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ORIGINAL INVESTIGATION

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Lack of effects of guanfacine on executive and memory functions in healthy male volunteers

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Abstract *Rationale:* Guanfacine is an α_2-adrenergic receptor agonist that has been shown to have beneficial effects on working memory and attentional functions in monkeys and in patients with attention deficit hyperactivity disorder. *Objectives:* The aim of this study was to further investigate the cognitive-enhancing properties of guanfacine using an established battery of tasks measuring executive and memory functions. *Methods:* Sixty healthy male volunteers were randomised into three groups. Cognitive testing was performed from +2 to +4 h after double-blind administration of a single oral dose of 1 or 2 mg of guanfacine or placebo. *Results:* Systolic blood pressure was significantly reduced by both doses of guanfacine at the end of the testing session. There were no statistically significant effects on any of the cognitive measures. Two trend effects were observed with poorer performance on digit span backward and slower 'Go' reaction times after guanfacine. *Conclusion:* This study found no improvement of prefrontal memory or executive functions after guanfacine. Negative effects on blood pressure and trend effects on digit span backward and go reaction time indicate a mild sedative effect of guanfacine at these doses, possibly via mechanisms of autoreceptor down-regulation.

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Introduction

Pharmacological stimulation with noradrenaline-enhancing drugs or agonists is a promising strategy to improve cognitive deficits in neuropsychiatric disorders like attention deficit hyperactivity disorder (ADHD), schizophrenia, depression or dementia (Arnsten 2004; Christman et al. 2004; Friedman et al. 2004; Marien et al. 2004). The number of drugs that can be used to selectively stimulate the coeruleo–cortical noradrenaline system in humans is limited, with psychostimulants, alpha receptor agonists and noradrenaline reuptake inhibitors being the obvious candidates (Robbins 2000; Arnsten and Robbins 2002; Barch 2004). Previous research on the α_2-adrenergic receptor has focused on the agonists like clonidine, dexmedotomidine and guanfacine. Guanfacine is a relatively selective α_{2A}-adrenergic receptor agonist that is generally better tolerated and has a longer half-life than clonidine, which allows for less frequent dosing and lowers the risk of rebound hypertension (Sorkin and Heel 1986; Cornish 1988; Mosqueda-Garcia 1990). In monkeys, guanfacine improved working memory and attentional functions in a dose-dependent manner; facilitatory effects were more prominent in elderly monkeys with presumed noradrenaline deficiency (Arnsten et al. 1988; Franowicz and Arnsten 1998). Working memory improvement was accompanied by enhanced regional cerebral blood flow in the dorsolateral prefrontal cortex (Avery et al. 2000). The cognitive and hypotensive effects of guanfacine were antagonised by idazoxan, an α_{2A}-adrenergic antagonist (Franowicz and Arnsten 2002; Wang et al. 2004), and guanfacine-induced cognitive enhancement was abolished in α_{2A}-receptor knock-out mice (Franowicz et al. 2002).

Investigations of the cognitive-enhancing potential of guanfacine in humans and its clinical relevance have been inconclusive. Only one study in healthy volunteers found some positive effects of a medium single dose of ~2 mg

(29 μg per kg) on Paired Associates Learning (PAL), Spatial Working Memory (SWM) and the Stockings of Cambridge (SoC) planning task, all from the Cambridge Neuropsychological Test Battery (CANTAB) (Jäkälä et al. 1999b,c). Another study in healthy volunteers found no effects of 1 mg on performance or task-related brain activation as measured by fMRI during a task of visuospatial attention with variably cued choice reactions (Coull et al. 2001).

Clinical efficacy of guanfacine for the treatment of ADHD is indicated by several case reports in children (Chappell et al. 1995; Horrigan and Barnhill 1995; Hunt et al. 1995; Posey et al. 2004) and was confirmed by three controlled studies in children with ADHD and tic disorders (Scahill et al. 2001; Cummings et al. 2002) and adults with ADHD (Taylor and Russo 2001). In Alzheimer's disease (Crook et al. 1992), Parkinson's disease (Sagar 1999) and schizophrenia (Friedman et al. 2001; Mehta 2002), guanfacine has been studied without conclusive results. Doses of 1 to 4 mg per day (in one or two doses) have been used in all cognitive studies, similar to recommendations of 0.5 to 3 mg (single dose) for treatment of hypertension (Cornish 1988).

