ adrenergic receptor antagonists disrupted go performance and sustained attention, respectively. No relevant effects were obtained after targeting DA D1, D2 or D4 receptors, while both a D3 receptor agonist and antagonist improved

post-error slowing and compulsive nose-poke behaviour, though generally impairing other task measures.

Conclusions Our results suggest that the use of specific pharmacological agents targeting $\alpha 2$ and β noradrenergic receptors may improve existing treatments for attentional deficits and impulsivity, whereas DA D3 receptors may modulate error monitoring and perseverative behaviour.

Keywords Noradrenaline · Dopamine · Impulsivity · Stop-signal task · Attention · Error monitoring · Response inhibition · Reaction time variability

Introduction

The discovery that drugs increasing catecholamine levels in prefrontal cortex (PFC) improve cognitive and behavioural deficits in disorders characterised by impulsivity (Bradley 1937; Oades 1987) has opened the way for the investigation of the role of dopamine (DA) and noradrenaline (NA) in behavioural inhibition and attention. A key question in the psychopharmacology of impulsive behaviour is whether the effects of anti-impulsivity drugs are mainly mediated by DA, NA or both (de Wit et al. 2002; Eagle et al. 2008; Robbins and Arnsten 2009), although this is not a simple task due to the complex interactions between the two catecholaminergic systems in the PFC (e.g., Antelman and Caggiula 1977; Pan et al. 2004). Noradrenergic projections from the locus coeruleus (LC) and dopaminergic neurons arising from the ventral tegmental area converge in the medial PFC (mPFC; Berger et al. 1974; Lindvall and Bjorklund 1974; Thierry et al. 1973). There, the NA transporter participates in the reuptake of DA (Carboni and Silvagni 2004; Moron et al. 2002; Tanda et al. 1997), compensating for the paucity of dopamine transporter (DAT) sites in this area (Ciliax et al. 1995; Sesack et al. 1998).

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The main goal of the present investigation is to better define the differential contribution of specific noradrenergic and dopaminergic agents on stop-signal task (SST) performance, which has been used extensively in the assessment of motor impulsivity in humans.

The SST measures the ability to stop an already initiated response as well as the speed of the inhibitory processes (i.e., the stop-signal reaction time, SSRT; Logan 1994). Response inhibition is impaired in several psychiatric disorders characterised by impulsive behaviour (Lipszyc and Schachar 2010), especially in patients with attention deficit/hyperactivity disorder (ADHD; Aron and Poldrack 2005; Schachar et al. 1995; Verbruggen and Logan 2008). Stimulant and non-stimulant ADHD medications include methylphenidate and atomoxetine as the prototypical drugs of these two classes, respectively. Both have comparable efficacy in ADHD (Hazell et al. 2011; van Wyk et al. 2012), although psychostimulants remain widely used for this purpose (Wilens 2008). However, their exact mechanism of action is still unknown. Rodent studies have shown that methylphenidate and atomoxetine increase *in vivo* extracellular levels of NA and DA in PFC, whereas only methylphenidate increases subcortical DA levels (Bymaster et al. 2002). Thus, the positive effects of atomoxetine and methylphenidate on SSRT may not be mediated exclusively by NA. Results obtained after the administration of various classes of agonist and antagonists at catecholaminergic receptors may contribute in advancing our understanding of the neural substrates and cognitive functions targeted by clinically effective compounds.

Several studies have investigated effects of adrenoceptor agonists and antagonists on attention and impulsivity in both human and non-human subjects. The α_2 receptor agonist guanfacine has been proposed as a potential treatment for ADHD and as a useful alternative to psychostimulant medication (Scahill et al. 2001; Taylor and Russo 2001). However, previous studies failed to find any improvement of guanfacine on SST performance in humans (Muller et al. 2005) and rats (Bari et al. 2009). α_1 -Adrenoceptor agonists improve sustained attention in rats, whereas α_1 antagonist administration has the opposite effect and abolishes the positive effects of the agonist (Puumala et al. 1997). Antagonists at the α_1 receptor also counteract the beneficial effects of methylphenidate (Berridge et al. 2012) and of the selective NA reuptake inhibitor (SNARI) reboxetine (Liu et al. 2009). In general α_1 -adrenoceptors are thought to influence behavioural states and arousal levels in synergy with β -adrenoceptors (Berridge and Espana 2000; Stone and Quartermain 1999). Thus, α_2 -, α_1 - and β -adrenoceptors may well be implicated in attention and response control as measured by the SST.

Although previous reports have attributed to DA an important role in behavioural activation, rather than inhibition (Eagle et al. 2008), recent findings have demonstrated a more complex role for dopaminergic neurotransmission during SST

performance: blocking D2 receptors in the dorso-medial striatum prolonged SSRT, whereas D1 receptor antagonism in the same area improved stopping (Eagle et al. 2011). Moreover, in humans and other animals, striatal dopamine D2/D3 receptors represent an important link between impulsivity and drug addiction (Caprioli et al. 2013; Dalley et al. 2007; Volkow et al. 2007). Dopamine D3 receptors modulating locomotor activity, and the reinforcing properties of drugs and food (Barik and de Beaufort 2005; Caine and Koob 1993; Daly and Waddington 1993; Duarte et al. 2003a; Pilla et al. 1999), are mainly located in the nucleus accumbens, cerebellum, olfactory tubercle and islands of Calleja (Bouthenet et al. 1991; Sokoloff et al. 1990). However, their exact function is not very well understood. Thus, since DA D1- and D2-like receptors may have opposite effects on impulsivity (Pattij et al. 2007; Pezze et al. 2007; van Gaalen et al. 2006), the systemic administration of selective compounds could produce results not observed previously on SST performance. The dopamine D4 receptor gene (DRD4), coding for a G-protein coupled receptor primarily found in cortico-limbic areas (Ariano et al. 1997; Oak et al. 2000), has been one of the most consistently implicated genes in ADHD (Faraone et al. 2001; Holmes et al. 2002; LaHoste et al. 1996; Langley et al. 2004; Smalley et al. 1998). The DRD4 7-allele repeat has been positively associated with novelty-seeking and impulsivity (Colzato et al. 2010; Congdon et al. 2008), and shown to affect prefrontal grey matter volume in normal and ADHD subjects (Durstun et al. 2005). Because of the high levels of D4 receptors in PFC and its high affinity for NA (Lanau et al. 1997; Newman-Tancredi et al. 1997), it is conceivable that drugs acting at D4 receptors may play a role in response inhibition as measured by the SST.

To better understand the differential contribution of the compounds tested on SST performance, we analysed several additional measures that were not reported in previous investigations using the rat SST. These include the intra-individual variability of reaction times (SDGoRT) and the post-error slowing (PES) that have been extensively investigated in the human literature and are found to be altered in ADHD, impulsive subjects and several pathological conditions (e.g., Adams et al. 2011; Baldwin et al. 2004; Boonstra et al. 2005; Epstein et al. 2006, 2011; Fitzpatrick et al. 1992; Frank et al. 2007; Jones et al. 2008; Kaiser et al. 2008; Kollins et al. 2008; MacDonald et al. 2009; Nandam et al. 2010; Spencer et al. 2009). High intra-individual variability of reaction times is probably the most replicated and stable finding in children with ADHD (Russell et al. 2006) and is considered diagnostic of 'lapses of attention' (Castellanos et al. 2006; Leth-Steensen et al. 2000). Although relatively few studies have reported SDGoRT in rats, reaction time variability seems to predict attentional performance in both normal animals and animals made distractible by experimental manipulations (Hausknecht et al. 2005; Loos et al. 2012;

Narayanan et al. 2006). On the other hand, PES depends on the ability of the subject to adjust ongoing performance on the basis of negative feedback (Rabbitt 1966). PES is thus regarded as a measure of performance monitoring (Botvinick et al. 2001; Kerns et al. 2004) and of the ability to dynamically implement cognitive control over one's behaviour (Gilmour et al. 2012). On trials following stop errors, normal subjects display slower reaction times as an attempt to improve performance. Comparing reaction times before and after a stop error in rats performing the SST produces a measure that is sensitive to pharmacological manipulations, partly confirming its construct validity. Other secondary variables reported that are specific to rodent behavioural testing are the reward collection latency (RCL) and nose-poke perseveration during TO periods (NP/TO), putative measures of motivation and compulsive behaviour, respectively.

Materials and methods

Subjects were male Lister Hooded rats purchased from Charles River, UK, in all the experiments. Rats were housed in groups of four, under a reversed 12:12-h light–dark cycle (lights off at 07:30), and were tested during the dark phase of this cycle. For behavioural training and testing, rats were food-restricted and maintained at 85 % of their free-feeding body weight feeding them 15 g of standard laboratory chow (Purina Rat Chow) on rest days and 10 g on SST days plus reinforcer pellets (Test Diet, 45 mg precision-weight, purified ingredient rodent tablets, Sandown Scientific). Water was freely available except during testing. All experiments were conducted in accordance with the United Kingdom Animals (Scientific Procedures) Act, 1986.

Behavioural training

Rats were trained following a procedure modified from Eagle and Robbins (2003) and written in Visual Basic by A. C. Mar to perform the SST. Subjects were first habituated to the testing apparatus where they learned to collect free pellets from the food well. On the next day, rats were presented with the right lever extended into the box and gradually learned to press it to receive a reward pellet into the food well. Collection of the reward started the subsequent trial with the right lever re-introduced into the box. When the animals reliably completed a session of 100 trials within 30 min on 2 consecutive days, they were presented with the left lever and learned to press it to extend the right one, which will result in the delivery of the reward if pressed within 30 s. The limited hold (LH) — the time available for the rats to press the right lever after pressing the left one — was progressively shortened until the rats reliably completed 100 trials with an LH of 5 s. Stop trials were then introduced using a stop-signal tone (4,500 Hz,

~80 dB) that lasted until the end of the LH period and the number of total trials was set to 210, to be completed within 30 min. The LH and stop-signal duration were made gradually shorter over several sessions until they were kept constant for each animal (final LH was 1.2 s). The tone length was further shortened until it reached 200 ms. For all sessions, the task was initiated when the rats nose-poked into the central food well. During go trials the rats were rewarded with a food pellet for pressing the left then the right lever in sequence before the LH ended. If the rats failed to press the right lever within the LH, they received a time-out period (TO; 5 s darkness, no levers available) and the trial was recorded as a go error. The latency of the go response (go reaction time [GoRT]) is the time elapsed from the left to the right lever presses (Fig. 1).

Stop trials were delivered pseudo-randomly on 20 % of total trials. Stop trials began in the same manner as a go trial, but after pressing the left lever, the stop-signal was played and animals were rewarded if they refrained from pressing the right lever for the duration of the LH. If the rats pressed the right lever after the stop-signal was played, they were punished with a TO, but if they pressed the right lever before the occurrence of a stop-signal in a stop trial, that trial was re-classified as a go trial. During training, stop-signals were played as soon as the rats pressed the left lever (zero delay [ZD]), whereas during baseline and testing sessions stop-signals were played at a pre-determined delay (stop-signal delay [SSD]). Four different SSDs were used (mean GoRT

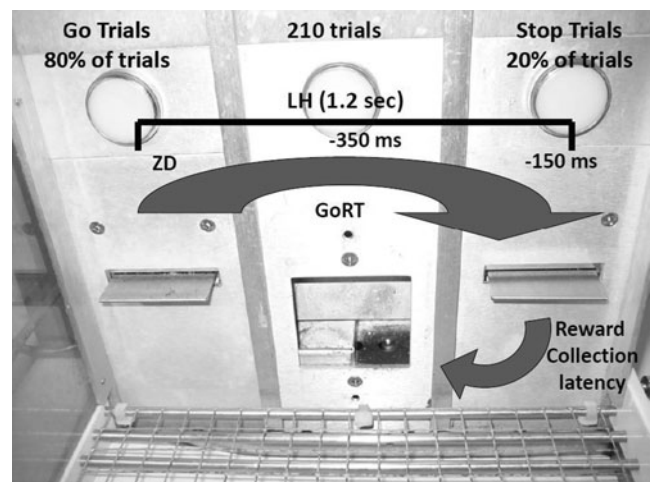


Fig. 1 Schematic illustration of the SST. A standard session consists of 210 trials to be completed within 30 min. On 20 % of the trials (stop trials), a stop-signal will be played after the left lever has been pressed and after a variable stop-signal delay (SSD), which is based on the mean reaction time (*mRT*) of the subjects on previous sessions: zero delay (ZD), *mRT* –350 or *mRT* –150 ms. The stop-signal instructs the animal that the go response to the right lever has to be inhibited in order to obtain the reward. On the remaining 80 % of the trials (go trials), the left and right levers have to be pressed in rapid sequence and the go reaction time (*GoRT*) has to be shorter than the limited hold (*LH*; 1.2 s) in order to receive a reward, which is delivered in the central food well (picture modified from Bari et al. 2011)

[mRT]: –350, –250, –150, and –50 ms) plus ZD pseudo-randomly interspersed among go trials in order to draw the baseline inhibition function (Logan 1994). For test sessions, two SSDs were used and were calculated from the mRTs averaged from three previous baseline sessions at ZD, and these were individual mRTs –350 and –150 ms for all the experiments. Rats were excluded from the experiment if they displayed one of the following characteristics during baseline sessions: (1) inverted inhibition function (i.e., better stop accuracy with longer SSDs); (2) too low or too high average stop accuracy (not within the 20–80 % range; Band et al. 2003); (3) go accuracy below 80 %. Given the complexity of the task and the elevated number of assumptions required by the model to be met by the subjects in order to reliably calculate the SSRT, a relatively high number of animals has to be excluded from the final data analysis, a problem encountered also in experiments with human subjects (e.g., Castellanos and Tannock 2002; Solanto et al. 2001).

SSRT calculation

SSRTs were estimated using the ‘race model’ protocol described by Logan (1994). Briefly, GoRTs were rank-ordered for each SSD and the n th GoRT was selected from the ranked list. The n value was obtained by multiplying the number of GoRTs in the distribution by the probability of responding on stop trials at one given SSD. To obtain the SSRT, the respective SSDs were subtracted from the n th GoRT. SSRTs were then averaged to give a single estimate for each rat for each test session. SSRT and stop accuracy (i.e., percent of stop trials in which the go response was correctly inhibited) were adjusted for the presence of omission errors on go trials (go errors) in order to correct for the stop trials when an inhibition could not be attributed to a successful stop, but could be accounted for by distraction or inattention. In other words, this procedure adjusts for those successful stop trials where the animals would not have completed the go response whatever the trial type (go or stop). Adjustment was performed using the correction factor of Tannock et al. (1989): adjusted $p_{(\text{inhibit})} = \text{observed } p_{(\text{inhibit})} - p_{(\text{omission})} / (1 - p_{(\text{omission})})$, where $p_{(\text{inhibit})}$ is the stop accuracy and $p_{(\text{omission})}$ is 1 – go accuracy, expressed as ratios.

Secondary variables

Dependent variables analyzed in the following experiments include mRT (the latency of the go response averaged over the number of correct go trials), stop accuracy (presented as a percentage of total stop trials) and go accuracy (presented as a percentage of total go trials).

Some additional measures to those previously described for the rat SST were analysed: the within-subject standard

deviation of reaction times during go trials (SDGoRT), which is considered diagnostic of ‘lapses of attention’ (Castellanos et al. 2006; Leth-Steensen et al. 2000) or of an inability to sustain stimulus–response contingencies (Picton et al. 2007). PES, which is derived from the difference between GoRTs on trials immediately *after*, and GoRTs on trials immediately *before*, a stop error. This latter variable is considered as a measure of performance monitoring/adjustment (Gehring et al. 1993; Li et al. 2006b; Schachar et al. 2004) in the human literature but, since rats usually show a *decrease* in GoRT after a failed stop trial, it is usually a negative value (see discussion). A significant change in PES in the experiments here described is interpreted as a change in the capacity of the animal to use errors to guide subsequent behaviour and/or as a variation in speed–accuracy trade-off strategy. Finally, the number of nose-pokes made into the food well during TO periods (total nose-pokes divided by the total number of TO periods; NP/TO), thus when there is no programmed consequence for this action, is considered as a measure of perseveration and the latency to collect the reward from the food well (RCL) is interpreted as a measure of motivation.

Drugs

Drug doses were adapted from available published data or chosen from previous dose–response curve experiments and published functional neurochemistry data. Solutions were freshly prepared every day. Different groups of animals were used for each drug and at least 2 days were allowed between drug injections. During the time between the administration of the compound and the beginning of the task, animals were singly housed in holding cages and left undisturbed in a quiet room. All drugs were administered via intraperitoneal injections at a volume of 1 ml/kg and according to a randomized Latin square design, unless otherwise stated.

Atipamezole ($\alpha 2$ adrenoceptor antagonist)

A group of 14 animals (350–400 g) were injected with the highly selective $\alpha 2$ antagonist atipamezole (Pertovaara et al. 2005; Antisedan, Pfizer). Atipamezole (0.03, 0.1, 0.3 mg/kg, plus vehicle) was diluted in 0.9 % saline and administered 45 min before test sessions (Haapalinna et al. 1998; Scheinin et al. 1988; Sirvio et al. 1993; Virtanen et al. 1989). Three animals were excluded from the final analysis for violation of the race model assumptions (final $n=11$).

Prazosin ($\alpha 1$ adrenoceptor antagonist)

Fourteen subjects weighing between 370 and 450 g were administered prazosin (0.05, 0.15, 0.5 mg/kg, plus vehicle), which was dissolved in double distilled water (DDW) and administered at a volume of 2 ml/kg, 45 min before test

sessions. Drug doses were chosen based on published studies (e.g., Darracq et al. 1998; Selken and Nichols 2007). Two subjects have been excluded from the final analysis in this study because of violation of the race model assumptions (final $n=12$).

Propranolol (β 1/2 adrenoceptor antagonist)

A group of fourteen animals (370–470 g) was administered propranolol (0.3, 1.5, 3 mg/kg, plus vehicle) which was dissolved in DDW and injected 45 min before test sessions (Hahn and Stolerman 2005). Three subjects violated the race model assumptions and were excluded (final $n=11$).

DA D1 and D2 receptor antagonists

Two groups of eighteen animals (320–440 g) were administered the selective DA D1 receptor antagonist SCH-23390 (Sidhu et al. 1986) and the DA D2/3 receptor antagonist sulpiride, both purchased from Sigma-Aldrich. For sulpiride, doses were 1, 5, 10 mg/kg, plus vehicle (0.9 % saline) injected 45 min before test and the solution adjusted with hydrochloric acid to give a pH of ~6 (Lacroix et al. 2003; Passetti et al. 2003; Sorge and Clarke 2009). SCH-23390 doses were 1, 5, 10 μ g/kg, plus vehicle (0.9 % saline) administered 45 min before testing (Koffarnus et al. 2011; van Gaalen et al. 2006). Five animals from each group were excluded from the final analysis, because of violation of the race model assumptions (final $n=13+13$).

DA D3 receptor agonist and antagonist

Two groups of twenty two rats weighing between 320 and 450 g were administered the DA D3 receptor-preferring agonist 7-OH-PIPAT or the antagonist nafadotride both purchased from Tocris (Bristol, UK). Doses were: nafadotride, 0.3, 1, 3 mg/kg, plus saline; 7-OH-PIPAT, 0.1, 0.3, 1 mg/kg, plus saline (Flietstra and Levant 1998; Khroyan et al. 1997; Levant and Vansell 1997). Both drugs were injected 30 min before test sessions. Six rats from the nafadotride experiment (final $n=16$) and three from the 7-OH-PIPAT one (final $n=19$) were excluded from the final analysis for not performing according to the requirements of the SST.