The pharmacological mechanisms underlying clinical benefits in patients with ADHD are unclear. Deficient motor inhibition on the Stop Signal Task (SST) is one of the most robust cognitive deficits associated with ADHD (Sonuga-Barke 2005), and motor inhibition is improved by psychostimulant drugs like methylphenidate that stimulate both mesocortical dopamine and noradrenaline release (Tannock et al. 1989; Aron et al. 2003). Preliminary evidence supports noradrenergic mediation of this effect in children with ADHD (Overtoom et al. 2003). Modulation of motor inhibition by guanfacine would implicate the α_{2A}-adrenergic receptor, specifically, in this effect. There is also preliminary evidence for decision-making deficits in ADHD (Ernst et al. 2003), and it has been reported that noradrenergic blockade with propranolol reduces feedback processing on a gambling task (Rogers et al. 2004).

Despite some evidence that guanfacine offers potential as a cognitive enhancer (Arnsten 2004), there is a relative paucity of specific and sensitive empirical studies assessing the cognitive effects of guanfacine in humans. The aim of this study was to further investigate the tolerability and cognitive profile of guanfacine in healthy male volunteers using an extensive neuropsychological assessment focusing on prefrontal cortical function. Selection of tests of memory and executive functions was guided by (1) cognitive domains previously shown to be impaired in ADHD (Mehta et al. 2004; Turner et al. 2004) and (2) cognitive domains previously shown to be affected by noradrenaline challenge (Coull et al. 1995; Jäkälä et al. 1999b,c; Middleton et al. 1999; Rogers et al. 2004). Good tolerability of guanfacine and dose-dependent improvements (fewer errors or faster reactions) in spatial and verbal working memory, attentional set-shifting, planning, decision-making and motor inhibition tasks were predicted.

Methods

Subjects Sixty healthy male volunteers (mean age±SD= 25.2±5.3, range=20–39 years) were recruited by advertisement in the local community. An experienced psychiatrist (UM) screened all volunteers to exclude past or present major somatic and psychiatric illness, including alcohol or recreational drug dependency. They were asked to abstain from alcohol for 12 h, as well as from caffeine and nicotine for 3 h, before the testing sessions and were advised to sleep sufficiently during the preceding night. A light breakfast or snack was allowed before, but not during, the experimental session. All participants were questioned about compliance with alcohol and caffeine restrictions before inclusion into the study. Each participant gave written informed consent prior to testing and received monetary compensation of £35. The protocol was approved by the Local Research Ethics Committee Cambridge (LREC No. 03/267) and the Medicines and Healthcare products Regulatory Agency (MHRA), London, the national drug licensing agency.

Pharmacological design This was a randomised, placebo-controlled and double-blind study with a parallel group design, deliberately chosen to avoid problems with practice effects that are common in studies with subjects design an executive tasks. Participants were randomly allocated to one of three blinded medications. This allowed us to control the matching of parallel groups in the course of the study. Unblinding of the medication followed after the first data analysis. All volunteers were asked to spend the waiting time with low arousing activities (reading, watching TV or napping) in a day room and were monitored by research nurses. Cognitive testing was performed from +2 to +4 h after drug administration in a silent consultation room at the Wellcome Trust Clinical Research Facility at Addenbrooke's Centre for Clinical Investigation.

A single oral dose of guanfacine (Tenex, A.H. Robins, Richmond, Virginia, USA) 1 or 2 mg (12.9 or 26.6 μg per kg of mean body weight) or placebo (lactose with microcrystalline cellulose) hidden in identical opaque gelatin capsules was administered. Dose selection and the timing of test administration were based on previous cognitive studies in healthy volunteers (Jäkälä et al. 1999a–c; Coull et al. 2001) and clinical studies in patients with hypertension (Cornish 1988; Mosqueda-Garcia 1990) and ADHD (Scahill et al. 2001; Taylor and Russo 2001; Posey et al. 2004). In studies with single dose application, the rate of side effects increased considerably with doses above 2 mg (Sorkin and Heel 1986).

Physiological measures A semiautomatic blood pressure monitor (model no. 90369, SpaceLabs Medical, Redmond, Washington, USA) was used to measure blood pressure and pulse hourly at baseline (0 h), during waiting time (+1 h), before cognitive testing (+2 h), during a short break (+3h) and after completion of the cognitive test battery (+4h).