DA D4 receptor agonist and antagonist

Two groups of 15 rats weighing between 360 and 470 g received the DA D4 selective agonist PD 168,077 or the DA D4 selective antagonist L-745,870. These compounds were purchased from Tocris (Bristol, UK) and dissolved in 0.9 % saline solution and 20 % β -hydroxypropyl-cyclodextrin, respectively. Doses were 0.5, 1, 5 mg/kg, plus vehicle, for both drugs (Koffarnus et al. 2011; Nayak and Cassaday 2003). Five

rats from each group were excluded from the final statistical analysis because of violation of the race model assumptions (final $n=10+10$).

Data analysis

Repeated measure ANOVA was used for all the experiments with drug dose level as a within-subjects factor and Sidak's post-hoc adjustment for multiple comparisons was applied if a main effect was found. Mauchly's test of sphericity was used and Huynh-Feldt corrected degrees of freedom rounded to the nearest integer are presented when the assumption of homogeneity of covariance was violated. All tests of significance were performed at $\alpha=0.05$. Graphs and tables display means and their standard errors (SEM); asterisks indicate significance at the level of $p<0.05$ (*) or $p<0.01$ (**).

Results

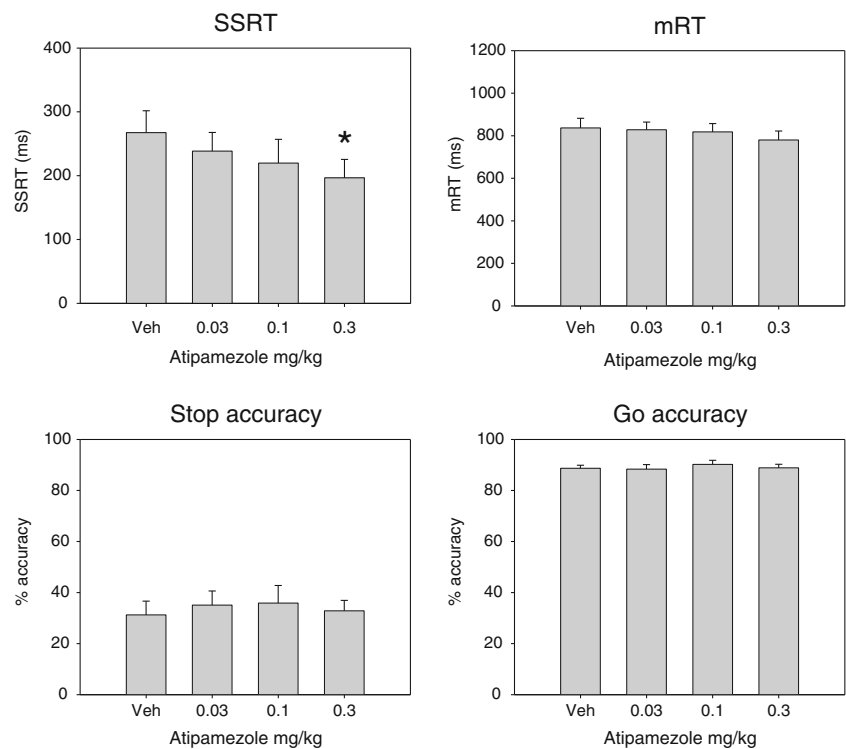
Effects of atipamezole

Atipamezole (Fig. 2) significantly affected SSRT ($F_{(3,30)}=3.09$, $p<0.05$). Post-hoc tests showed that SSRT was decreased (i.e., speeded) at 0.3 mg/kg compared with the vehicle condition ($p<0.05$). ANOVA also revealed a main effect of the drug on mRT ($F_{(3,30)}=3.46$, $p<0.05$). However, Sidak corrected post-hoc analyses did not show any significant differences between doses. No significant effect (ns) was detected for stop accuracy ($F_{(3,30)}=0.43$, ns), go accuracy ($F_{(3,30)}=0.74$, ns), PES ($F_{(1,14)}=1.9$, ns), NP/TO ($F_{(2,18)}=2.64$, ns) and RCL ($F_{(2,24)}=0.71$, ns). There was a significant main effect of the drug on SDGoRT ($F_{(3,30)}=5.16$, $p<0.01$; Table 1). According to pairwise comparisons the highest dose (0.3 mg/kg) significantly decreased SDGoRT compared to vehicle ($p<0.05$).

Effects of prazosin

Prazosin administration did not affect SSRT ($F_{(3,33)}=0.61$, ns; Fig. 3). ANOVA revealed a main effect of the drug on mRT ($F_{(3,33)}=10.66$, $p<0.01$). Both 0.15 mg/kg ($p<0.05$) and 0.5 mg/kg ($p<0.01$) increased mRT compared with vehicle, according to post-hoc analyses. Stop accuracy was not affected ($F_{(3,33)}=1.44$, ns), but there was a significant main effect on go accuracy ($F_{(3,33)}=8.9$, $p<0.01$). Post-hoc analyses revealed that at 0.5 mg/kg go accuracy was significantly lower compared with vehicle ($p<0.01$) and 0.05 mg/kg ($p<0.05$). SDGoRT was also significantly affected by prazosin administration ($F_{(3,33)}=3.26$, $p<0.05$). Pairwise comparisons, however, showed no significant differences after Sidak's correction. There was no difference regarding PES ($F_{(1,14)}=0.55$, ns) and RCL ($F_{(1,16)}=2.31$, ns), while a significant difference was found for NP/TO

Fig. 2 Atipamezole (α_2 agonist) administration significantly decreased SSRT at 0.3 mg/kg compared with the vehicle condition. There was only a significant main effect of the drug on mRT. Stop and go accuracy were not affected at any of the doses tested. * $p < 0.05$ vs. vehicle (Veh) condition



($F_{(3,33)}=6.13$, $p < 0.01$; Table 1). Pairwise comparisons showed that only at 0.05 mg/kg animals made fewer perseverative nose pokes (NP/TO) into the food well during time-out periods compared with the vehicle condition ($p < 0.05$).

Effects of propranolol

There was no effect of propranolol on SSRT ($F_{(3,30)}=2.16$, ns; Fig. 4) and stop accuracy ($F_{(3,30)}=0.05$, ns). mRT was

Table 1 Effects of noradrenergic compounds on the secondary SST measures

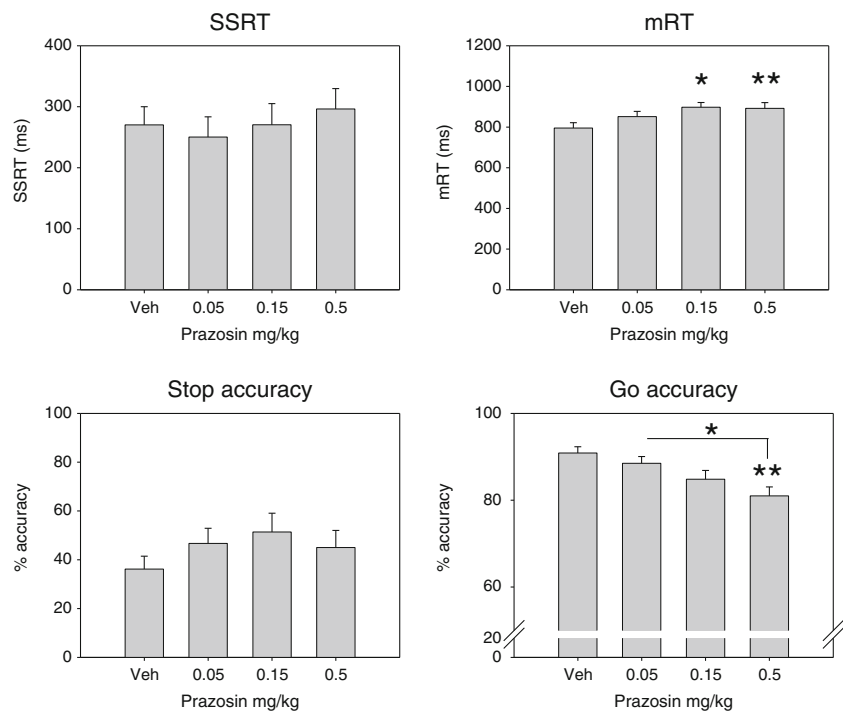
Drug	Dose (mg/kg)	SDGoRT (ms)	PES (ms)	NP/TO	RCL (ms)
Atipamezole					
(α_2 ago)	Veh	150.2 (9.6)	13.1 (58.2)	2.4 (0.2)	506.3 (24.2)
	0.03	143 (9.8)	-91.9 (30.1)	2.7 (0.1)	490.3 (26.5)
	0.1	138.5 (8)	-54.6 (28.6)	2.5 (0.1)	491.3 (24.4)
	0.3	123.9 (6.5)*	-46.7 (25.6)	2.9 (0.2)	472.6 (27.5)
Prazosin					
(α_1 ant)	Veh	155.6 (9.6)	-76 (12.4)	2.3 (0.3)	534.8 (34.4)
	0.05	160.4 (10.6)	-83.5 (18.5)	1.7 (0.2)*	589.5 (32.5)
	0.15	173.2 (7.9)	-25.3 (21.1)	1.5 (0.1)	627 (43.4)
	0.5	172.1 (7.8)	-24.7 (76.7)	1.5 (0.2)	581.3 (34.5)
Propranolol					
(β 1/2 ant)	Veh	140.7 (11.2)	-95.5 (21.7)	1.9 (0.2)	523.9 (35.9)
	0.3	144.9 (11.2)	-99.7 (23.7)	2.3 (0.3)	503.9 (39.8)
	1.5	156 (10.7)	-81.9 (17.4)	2.2 (0.3)	500 (36.9)
	3	159.6 (11.5)*	-101.2 (20.9)	2.4 (0.2)	513.4 (40.9)

Values represent means and their standard errors (between brackets). Atipamezole and propranolol significantly decreased SDGoRT at the dose of 0.3 and 3 mg/kg, respectively. Prazosin significantly decreased the number of nose-pokes made during the time-out periods at 0.05 mg/kg only. All the other secondary variables were not affected by these drugs

SDGoRT standard deviation of go reaction time, PES post-error slowing, NP/TO nose pokes during time-out periods, RCL reward collection latency, ago agonist, ant antagonist

* $p < 0.05$ vs. vehicle

Fig. 3 Administration of the α_1 antagonist prazosin resulted in longer mRT at the doses of 0.15 and 0.5 mg/kg. SSRT and stop accuracy were not affected by the drug, while go accuracy was decreased at 0.5 mg/kg compared with vehicle (Veh; ** $p < 0.01$) and to 0.05 mg/kg (* $p < 0.05$)



significantly affected by the drug ($F_{(3,30)}=3.41$, $p < 0.05$), but pairwise comparisons reported no significant differences between doses. There was also a significant main effect on go accuracy ($F_{(3,30)}=3.51$, $p < 0.05$), but no significant differences after correcting for multiple comparisons. Propranolol significantly affected SDGoRT ($F_{(3,30)}=3.82$, $p < 0.05$; Table 1) and pairwise comparisons showed that it was higher after the 3 mg/kg dose, compared with the vehicle condition ($p < 0.05$). There was no effect on PES ($F_{(3,26)}=0.3$, ns), NP/TO ($F_{(3,30)}=1.63$, ns) and RCL ($F_{(2,20)}=0.31$, ns).

Effects of D1 and D2 receptor antagonists

SCH-23390 (Fig. 5 and Table 2) had no significant effect on SSRT ($F_{(3,36)}=1.1$, ns), mRT ($F_{(3,36)}=0.94$, ns), stop accuracy ($F_{(3,36)}=1.81$, ns), go accuracy ($F_{(3,36)}=1.29$, ns), SDGoRT ($F_{(3,36)}=1.33$, ns), NP/TO ($F_{(1,13)}=1.96$, ns), PES ($F_{(3,36)}=0.73$, ns) or RCL ($F_{(3,36)}=0.67$, ns).

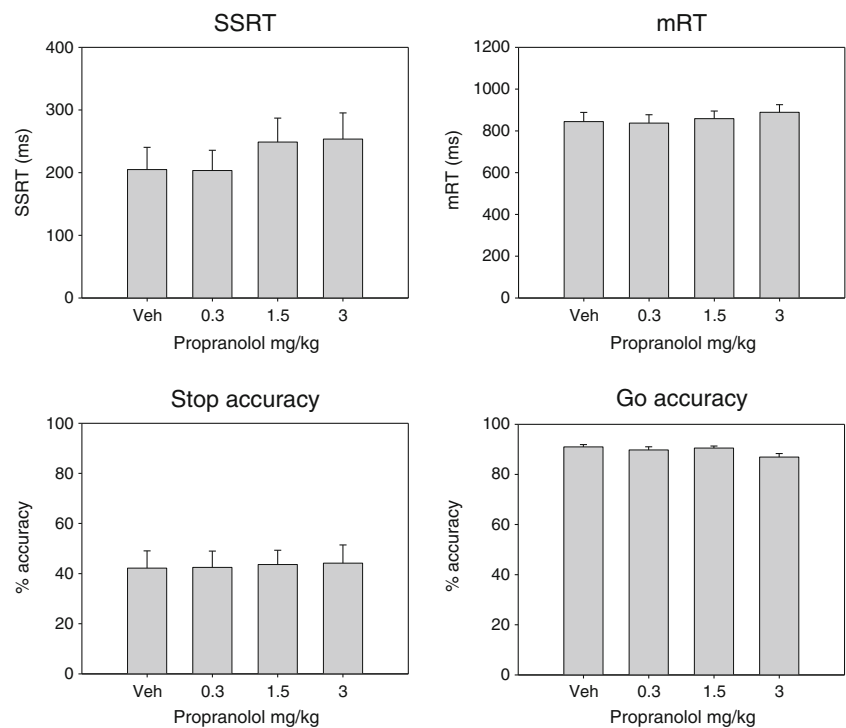
Sulpiride administration (Fig. 6 and Table 2) did not affect SSRT ($F_{(3,36)}=1.49$, ns), mRT ($F_{(3,36)}=1.23$, ns) or go accuracy ($F_{(3,36)}=1.58$, ns). There was a significant main effect to impair stop accuracy ($F_{(3,36)}=3.0$, $p < 0.05$). Pairwise comparisons showed that at 10 mg/kg the animals displayed higher stop accuracy compared to 5 mg/kg. SDGoRT was not changed by sulpiride administration ($F_{(3,36)}=1.3$, ns) and PES ($F_{(3,36)}=0.71$, ns) and NP/TO ($F_{(2,22)}=1.38$, ns) were also left unchanged. There was a trend towards a significant effect on RCL ($F_{(3,36)}=2.75$, $p=0.057$).

Effects of DA D3 receptor agonist and antagonist

7-OH-PIPAT administration (Fig. 7) had no effect on SSRT ($F_{(3,54)}=1.17$, ns). The drug, however, had a strong effect to slow mRT ($F_{(3,54)}=31.24$, $p < 0.01$). Pairwise analyses showed that all doses slowed mRT compared with vehicle ($p < 0.01$) and that at the highest dose (1 mg/kg) mRT was slower compared with all the other conditions ($p < 0.01$). 7-OH-PIPAT also affected stop accuracy ($F_{(3,54)}=3.10$, $p < 0.05$), but pairwise comparisons did not detect significant differences between doses. Repeated measures ANOVA showed that 7-OH-PIPAT administration significantly affected go accuracy ($F_{(2,30)}=34.11$, $p < 0.01$). According to post-hoc pairwise comparisons, 1 mg/kg impaired go accuracy compared with all the other conditions ($p < 0.01$), 0.3 mg/kg also being different from the vehicle condition ($p < 0.01$). There was no effect of the drug on SDGoRT ($F_{(2,42)}=0.77$, ns), but a main effect was detected for PES ($F_{(2,36)}=7.31$, $p < 0.01$; Table 2). In this case, the highest dose (1 mg/kg) increased PES compared with the vehicle ($p < 0.01$) and the 0.1 mg/kg ($p < 0.05$) conditions. Also, 0.3 mg/kg increased PES compared with 0.1 mg/kg ($p < 0.05$), but not compared with vehicle. ANOVA revealed a significant effect on NP/TO ($F_{(2,31)}=4.25$, $p < 0.05$) and RCL ($F_{(2,41)}=3.87$, $p < 0.05$); only in this latter case, pairwise comparisons showed that the highest dose (1 mg/kg) slowed the rats compared with the vehicle condition ($p < 0.05$), but failed to find a significant difference between doses for NP/TO.

Repeated-measures ANOVA revealed a main effect of nafadotride on SSRT ($F_{(3,45)}=3.49$, $p < 0.05$; Fig. 8);

Fig. 4 Propranolol (β 1/2 antagonist) administration caused only a significant main effect on mRT and go accuracy without affecting SSRT or stop accuracy



pairwise comparisons showed that the highest dose (3 mg/kg) significantly slowed SSRT compared with vehicle controls ($p < 0.05$). A main effect of the drug on mRT was also found ($F_{(2,35)} = 11.78$, $p < 0.01$). Post-hoc analyses revealed that 3 mg/kg of nafadotride slowed mRT compared with both vehicle ($p < 0.01$) and 0.3 mg/kg ($p < 0.01$), while mRT at 1 mg/kg was slower only compared with the 0.3 mg/kg dose ($p < 0.05$). No effects of nafadotride were

detected on stop accuracy ($F_{(3,45)} = 2.26$, ns) and SDGoRT ($F_{(3,45)} = 2.58$, $p = 0.065$, ns). Go accuracy was affected by the drug ($F_{(1,22)} = 21.57$, $p < 0.01$) only at the highest dose (3 mg/kg) at which it was lower compared with all the other conditions ($p < 0.01$). There was a main effect of the drug on PES ($F_{(3,45)} = 5.39$, $p < 0.01$; Table 2), with the highest dose (3 mg/kg) making the animals significantly slower after a stop error ($p < 0.05$). ANOVA revealed a significant effect of

Fig. 5 The dopamine D1 receptor antagonist SCH 23390 had no effect on any of the main variables of the SST