Mood rating scale A visual analogue scale (VAS) for self-rating of mood within 16 dimensions (Norris 1971) was administered three times at −15, +110 and +240 min. The items used in this study were alert–drowsy, calm–excited, strong–feeble, muzzy–clear-headed, well coordinated–clumsy, lethargic–energetic, contented–discontented, troubled–tranquil, mentally slow–quick-witted, tense–relaxed, attentive–dreamy, incompetent–proficient, happy–sad, antagonistic–amicable, interested–bored and withdrawn–gregarious. These 16 dimensions were presented as 100-mm lines with the two extremes written at each end, and participants marked their current state on each line. Factors of "alertness", "contentedness", "calmness" and "tranquility" were calculated as proposed by Bond and Lader (1974) and Herbert et al. (1976).

Cognitive tasks Patients were tested on a comprehensive neuropsychological test battery including original and modified tests from CANTAB (http://www.camcog.com) (Sahakian and Owen 1992; Robbins et al. 1998). Computerised tasks were run on an Advantech personal computer (Model PPC-120T-RT), and responses registered either via the touch-sensitive screen or a button box, depending on the task. A brief description of the key measures for each of the tasks is presented in Table 1.

To measure verbal and non-verbal declarative memory, we used the Auditory Verbal Learning Task (AVLT) (Lezak et al. 2004), the PAL and the Pattern Recognition Memory (PRM) tasks from CANTAB, amended as in our previous study (Turner et al. 2003) to include an additional delayed recognition test after 20 min. For assessment of verbal and non-verbal working memory, we used forward and backward digit span from the Wechsler Adult Intelligence Scale (Lezak et al. 2004) and the SWM task from CANTAB with an additional 12-boxes level. Executive functions were tested by two novel variants of CANTAB tasks that also allow for greater sensitivity: a three-dimensional version of the attentional set-shifting task (3D-IDED) (Rogers et al. 1999) and the 'one-touch' version of the SoC spatial planning task (Owen et al. 1995). Further tests included the SST with cued dual-choice responses and an acoustic stop signal as previously described (Aron et al. 2003) and the Cambridge Gamble Task (CGT), a decision-making task developed by our group (Rogers et al. 1999) that is sensitive to prefrontal lesions (Manes et al. 2002).

The order of single tasks in the battery was fixed and carefully composed to minimise pro- and retroactive interferences: CGT, 3D-IDED, PRM, AVLT, Digit Spans, delayed PRM trial, delayed AVLT trial, one-touch SoC

Table 1 Summary of neuropsychological test battery

Task	Description	Reference	Important measures
Declarative memory			
AVLT	Auditory Verbal Learning Task: a paper-pencil test of word list learning with recall after multiple presentation, interference and delay	Lezak et al. 2004	Percentage correct
PRM	Pattern Recognition Memory: a computerised dual-choice test of abstract visual pattern recognition	Mehta et al. 1999	Percentage correct, response latency
PAL	Paired Associates Memory: delayed matching of one to eight shapes to learned locations on a touch screen	Blackwell et al. 2004	Total errors, trials to criterion
Working memory			
Digit spans	A paper-pencil test of verbal memory with immediate recall of digit sequences of increasing length	Lezak et al. 2004	Maximal span forward and backward
SWM	Spatial Working Memory: a computerised test of spatial working memory and strategic search of 'blue tokens' hidden in boxes, problems with 3 to 12 boxes	Owen et al. 1990	Total errors, between errors, within errors, strategy score
Planning and decision-making			
One-touch SoC	Stockings of Cambridge: a computerised test involving planning a sequence of moves to achieve a goal arrangements of coloured balls without moving the balls	Owen et al. 1995	Mean attempts, overall latency
CGT	Cambridge Gamble Task: computerised task that requires betting variable amounts of capital points (5 to 95%) in trials with varying chances to win (10 to 90%)	Clark et al. 2003	Percent likely choice, percent bet, deliberation times
Motor inhibition and attention			
SST	Stop Signal Task: computerised dual-choice reaction task with cued visual stimuli; reactions have to be stopped after an auditory signal	Aron et al. 2003	Go reaction time (Go RT), stop signal reaction time (SSRT), discrimination errors
3D-IDED	Three dimensional, intra- and extra-dimensional attentional set-shifting task	Rogers et al. 1999	Total errors, reversal errors, extra-dimensional shift (EDS) errors