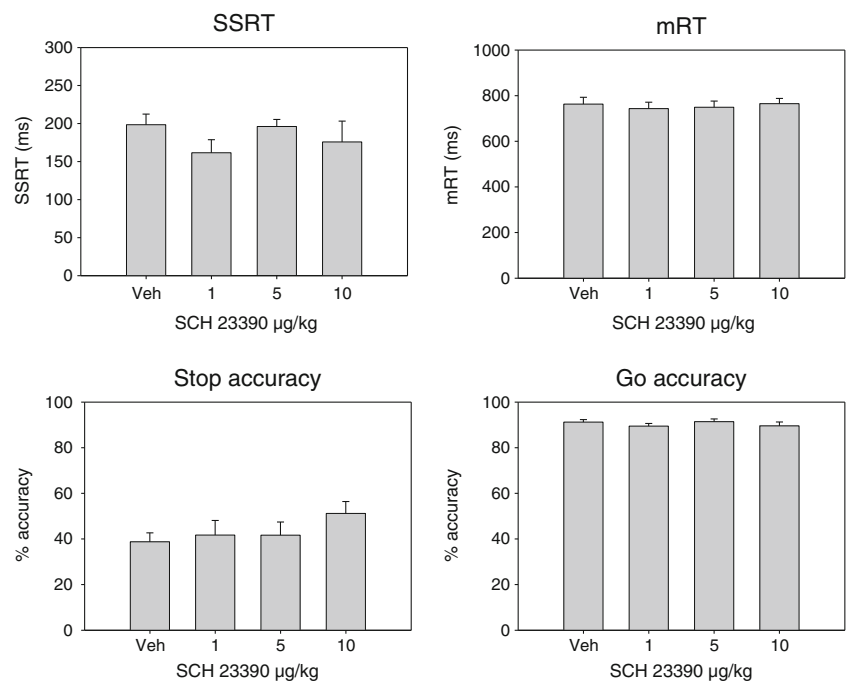


Table 2 Effects of dopaminergic compounds on the secondary SST measures

Drug	Dose	SDGoRT (ms)	PES (ms)	NP/TO	RCL (ms)
SCH 23390 (D1 ant)	µg/kg				
	Veh	109.6 (8.2)	-7.6 (23.2)	3.4 (1.1)	452.2 (29.1)
	1	100.2 (7)	-17.6 (14.1)	4.5 (2.1)	468 (28.4)
	5	100.6 (8)	4 (21.5)	3.7 (1.7)	469.7 (33.1)
Sulpiride (D2 ant)	mg/kg				
	Veh	133.1 (8.1)	-29 (21.5)	3.5 (0.4)	516.9 (30.3)
	1	122.1 (8.6)	-24.4 (19.3)	3.1 (0.4)	522.3 (28.2)
	5	124.3 (6)	-43.8 (18)	3.9 (0.6)	478.5 (28.4)
7-OH-PIPAT (D3 ago)	mg/kg				
	Veh	140 (6.1)	-68 (26.3)	2.3 (0.4)	469.3 (31.2)
	0.1	145.3 (5.4)	-44.7 (22.1)	1.8 (0.2)	530 (40)
	0.3	149.9 (4.9)	68 (26.3)	1.6 (0.2)	555.4 (32.2)
Nafadotride (D3 ant)	mg/kg				
	Veh	140.3 (8.4)	-77.5 (27.8)	2 (0.1)	505.2 (47.7)
	0.1	139.1 (8.6)	-60.6 (24.3)	2 (0.2)	499.2 (50.7)
	0.3	142.2 (8)	-58.1 (22.3)	2 (0.1)	501.9 (40.7)
PD-168,077 (D4 ago)	mg/kg				
	Veh	138.1 (10.4)	-63.8 (21)	2.8 (0.2)	462 (26.3)
	0.5	140.5 (7.2)	-63.7 (15.3)	2.8 (0.3)	444.2 (28.9)
	1	134.8 (8.4)	-56.2 (26.5)	2.7 (0.2)	442 (32.9)
L-745,870 (D4 ant)	mg/kg				
	Veh	135.9 (8.5)	-54.3 (19.3)	2.7 (0.4)	514.7 (34.1)
	0.5	129.3 (6.1)	-4.5 (25)	2.6 (0.3)	501.5 (32)
	1	127.3 (10.8)	-57.1 (23.9)	2.4 (0.3)	500 (35.1)
	mg/kg				
	5	133.2 (11.4)	-25.9 (34.2)	2.3 (0.2)	511.9 (34.8)

Values represent means and their standard errors (between *brackets*). SCH 23390 did not affect any of the secondary SST variables. Sulpiride administration had no significant effect on SDGoRT, PES, or NP/TO. Sulpiride effects only approached significance for RCL ($p=0.057$). The highest dose of 7-OH-PIPAT (1 mg/kg) produced a significant increase in PES compared with vehicle ($p<0.01$) and with the 0.1 mg/kg condition ($p<0.05$). The same drug also increased PES ($p<0.05$) at the dose of 0.3 mg/kg compared with 0.1 mg/kg only. There was only a main effect of 7-OH-PIPAT on NP/TO, while 1 mg/kg of this drug significantly prolonged the latency to collect the reward from the food well (RCL; $p<0.05$). Nafadotride administration significantly increased and decreased PES and NP/TO, respectively. Finally, administration of PD-168,077 or L-745,870 had no significant effects on any of the secondary SST variables

SDGoRT standard deviation of go reaction time, PES post-error slowing, NP/TO nose pokes during time-out periods, RCL reward collection latency, ago agonist, ant antagonist

* $p<0.05$ and ** $p<0.01$ compared with vehicle

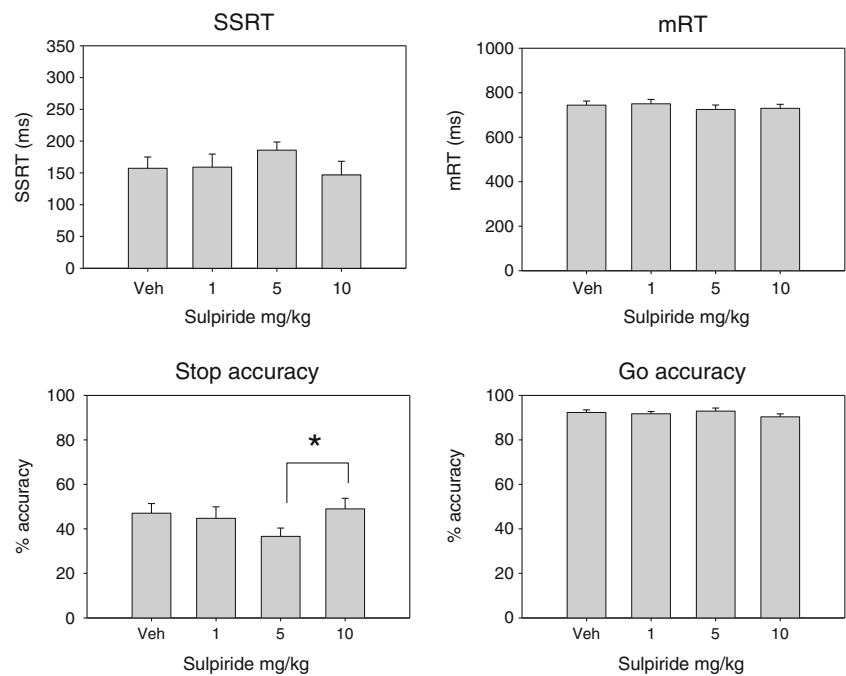
the drug on NP/TO ($F_{(3,45)}=13.7$, $p<0.01$), but not on RCL ($F_{(2,24)}=0.015$, ns). Pairwise comparisons showed that, at the highest dose (3 mg/kg), NP/TO was significantly lower than in all the other conditions ($p<0.05$).

Effects of DA D4 agonist and antagonist

There was a main effect of PD-168,077 to prolong SSRT ($F_{(3,27)}=4.92$, $p<0.01$; Fig. 9). Pairwise comparisons

showed that 5 mg/kg significantly increased SSRT compared with 0.5 mg/kg ($p<0.05$). PD-168,077 administration did not significantly influence mRT ($F_{(3,27)}=2.88$, $p=0.054$, ns), stop accuracy ($F_{(2,17)}=0.77$, ns) or go accuracy ($F_{(2,14)}=1.08$, ns). SDGoRT ($F_{(2,14)}=0.17$, ns) and PES ($F_{(3,27)}=1.29$, ns) were also not affected by the drug at any of the doses tested (Table 2). There was no significant effect on RCL ($F_{(2,27)}=0.25$, ns) or NP/TO ($F_{(1,19)}=0.11$, ns).

Fig. 6 The dopamine D2 antagonist sulpiride had no significant effect on SSRT, mRT or go accuracy. The highest dose tested (10 mg/kg) affected significantly stop accuracy, which was higher compared to the 5 mg/kg condition only. * $p < 0.05$



There was no effect of L-745,870 on SSRT ($F_{(3,27)}=0.76$, ns; Fig. 10), mRT ($F_{(3,27)}=1.92$, ns), stop accuracy ($F_{(3,27)}=0.81$, ns), SDGoRT ($F_{(3,27)}=0.25$, ns) or PES ($F_{(3,27)}=0.76$, ns). There was a main effect of the drug on go accuracy ($F_{(3,27)}=8.02$, $p < 0.01$) and post-hoc analyses showed that the highest dose (5 mg/kg) impaired go accuracy compared with vehicle and 0.5 mg/kg ($p < 0.05$). There was no effect of the drug on NP/TO ($F_{(1,21)}=0.45$, ns) or RCL ($F_{(2,35)}=0.092$, ns; Table 2).

Discussion

We aimed to characterise mechanisms underlying the beneficial effects on SST performance in rats of catecholamine reuptake blockers and other agents used for the treatment of disorders such as ADHD that exhibit impulsive behaviour. Commonly used stimulant and non-stimulant medications act globally on the catecholaminergic systems and that lead to unwanted side effects as well as preventing the formulation of

Fig. 7 Administration of the dopamine D3 receptor agonist 7-OH-PIPAT produced strong detrimental effects, specifically on go measures. mRT was longer than vehicle at all the doses tested ($p < 0.01$) and the highest dose was also different from all the other conditions ($p < 0.01$). Go accuracy was lower at 1 mg/kg ($p < 0.01$ compared with all the other conditions) and at 0.3 mg/kg ($p < 0.01$) compared with vehicle (Veh). ** $p < 0.01$