Table 2 Demographic data and other baseline comparisons for each group of volunteers (mean±SD)

	Placebo (n=20)	Guanfacine 1 mg (n=20)	Guanfacine 2 mg (n=20)	p
Age (years)	25.4±4.7	25.8±5.9	26.9±6.5	0.701
NART (all)	118.6±4.8	116.7±7.5	115.5±8.5	0.380
FLE (only)	119.7±3.6	118.4±5.4	118.5±2.9	0.587
FLE (n)	16	15	15	
Students (n)	11	9	10	
YoE	17.1±2.1	16.5±1.7	16.4±1.5	0.401
ESS	9.1±3.9	8.8±3.1	7.3±3.6	0.233
Body weight (kg)	74.7±10.9	77.8±11.5	75.2±10.1	0.631

ESS Epworth sleepiness scale, *FLE* first language English, *NART* verbal IQ score as predicted by the National Adult Reading Test, *SD* standard deviation, *YoE* years of education

(after short training on original CANTAB version up to three move problems), PAL and SST. The whole battery took between 100 and 150 min to complete.

Statistical analysis All data were analysed using Windows versions of SPSS (Statistical Package for the Social Sciences). One-way and repeated measures ANOVAs were calculated for the planned main effects and interactions. Normal distribution was controlled and non-parametric tests used when necessary. All tests employ two-tailed statistics thresholded at $p<0.05$.

Results

The three randomly assigned groups were well matched for age, years of education, verbal intelligence (as evaluated with the National Adult Reading Test, NART) and daytime sleepiness (as evaluated with the Epworth Sleepiness Scale, ESS) (Table 2). Both doses of the study drug, guanfacine (Tenex) 1 or 2 mg, were well tolerated without side effects or complications. Two volunteers (n=1 on guanfacine 1 mg and n=1 on placebo) complained about headaches at the end of the testing session, which resolved after a cup of coffee and were therefore considered to be related to caffeine withdrawal rather than to the study medication. Debriefing at the end of the testing session revealed effective blinding: 71% in the placebo group and 36% in the drug groups (47% after 1 mg and 25% after 2 mg of guanfacine) made a correct judgment.

Physiological effects There was a significant Time×Drug interaction for systolic blood pressure [$F(8, 168)=2.5$, $p<0.02$], but no significant effects on diastolic blood pressure or pulse. At the end of the testing session (at +4 h), systolic blood pressure was significantly higher after placebo when compared to guanfacine 2 mg ($p=0.011$) and at trend level when compared to guanfacine 1 mg ($p=0.069$) (Fig. 1).

Subjective effects There were significant time (0 vs 4 h) effects for all VAS factors (all $p<0.01$) with less alertness,

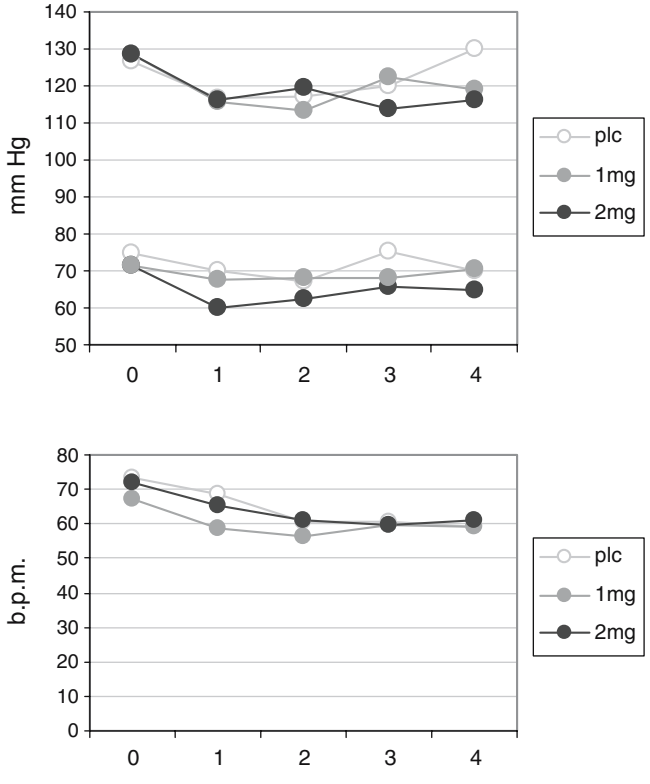

Fig. 1 Mean systolic (*upper group of lines*) and diastolic (*lower*) blood pressure (*top*) and pulse (*bottom*) after a single dose of guanfacine 1 mg, 2 mg or placebo (n=20 per group)

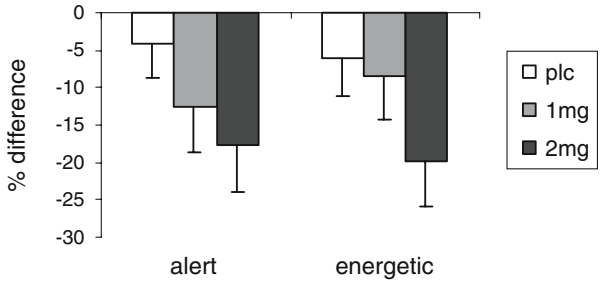

Fig. 2 Baseline minus end-of-study differences on selected self-ratings on visual analogue scale (VAS) after a single dose of guanfacine 1 mg, 2 mg or placebo (n=20 per group)

contentedness, calmness or tranquillity in the course of the testing session, but no significant drug effects or time by drug interactions. Visual inspection of individual items revealed numeric trends for reduced "alertness" and "energy" after guanfacine (Fig. 2).

Declarative memory (AVLT, PAL, PRM) There were significant verbal learning [$F(3,171)=220.9$, $p<0.001$], interference [$F(1,57)=54.7$, $p<0.001$] and delay [$F(1,57)=34.6$, $p<0.001$] effects, but no drug effects on AVLT performance.

All subjects but one completed the eight-shapes level of the PAL with ten or less trials. When comparing the six- and eight-shapes levels, there was a main effect of difficulty on trials to criterion [$F(1,55)=24.5$, $p<0.001$], but no significant drug effect or drug by difficulty interaction.

Similarly, in the PRM task, there was a significant delayed recognition effect [$F(1,51)=17.7$, $p<0.001$], but no significant drug effects on performance (Table 3).

Working memory (digit spans, SWM) There was a trend for dose-dependent effects of guanfacine on digit spans back-

Table 3 Summary of test results (mean±SD)

Task (time on task in this study)	Placebo	Guanfacine		*P*
		1 mg	2 mg	
AVLT (8.2±2.9 min)				
Percent correct (1st to 4th recall)	82.6±6.7	81.0±7.9	79.9±9.5	0.545
Percent correct (interference)	84.2±9.7	82.5±16.0	78.3±17.2	0.437
Percent correct (delayed)	84.2±15.0	80.8±20.3	79.6±17.6	0.702
PRM (7.1±2.7 min)				
Percent correct, immediate	97.2±4.0	91.3±14.7	96.7±6.3	0.111
Percent correct, delayed	90.3±10.4	81.6±17.7	87.3±10.5	0.141
Latency, immediate (ms)	1,719±493	1,765±383	1,682±320	0.807
Latency, delayed (ms)	2,077±840	1,953±398	1,695±217	0.101
PAL (8.2±3.0 min)				
Total errors	6.8±8.3	8.9±15.5	5.5±5.0	0.608
Trials to criterion, 8 shapes	3.0±2.1	2.6±1.6	2.3±1.1	0.360
Digit spans (5.1±1.1 min)				
Forward (max. 8)	7.2±1.1	7.4±1.0	7.2±1.0	0.836
Backward (max. 7)	6.3±0.8	6.0±1.1	5.5±1.4	0.082
SWM-12 (12.8±4.1 min)				
Total errors	27.2±21.1	36.4±23.3	26.5±19.6	0.271
Between errors	26.4±20.5	34.9±22.4	25.6±19.3	0.304
Within errors	2.5±3.2	4.6±6.7	2.3±2.7	0.233
Strategy score	33.0±6.0	31.5±8.0	33.4±7.3	0.676
One-touch SoC (14.6±4.5 min)				
Problems solved at 1st attempt	20.2±2.6	19.9±2.8	19.4±3.3	0.682
Mean attempts, 4–6 move problems	1.4±0.3	1.4±0.4	1.5±0.4	0.796
Latency, 4–6 move problems (s)	27.3±13.5	27.5±16.1	27.0±15.4	0.994
CGT (25.9±4.3 min)				
Percent likely choice	96.6±5.7	97.6±3.9	98.1±4.0	0.510
Percent bet	60.7±10.3	62.7±7.4	64.4±10.4	0.466
Latency (ms)	1,940±851	2,000±816	1,943±543	0.916
Stop Signal Task (22.5±4.8 min)				
Go reaction time (ms)	381.7±61.6	429.9±64.4	400.7±66.6	0.070
Go reaction time variability (SD)	159.1±146.1	163.2±99.6	126.0±46.2	0.493
Stop-signal reaction time (ms)	215.9±62.0	209.4±63.1	205.3±72.9	0.884
Discrimination errors	5.5±4.4	2.7±3.6	5.7±7.1	0.142
3D-IDED (6.4±2.3 min)				
Total errors	17.3±10.1	19.0±10.7	17.0±9.3	0.796
Total reversal errors	7.1±7.2	7.3±5.1	8.5±6.3	0.754
Total EDS errors	7.9±8.1	8.4±8.5	4.7±3.6	0.233