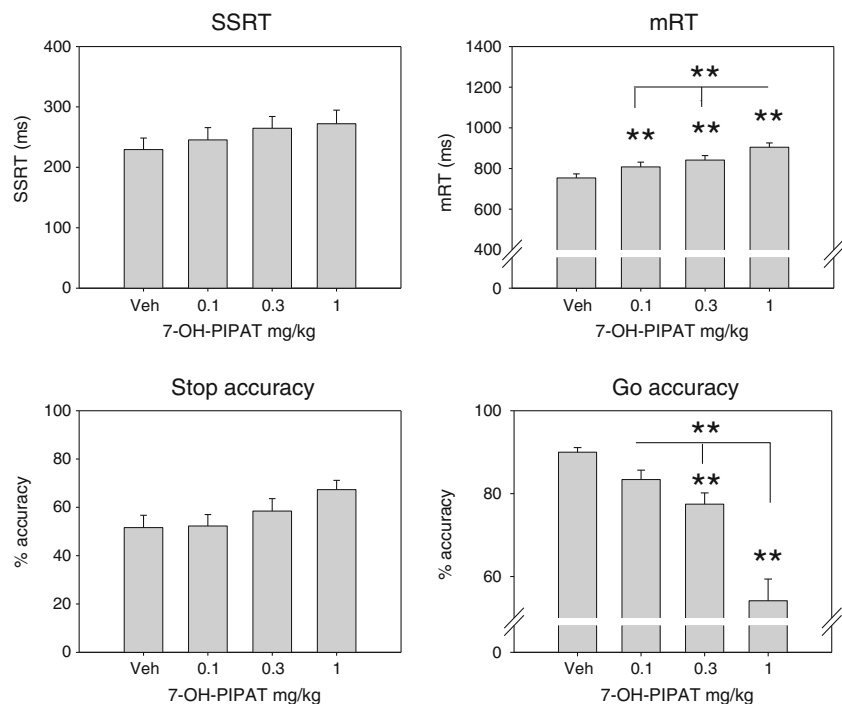
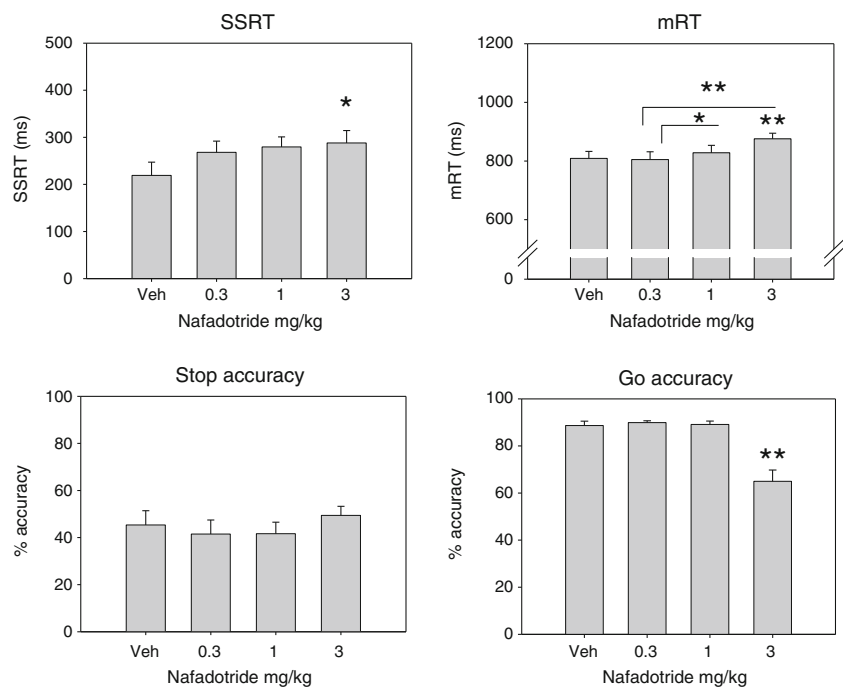


Fig. 8 Nafadotride (D3 antagonist) significantly increased SSRT at 3 mg/kg compared with vehicle administration ($p < 0.05$). The same dose produced longer mRT ($p < 0.01$ compared with vehicle) and lower go accuracy ($p < 0.01$ compared with all the other conditions). At the dose of 0.3 mg/kg mRT was faster than both 1 ($p < 0.05$) and 3 mg/kg ($p < 0.01$). * $p < 0.05$; ** $p < 0.01$



hypotheses regarding the mechanisms by which these drugs affect specific executive functions. To parcel out the contribution of different receptors, we also analysed secondary variables of the SST for rats that are commonly reported in experiments with human subjects. Variations of these measures in response to specific receptor activation or blockade can aid the interpretation of the standard SST measures, the comparison with human data and the understanding of the underlying cognitive processes affected by therapeutic drugs acting as so-called cognitive enhancers.

Effects of noradrenergic ligands

We showed that atipamezole, a very selective and potent $\alpha 2$ -adrenergic receptor antagonist (Haapalinna et al. 1997; Virtanen 1989), speeded SSRT at the 0.3 mg/kg dose and decreased response variability (i.e., improved sustained attention). From the present results, it seems that the speeding of inhibitory processes and the improved sustained attention after atipamezole administration are not necessarily causally related since stop accuracy was not significantly affected by this drug.

Fig. 9 The dopamine D4 receptor agonist PD-168,077 only affected SSRT which was slower at 5 mg/kg compared with the 0.5 mg/kg condition * $p < 0.05$

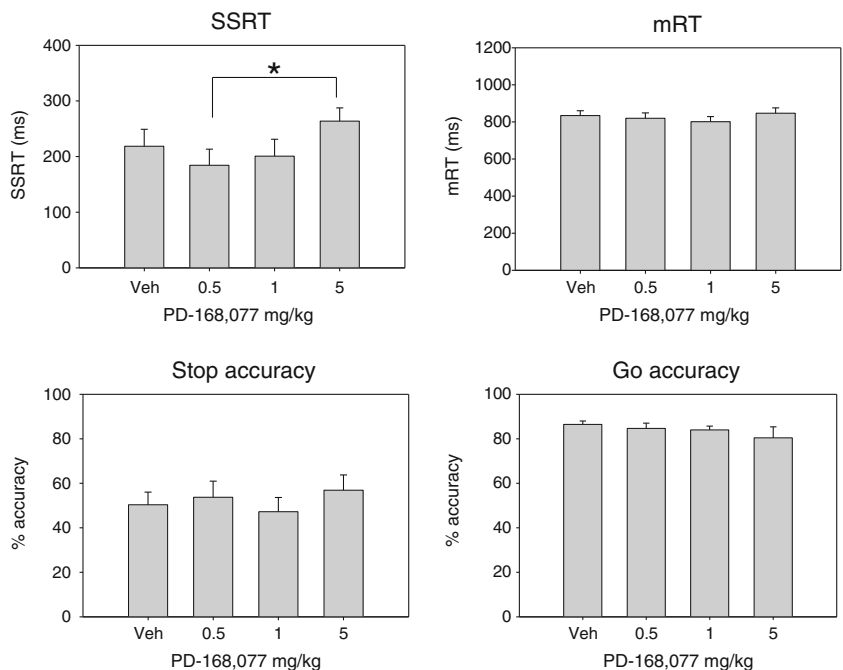
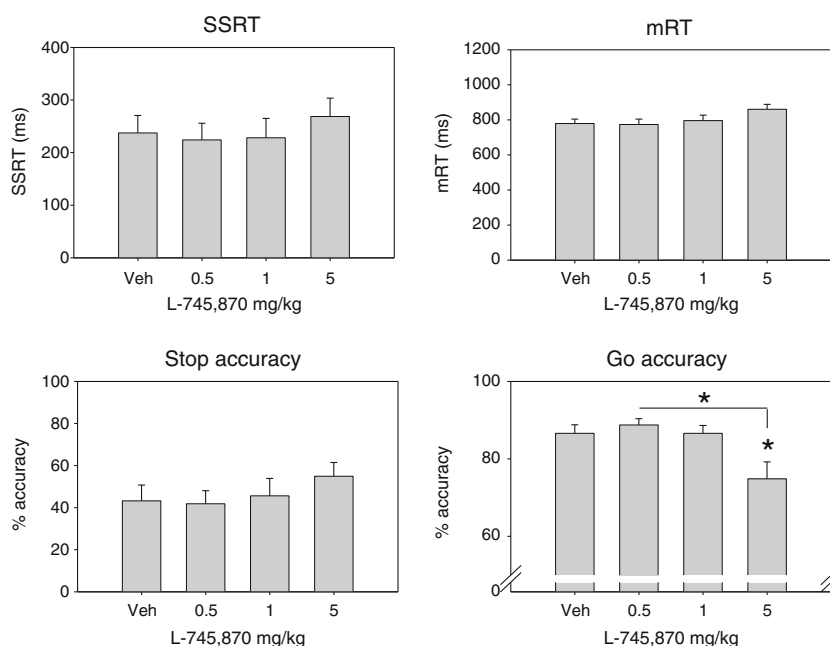


Fig. 10 The DA D4 receptor antagonist L-745,870 impaired go accuracy at the dose of 5 mg/kg, which was significantly lower than both vehicle and 0.5 mg/kg. * $p < 0.05$



This pattern of results apparently contrasts with previous evidence of a deleterious effect of the less selective $\alpha 2$ receptor antagonists idazoxan and yohimbine on attention and impulsivity (Arnsten and Li 2005; Rowe et al. 1996; Sun et al. 2010; Swann et al. 2005, 2013). However, these results might be non-specific to $\alpha 2$ receptor antagonism because the more selective drug atipamezole improves attention and other cognitive functions (Devauges and Sara 1990; Haapalinna et al. 1998; Lapid and Morilak 2006; Mervaala et al. 1993; Pertovaara et al. 2005), consistent with the present findings. Alternatively, the different attentional and inhibitory requirements of the SST, compared to other behavioural tasks, may be the reason for this discrepancy. On the other hand, $\alpha 2$ receptor agonist administration has deleterious consequences on attention (Smith and Nutt 1996) and target detection (Brown et al. 2012; Coull et al. 2004) in some studies, but positive effects in others (Fernando et al. 2012). Thus, a better understanding of the effects of drugs acting directly at the noradrenergic $\alpha 2$ receptor requires a more specific definition of the cognitive construct measured as well as the knowledge of the $\alpha 2$ receptor subtype affected by the drug.

Atipamezole's positive effects on cognitive tasks are thought to be mediated mainly through its actions on pre-synaptic $\alpha 2$ receptors to which it preferentially binds at low doses, while post-synaptic $\alpha 2$ receptors have been implicated in the memory improvements seen after $\alpha 2$ receptor agonist administration (Ji et al. 2008), especially in animals with memory impairments (Arnsten and Cai 1993; Arnsten et al. 1988; Berridge et al. 1993; Franowicz and Arnsten 1998; Rama et al. 1996). Similarly, the beneficial effects of atipamezole on cognition are most reliably seen in aged or poor performing subjects, or in situations of increased

attentional demand (Coull et al. 1996; Haapalinna et al. 1998, 2000; Jakala et al. 1992; Sirvio et al. 1993). These baseline-dependent effects are consistent with the finding that atipamezole increases NA turnover rate significantly more in the brains of aged than that of young adult rats (Haapalinna et al. 2000), suggesting that it acts by restoring optimal levels of noradrenergic transmission. These results, however, do not rule out the possibility that atipamezole's positive effects are mediated also by DA, since this and other $\alpha 2$ -adrenergic receptor antagonists increase DA release in the rat mPFC (Devoto et al. 2001; Gobert et al. 1997; Gresch et al. 1995; Matsumoto et al. 1998; Yamamoto and Novotney 1998), possibly via indirect activation of $\alpha 1$ receptors (Anden et al. 1982).