AVLT Auditory Verbal Learning Test, *CGT* Cambridge Gamble Task, *PAL* Paired Associates Learning, *PRM* Pattern Recognition Memory, *P* main effect drug (ANOVA), *SD* standard deviation, *SoC* Stockings of Cambridge, *SWM-12* Spatial Working Memory (12 boxes version), *3D-IDED* three-dimensional, intra- and extra-dimensional set-shifting task

ward [$F(2,57)=2.6$, p=0.082], but not for forward spans. Post-hoc contrasts showed a trend for worse verbal working memory performance in the backward spans after guanfacine 2 mg ($p=0.069$), but not after 1 mg as compared to placebo. Digit spans backward correlated significantly ($r_S=0.347$; uncorrected $p<0.01$) with the decrease of alertness (Herbert et al. 1976) in the course of the testing sessions (final VAS minus baseline VAS).

In the SWM task, there was a difficulty (number of boxes) effect for between search [$F(3,55)=35.6$, $p<0.001$] and overall errors [$F(3,55)=35.5$, $p<0.001$], but no drug effects or drug by difficulty interactions, either on errors, latency or strategy score (Table 3).

Planning (one-touch SoC) There were significant difficulty effects on trials to criterion [$F(3,53)=11.5$, $p<0.001$] and latencies [$F(3,53)=33.0$, $p<0.001$] with more attempts and longer latencies in conditions with more minimal moves required, but no drug effects or drug by difficulty interactions on performance measures in the one-touch SoC task.

Attentional set-shifting (3D-IDED) All participants passed the (penultimate) extra-dimensional stage of this task. There were no drug effects on total errors, reversal errors, extra-dimensional errors or latencies in the 3D-IDED task (Table 3).

Decision-making (CGT) Data for the proportion of choices to the likely outcome in the CGT were highly skewed such that the majority of subjects in each group always selected the box colour (placebo=50% of subjects, 1 mg=60%, 2 mg=70%). Kolmogorov–Smirnov tests indicated significant deviation from normality even after arcsine transformation (Howell 2001), and consequently, the effect of drug condition was assessed using a non-parametric Kruskal–Wallis test on the proportion of likely choices, averaged across condition (ascend, descend) and box ratio. There was no significant effect of group ($\chi^2=1.35$, df 2, $p=0.510$) on this averaged score. Betting data were normally distributed. A 2 (condition: ascend, descend)×4 (ratio: 9–1, 8–2, 7–3, 6–4)×3 (drug: placebo, 1 or 2 mg) mixed-model ANOVA indicated significant main effects of condition [$F(1,57)=67.8$, $p<0.001$] and ratio [$F(3,171)=388.5$, $p<0.001$], due to subjects placing higher bets in the descend condition compared to the ascend condition and subjects placing higher bets at greater ratios (9–1 vs 6–4). There were no significant main effects of drug treatment, and drug treatment did not interact significantly with condition or ratio (all $F<1.0$). Deliberation times were square root transformed to reduce deviation from the normal distribution (Howell 2001). A 2×4×3 mixed-model ANOVA (as for percentage bet) indicated a main effect of ratio [$F(3,171)=21.2$, $p<0.001$] due to faster responses at higher ratios (i.e. 9–1 decisions faster than 6–4 decisions), but no significant effects of drug treatment or interaction terms (all $F<1.3$). In summary, guanfacine did not modulate probabilistic judgment or deliberation, or betting behaviour, on the CGT.