Blocking $\alpha 1$ -adrenergic receptors by prazosin increased mRT and decreased go accuracy and NP/TO, consistent with a mild sedative effect of this drug (Berridge and Espana 2000) and, more generally, with the role of $\alpha 1$ adrenoceptors in locomotor activity and arousal (Sirvio and MacDonald 1999). Prazosin inhibits the electrically or pharmacologically-evoked release of DA in the nucleus accumbens and PFC, as well as the locomotor enhancing effects of amphetamine and cocaine (Darracq et al. 1998; Drouin et al. 2002; Gioanni et al. 1998). These secondary effects of prazosin on the dopaminergic system are consistent with the disruptive effects on go performance observed here. Moreover, since mRT and go accuracy are often considered as secondary measures of sustained attention (Castellanos and Tannock 2002; Lijffijt et al. 2005, 2006; Overtoom et al. 2002), the effects of prazosin on SST performance are indicative of detrimental effects on attention but not impulsivity, in keeping with previous results on five-choice serial reaction time task (5-CSRTT) performance (Hahn and Stolerman 2005; Puumala et al. 1997).

The effect of propranolol administration on SST variables was similar to that of prazosin. Both drugs mainly affected go performance, although for propranolol the effects were not significant after adjusting for multiple comparisons. Propranolol blocks both β 1- and β 2-adrenergic receptors (Sibley et al. 1986) and has been shown to impair attentional performance in humans (De Martino et al. 2008; Strange and Dolan 2007) and rats (Hahn and Stolerman 2005), which is consistent with the increase in response variability (SDGoRT) observed in the present study. Recently, Pattij and co-workers (2012) have shown that selective β 1 and β 2 adrenoceptor agonists improve attention and impulsivity in the 5-CSRTT (Bari et al. 2008; Robbins 2002). These results are consistent with the evidence that methylphenidate-induced premature responses in the 5-CSRTT can be abolished by co-administration of the β 1/2 antagonist propranolol (Milstein et al. 2010). Taken together with the present results, this evidence confirms the important contribution of both α 1 and β -adrenergic receptors in attentional processes and stimulus detection.

The results described above are consistent with the suggestion that NA acts post-synaptically to enhance stimulus-evoked neural responsiveness and to regulate tonic spontaneous firing during attentional tasks (Aston-Jones et al. 2000; Berridge and Waterhouse 2003). The positive effects of atomoxetine (Robinson et al. 2008) and atipamezole (present experiment) on SST performance, point to a beneficial role of increasing NA neurotransmission in forebrain areas, although achieved by different mechanisms. NA reuptake blockers like atomoxetine increase extrasynaptic NA content which in turn decreases spontaneous noradrenergic system activity through α 2-adrenoceptor stimulation at the level of the LC (Bari and Aston-Jones 2013; De Sarro et al. 1987; Fernandez-Pastor et al. 2005; Grandoso et al. 2004; Szabo and Blier 2001), while atipamezole increases prefrontal NA release by disrupting the feedback inhibitory mechanism (Gobert et al. 1997). These differences are reflected in the behavioural performance of the animals on the SST, with atomoxetine causing an increase in mRT and Go accuracy in addition to its SSRT-speeding effects (Bari et al. 2009), whereas atipamezole is devoid of sedative effects at functionally relevant doses (present results). The motor slowing effects of atomoxetine reflect indirect activation of inhibitory α 2 autoreceptors, while the improvements in go accuracy may possibly be due to indirect activation of α 1 adrenoceptors. In summary, the advantages of enhancing noradrenergic neurotransmission via α 2 receptor antagonism rather than blocking NA reuptake are at least twofold: it prevents (1) the α 2 pre-synaptic autoreceptor-mediated negative feedback on NA activity (Gobert et al. 1997) and (2) the post-synaptic α 2 receptor-mediated decrease in stimulus-evoked neural responsiveness (Carr et al. 2007; Ji et al. 2008) (Table 3).

Table 3 Summary of the effects of noradrenergic receptor and transporter manipulations

Variables	SNARI ^a	α 1 ant	α 2 ago ^a	α 2 ant	β 1/2 ant
SSRT	↓	–	↑	↓	–
mRT	↑	↑	↑	M	M
Stop accuracy	–	–	↓	–	–
Go accuracy	↑	↓	↓	–	–
SDGoRT	–	M	–	↓	↑
PES	na	–	na	–	–
NP/TO	↓	↓	↓	–	–
RCL	–	–	–	–	–

In general, increasing noradrenergic neurotransmission by either blocking its reuptake or α 2 presynaptic autoreceptors positively affects response inhibition (SSRT) and attention-related measures (SDGoRT), whereas decreasing noradrenergic function by α 2 agonists impairs general performance on the SST. Moreover, α 1 antagonism specifically and detrimentally affects go performance, while β receptor antagonism disrupts sustained attention (higher SDGoRT)

SSRT stop-signal reaction time, mRT mean reaction time, SDGoRT standard deviation of go reaction time, PES post-error slowing, NP/TO nose pokes during time-out periods, RCL reward collection latency, ↑ increased, ↓ decreased, – no change in the specific measure, na not available, ago agonist, ant antagonist, SNARI selective noradrenaline reuptake inhibitor, M main effect only

^a Data for SNARI (atomoxetine) and α 2 ago (guanfacine) are from Bari et al. (2009)

Effects of dopaminergic ligands

From the results obtained after SCH-23390 or sulpiride administration, at least at the doses used here, it seems that blocking DA D1 or D2 receptors separately does not influence SST performance. In keeping with the present results, systemic administration of the mixed D1/D2 DA receptor antagonist *cis*-flupenthixol did not alter SST performance up to doses that impaired the ability of the animals to complete the task and also failed to antagonise the beneficial effects of methylphenidate or modafinil (Eagle et al. 2007). We chose low dose levels for the drugs used in the present experiments in order to preserve the receptor specificity of the compound tested, although it is possible that these doses were too low for SCH-23390 and sulpiride to elicit significant behavioural effects on SST performance. However, previous studies have found significant effects on impulsivity in the 5-CSRTT after 10 μ g/kg of SCH-23390 (Koskinen and Sirvio 2001; van Gaalen et al. 2006) and increased risk-aversion after 5 μ g/kg (St Onge and Floresco 2009).

On the other hand, sulpiride is known to preferentially affect PFC DA receptors at low doses (Bowers 1984; Kaneno et al. 2001; Kaneno et al. 1991; Kohler et al. 1981; Scatton 1977; Thierry et al. 1986) and to cause place aversion at doses as low as 1 mg/kg (Karami and Zarrindast 2008). Higher doses than the ones used in the present investigation

may have produced spurious impairments on SST performance by negatively affecting locomotor activity and incentive motivation. For instance, sulpiride infused directly into the dorso-medial striatum generally impairs SST performance in rats (Eagle et al. 2011), but does not affect 5-CSRTT performance when infused in the mPFC (Granon et al. 2000). Finally, the near-significant effect of sulpiride on RCL is consistent with the increased motivation for food caused by low doses of this drug (Guyon et al. 1993).

The DA D3-preferring agonist 7-OH-PIPAT selectively and negatively influenced motor- and motivation-related measures, without significantly affecting stop-related variables. 7-OH-PIPAT slowed mRT, RCL and decreased go accuracy, consistent with published reports on its strong effects on locomotor activity (e.g., Khroyan et al. 1997). On the other hand, nafadotride administration slowed SSRT and mRT, and decreased go accuracy and NP/TO at 3 mg/kg. The detrimental effects of nafadotride at doses higher than 1 mg/kg are in agreement with the strong cataleptic effect of this drug (Sautel et al. 1995). Nafadotride displays greater selectivity for D3 over D2 receptors *in vivo* only at doses below ~3 mg/kg when administered via intraperitoneal injection (Levant and Vansell 1997). Thus, since the effects observed in the present experiment are significantly different from the control condition only at 3 mg/kg, it is possible that they are partly due to the drug's action on D2 receptors. Both nafadotride and 7-OH-PIPAT increased performance monitoring/adjustment as measured by PES, which may be mediated by the mesolimbic DA system where D3 receptors are located (Sokoloff et al. 1990; Stanwood et al. 2000). Although all the behavioural effects of D3 ligands arose in a context of psychomotor depression, the increase in PES cannot be readily assimilated to motor impairments for the way this variable is calculated. However, for both compounds, the beneficial effects on performance control or compulsive nose-poking did not translate in improved stopping. The relatively similar effects produced by administration of D3-preferring agonist and antagonist are puzzling, but not surprising. For instance, both agonist (Duarte et al. 2003b) and antagonist (Vorel et al. 2002) have been shown to attenuate cocaine-induced conditioned place preference. Finally, the similarity of the behavioural effects elicited by nafadotride and 7-OH-PIPAT may be due to the characteristic biphasic dose–effect relationship exhibited by D3 ligands on motivated behaviour (e.g., Depoortere et al. 1996, 1999; Khroyan et al. 1997).

DRD4 knock-out mice do not show enhanced levels of impulsivity in delay discounting and go/no-go tasks. However, these animals display enhanced novelty-seeking behaviour (Helms et al. 2008) and impaired response inhibition in the murine version of the continuous performance task (Young et al. 2011). Contrary to expectations, in the present experiments D4 receptor ligands were ineffective on most SST measures. PD-168,077 mildly slowed SSRT and L-

745,870 impaired go accuracy at the higher dose tested. Our results concur with the finding that the presence of a DRD4 polymorphism (7-repeat allele) in children with ADHD does not influence inhibitory processes as measured by the go/no-go task and SST, although these subjects display faster and less accurate response style in neuropsychological tasks compared to non carriers (Langley et al. 2004). Together, these results suggest that the modulation of impulsive behaviour by D4 receptors may depend on the long term effects of their reduced function in the DRD4 7-repeat allele carriers and on the pre-existing state of the dopaminergic and noradrenergic systems. Acute treatment with dopaminergic compounds targeting the D4 receptor may be insufficient in altering inhibitory performance in normal subjects. Baseline-dependent effects have been described for tasks depending on frontostriatal circuitry in rodents (Milstein et al. 2010; Zhang et al. 2002, 2004) and primates (Arnsten et al. 2000; Jentsch et al. 1999) after administration of D4 antagonists, suggesting that D4 modulation may normalize naturally or chemically altered levels of catecholamines in the PFC. The present study did not take into account baseline differences in performance on response inhibition and is thus not suited to detect such effects. However, future studies will need to investigate the effects of chronic administration of D4-targeting drugs as well as a wider range of doses of the D4 agonist PD-168,077, which had a biphasic effect on SSRT and may have stronger effects at very low doses (e.g., Nayak and Cassaday 2003) (Table 4).