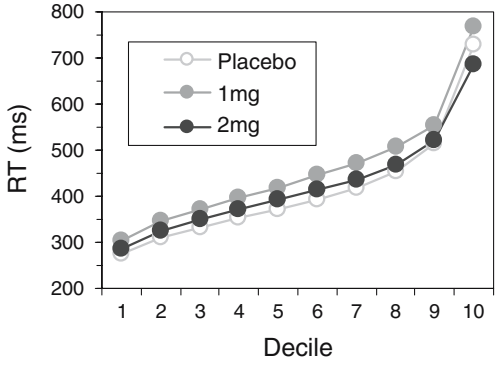

Fig. 3 Distribution of reaction times (*RT*) in the 'Go' condition of the Stop Signal Task after placebo and guanfacine (1 mg or 2 mg)

Motor inhibition (SST) Two subjects ($n=1$ from the placebo and $n=1$ from the 2 mg group) were excluded from the analysis of SST data for very slow performance, greater than three standard deviations from the mean for their group. It is likely that these subjects delayed motor responding to improve stop accuracy, invalidating a core assumption of the race model (Logan et al. 1983). There were no significant effects of guanfacine on either SSRT [$F(2,55)=0.124$, $p=0.884$] or discriminative response errors [$F(2,55)=2.02$, $p=0.142$]. The effect of group on median Go reaction time approached significance [$F(2,55)=2.79$, $p=0.07$] with a significant difference between placebo and 1 mg dose ($t=2.34$, $p=0.023$), but no difference between placebo and 2 mg ($t=0.914$, $p=0.365$). Reaction time distributions in each condition were further analysed using Vincentized cumulative probability curves, averaged across each group. Figure 3 illustrates that the 1 mg dose of guanfacine shifted the entire RT distribution, indicating a generalised slowing effect rather than a specific effect on attentional arousal which would predominantly affect the slower part of the distribution (Ratcliff 1979).

Discussion

This is the first dose-ranging study to investigate the effects of guanfacine (1 and 2 mg) on prefrontal cognitive functions in healthy male adults using a double-blind and placebo-controlled parallel groups design. The results of this study indicate a mild sedative effect of guanfacine, but no unequivocal effects on executive or memory functions. We could not replicate findings of Jäkälä et al. (1999a,c), who reported improved cognitive performance after guanfacine ~2 mg on the SWM, PAL and SoC tasks. Differences of sample size (20 per group in our study vs 9 to 12 in the Finish study), homogeneity of groups (general population including students vs students only), pharmacological design (fixed dose vs individual dose), influence of practice effects (parallel groups vs mixed design with one drug and one placebo condition per volunteer) and differing task versions (modified higher sensitivity vs standard versions of SWM and SoC) may explain the divergent findings of these otherwise comparable studies.

In our study, guanfacine was mildly hypotensive, especially at the end of the testing session. The drug had no clear subjective effects as measured by VAS. The higher (2 mg) dose was associated with a trend for impairment on backwards digit span, a measurement of manipulation in verbal working memory. This effect has to be interpreted carefully because it was in the opposite direction from our prediction, and we did not adjust the significance level for multiple comparisons. On the SST, the lower (1 mg) dose of guanfacine slowed motor responding (Go RT), but did not affect motor inhibition, in terms of stop signal reaction time (SSRT). The trend effect on Go RT is consistent with a de-arousing sedative action rather than a stimulant effect. Reaction time distributions on the SST suggest that the 1 mg dose of guanfacine affected all parts of the RT distribution, indicating a generalised sedative effect rather than fluctuations in attentional processing (Ratcliff 1979), which predominantly affect the slower tail of the RT distribution.

Guanfacine is proposed as a potential treatment for ADHD, with positive findings in open (Chappell et al. 1995; Horrigan and Barnhill 1995; Hunt et al. 1995; Posey et al. 2004) and controlled studies (Scahill et al. 2001; Taylor and Russo 2001; Cummings et al. 2002). An extended release preparation of guanfacine is currently under evaluation for the treatment of ADHD in children. Traditional psychostimulant medications for ADHD (methylphenidate and amphetamine) act to increase extracellular catecholamine levels via effects at transporter molecules. Although there is no doubt that psychostimulants are effective in ADHD, around 30% of patients do not adequately respond or cannot tolerate treatment (Biederman et al. 2004). With greater selectivity to noradrenaline, guanfacine has been suggested to provide a useful alternative to psychostimulant medication. Differential contributions of dopamine and noradrenaline to clinical effects of ADHD treatments are an important area of ongoing research.

Impaired motor inhibition (as indicated by increased SSRT) is a core cognitive deficit in ADHD (Barkley 1997; Sonuga-Barke 2005) and is improved by psychostimulant treatment. A recent study in ADHD children with selective noradrenaline and dopaminergic agents (desipramine and levodopa, respectively) indicated noradrenergic mediation of the SSRT improvement (Overtoom et al. 2003). The SWM task from CANTAB is also highly sensitive to ADHD diagnoses, and performance in ADHD and healthy volunteers is improved by methylphenidate treatment (Elliott et al. 1997; Mehta et al. 2004). The present data suggest that the putative modulatory effects of noradrenaline on inhibitory control and working memory are not modulated via the α_{2A}-adrenergic receptor specifically. Presumably, in normal young subjects, noradrenaline regulates higher-level cognitive function through effects at other receptors (Arnsten and Robbins 2002; Barch 2004; Müller et al. 2005). For example, whereas there were no effects of reboxetine (O'Carroll and Papps 2003) and guanfacine (present study) on decision-making performance, Rogers et al. (2004) previously reported impaired decision-making on a similar gambling task following an acute dose of propranolol, which antagonises the beta-adrenergic receptor.

It is possible that guanfacine has qualitatively distinct neurocognitive properties in patients with ADHD as compared to healthy volunteers. Beneficial effects of guanfacine in patients with ADHD included improved response inhibition in a Stroop task (Taylor and Russo 2001) and better performance on a continuous performance task (Scahill et al. 2001). In the latter study, however, the cognitive effects of guanfacine were compromised by considerable baseline differences between the two groups, both for omission and commission errors. Alternatively, the positive clinical effects of guanfacine on hyperactivity and tics may be explained by its mild sedative properties. Spontaneously hypertensive rats are an established animal model of ADHD: guanfacine improves sustained attention, impulsivity and hyperactivity in these rats and has a sedating effect on normal rats (T. Sagvolden, personal communication). The pharmacological mechanism of de-arousing actions of α_2 agonists is not clear. Down-regulation of meso-prefrontal dopamine neurons has been excluded in an animal study (Morrow et al. 2004), and, for lower doses, feedback inhibition of noradrenaline release via presynaptic α_2 receptors seems to be the most plausible mechanism (Sorkin and Heel 1986; Mosqueda-Garcia 1990). In contrast to benzodiazepine sedation, subjects treated with noradrenergic α_2 agonists can switch rapidly from a state of extremely low to almost full consciousness following phasic increases in arousal or cognitive demand, as demonstrated in an elegant fMRI study comparing the effects of dexmedotomidine and midazolam (Coull et al. 2004).

Limitations of our study include the use of a relatively heterogeneous and well-educated sample of male volunteers, the decision not to use a dose of guanfacine higher than 2 mg to avoid potential side effects and the sample size. However, cognitive-enhancing effects of psychostimulants like methylphenidate and modafinil have been shown in similar studies using parallel group designs (e.g. Turner et al. 2003). Furthermore, equivalent doses between studies in experimental animals (rats, monkeys) and humans are difficult to calculate; we can therefore not exclude the possibility of under-dosing. Accepting the good tolerability of 1 and 2 mg doses in this study, cognitive effects of higher doses (3 or 4 mg) of guanfacine would be a worthwhile target for future research; however, higher doses are likely to increase sedation and other side effects.

In conclusion, this study in healthy male volunteers found no improvement of memory or executive functions after 1 or 2 mg of guanfacine. There was a trend for a dose-dependent impairment of backwards digit span and a significant slowing of Go reaction time in the Stop Signal Task. These actions of the drug are likely related to sedative effects on systolic blood pressure and self-rated alertness. A de-arousing effect of guanfacine is presumably mediated via presynaptic α_{2A}-adrenergic receptors. It remains unclear whether beneficial cognitive effects can be seen in

healthy volunteers at higher doses and whether the efficacy of guanfacine in patients with ADHD and tic disorders is related to cognitive enhancement or mild sedation. Finally, these results in healthy volunteers cannot exclude the possibility that guanfacine may have significant cognitive-enhancing effects in other settings where noradrenergic arousal systems are compromised, either because of age, concurrent medication or disease. Further studies are required to address these issues.

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