Relevance of secondary SST variables

Here we showed, for the first time in the rat, a dissociation between SSRT and SDGoRT measures; the first assessing the speed of the inhibitory processes (Logan 1994) and the second the intra-individual variability of the go response (Tannock et al. 1995; Teicher et al. 2004). Both measures represent potential endophenotypes to be used as 'biomarkers' (Gottesman and Gould 2003; Rommelse et al. 2008) that would help the diagnosis and treatment of clinical disorders such as ADHD and schizophrenia (Castellanos and Tannock 2002; Gilmour et al. 2012; Vaurio et al. 2009). In the present experiments, systemically administered atipamezole improved performance on both SSRT and SDGoRT, whereas propranolol, and to a lesser extent prazosin, selectively impaired SDGoRT. These data complement previous reports on the efficacy of psychostimulants in modulating the trial-to-trial variability of the go response (Baldwin et al. 2004; Boonstra et al. 2005; Epstein et al. 2006, 2011; Fitzpatrick et al. 1992; Nandam et al. 2010; Spencer et al. 2009) and point to a possible involvement of noradrenergic neurotransmission in this behavioural measure (Frank et al. 2007; Kollins et al. 2008; Lee et al. 2010).

In rats, the intra-individual variability of reaction times has been previously shown to increase following various

Table 4 Summary of the effects of dopaminergic manipulations on the SST variables

Variables	DARI ^a	D1 ant	D2 ant	D3 ago	D4 ant	D4 ago
SSRT	–	–	–	↑	–	–
mRT	↓	–	–	↑	–	–
Stop accuracy	↓	–	–	–	–	–
Go accuracy	↓	–	–	↓	↓	–
SDGoRT	–	–	–	–	–	–
PES	–	–	–	↑	–	–
NP/TO	–	–	–	M	–	–
RCL	–	–	–	↑	–	–

Increasing dopaminergic subcortical neurotransmission by GBR 12909 administration disrupts go and stop performance, whereas D1 and D2 receptor antagonists do not influence any of the variables considered. Administration of D3 receptor agonist and antagonist have similar effects, principally affecting motor behaviour. Notably, D3 receptor manipulation is the only one affecting variables related to motivation (RCL) and error processing (PES). Finally, D4 receptor antagonism decreases go accuracy, while administration of the agonist of the same receptor does not produce any significant effect

SSRT stop-signal reaction time, mRT mean reaction time, SDGoRT standard deviation of go reaction times, PES post-error slowing, NP/TO nose pokes during time-out periods, RCL reward collection latency, ↑ increased, ↓ decreased, – no change in the specific measure, ago agonist, ant antagonist, DARI dopamine reuptake inhibitor, M main effect only

^a The data for GBR 12909 are from Bari et al. (2009)

manipulations that cause distractibility, such as distractors presented during reaction time tasks, PFC inactivation and pre-natal alcohol intoxication (Hausknecht et al. 2005; Narayanan et al. 2006). Experimental manipulations known to decrease reaction time variability in rodents are increased stimulus salience and, like in humans, stimulant administration (Sabol et al. 2003). Rodent models of ADHD, such as the spontaneously hypertensive rat, also display highly variable reaction times (Perry et al. 2010b), which suggests a genetic origin for this behavioural trait (Loos et al. 2012; Perry et al. 2010a). Few studies have investigated the relationship between reaction time variability and performance in the 5-CSRTT. Loos et al. (2012) reported a strong correlation between response accuracy (the main attentional measure of the 5-CSRTT) and intra-individual response variability in mice, which is consistent with findings in humans performing an analogous attentional task (Bidwell et al. 2007; Klein et al. 2006). They also identified a quantitative trait locus in common for the two attentional measures on chromosome 16, suggesting that response accuracy and response variability in the 5-CSRTT share underlying genetic origins.

In contrast to human subjects and for rats performing other tasks, rats in the SST show a speeding of GoRT after a stop error. One possible reason for this discrepancy may be the presence of the TO period after a stop error, since it is

known that PES decreases as a function of the inter-trial (Rabbitt and Rodgers 1977), or the response–stimulus (Danielmeier and Ullsperger 2011; Jentsch and Dudschig 2009) interval. Alternatively, subjects may perceive the probability of occurrence of two consecutive stop trials to be low, or they may simply respond impulsively (i.e., faster) after having received punishment (5 s TO). In future studies, eliminating the TO period or varying the percentage of stop trials in a session could help to elucidate the differences in PES between humans and rats performing the SST. Here we considered a positive departure from this baseline post-error ‘speeding’ as an improvement in the capacity of the animal to dynamically adjust ongoing behaviour in order to increase stop accuracy.

Error monitoring, conflict detection and the subsequent adjustment of performance are known to depend on the dorso-medial PFC in humans and rats (Brown and Braver 2005; Chevrier et al. 2007; Falkenstein et al. 2000; Kerns et al. 2004; Li et al. 2008; Modirrousta and Fellows 2008; Narayanan and Laubach 2008; Ridderinkhof et al. 2004; Swick and Turken 2002), and on dopaminergic signalling therein (Chevrier and Schachar 2010; de Bruijn et al. 2004; Holroyd and Coles 2002; Kattoulas et al. 2010; Kramer et al. 2007). Moreover, these evaluative and regulative functions are found to be impaired in ADHD children (Korenblum et al. 2007; O’Connell et al. 2009; Schachar et al. 2004) and other patient populations.

The present data suggest that DA D3 receptors are involved in the PES component of the SST, consistent with previous literature on the role of DA in error-monitoring and behavioural adjustment (Chevrier and Schachar 2010; de Bruijn et al. 2004; Hester et al. 2012; Holroyd and Coles 2002; Nandam et al. 2012; Nieuwenhuis et al. 2002; Wardle et al. 2012; Zirnheld et al. 2004).

The presence of D3 mRNA in key fronto-striatal loops involved in drug-seeking, relapse to drug addiction and impulsive/compulsive behaviour is consistent with their role in motivation and self-control (Everitt and Robbins 2005; Heidbreder and Newman 2010; Koob and Le Moal 1997). Interestingly, the D3 receptor agonist pramipexole has been associated to the pursuit of risky behaviours (i.e., pathological gambling) in Parkinson’s disease patients receiving this medication (Dodd et al. 2005; Szarfman et al. 2006). However, these effects usually develop only after months of escalating dosage (Dodd et al. 2005), which may explain the inconsistency with the risk-adverse behaviour (St Onge and Floresco 2009) and the increase in post-error behavioural adjustment (present investigation) observed in rats after acute D3 agonist administration. Finally, recent evidence described a significant effect of cabergoline (Nandam et al. 2012), a compound with D3 receptor affinity comparable to that of pramipexole (Gerlach et al. 2003) on error awareness, consistent with the present results.

Summary and conclusions

Converging evidence points to noradrenergic neurotransmission being primarily involved in the therapeutic effects of anti-ADHD drugs (Biederman and Spencer 1999; Robbins and Arnsten 2009). Reduced NA neurotransmission caused by a hypofunctional DA β -hydroxylase — the enzyme responsible for synthesizing NA from DA — produces executive deficits including inattention and impulsivity (Bellgrove et al. 2006; Hess et al. 2009; Kieling et al. 2008). Moreover, the stimulant methylphenidate preferentially releases NA in PFC at clinical doses (Berridge et al. 2006; Kuczenski and Segal 2002), which may underlie its efficacy on ADHD symptoms. Finally, the SNARI atomoxetine improves attention in ADHD patients (Barry et al. 2009; Chamberlain et al. 2007; Maziade et al. 2009), healthy volunteers (Chamberlain et al. 2006a; Marquand et al. 2011) and rodents (Blondeau and Dellu-Hagedorn 2007; Navarra et al. 2008; Robinson et al. 2008). Thus, any attempt to dissect the beneficial effects of generally increasing NA levels in the brain to more specific receptor-mediated modulation of higher cognitive functions, would improve the quality and safety of available pharmacotherapy.

In the present investigation, propranolol administration impaired attentional performance as observed in humans (De Martino et al. 2008; Strange and Dolan 2007). These results suggest that β -adrenergic agonists may be used therapeutically to improve response inhibition and attention, in keeping with the findings that β -adrenoceptor agonists improve response accuracy and impulsivity in the 5-CSRTT (Pattij et al. 2012). Conversely, excessive β -adrenoceptor stimulation as occurs during stress or acute drug withdrawal, may impair cognitive processes (Chamberlain et al. 2006b; Kelley et al. 2005), and β -adrenoceptor blockade is able to reverse this impairment (Alexander et al. 2007; Kelley et al. 2007). Similarly, blockade of α 2-adrenoceptors represents a promising target mechanism for future pharmacological treatments of cognitive impairments (Coull et al. 1996; Haapalinna et al. 2000; Sahakian et al. 1994), whereas D3 receptor modulation by pharmacological agents may improve deficits in error monitoring and performance adjustment, which are commonly observed in schizophrenia, ADHD and drug addiction (Carter et al. 2001; Gilmour et al. 2012; Li et al. 2006a; Rubia et al. 2005). Further investigation is warranted to better validate SDGoRT and PES as useful measure, respectively, of sustained attention and dynamic performance adjustment in the rodent SST. Such efforts will contribute to the improvement of the rodent SST as a tool for the screening of drugs directed at ameliorating attention and response control as well as for the investigation of behavioural and cognitive deficits characteristic of ADHD and related disorders.

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