

Guanfacine, But Not Clonidine, Improves Planning and Working Memory Performance in Humans

Pekka Jäkälä, M.D., Minna Riekkinen, M.D., Jouni Sirviö, Ph.D., Esa Koivisto, B.Sc., Kosti Kejonen, B.Sc., Matti Vanhanen, B.Sc., and Paavo Riekkinen, Jr., M.D.

The present study compares, using a double-blind, placebo controlled design the effects of two α 2-agonists, clonidine (0.5, 2, and 5 μ g/kg) and guanfacine (7 and 29 μ g/kg) on spatial working memory, planning and attentional set-shifting, functions thought to be dependent on the "central executive" of the prefrontal cortex. Blood pressure and the subjective feeling of sedation were affected equally by clonidine and guanfacine. The 0.5 μ g/kg and 5 μ g/kg doses of clonidine disrupted spatial working memory, but the medium dose had no effect. The 0.5 and 2 μ g/kg doses of clonidine increased impulsive responding in the planning test. The 5 μ g/kg dose of clonidine slowed responding at

effortful levels of planning and attentional set-shifting tests. The 29 μ g/kg dose of guanfacine improved spatial working memory and planning. Guanfacine had no effect on attentional set-shifting. These data indicate that guanfacine improved planning and spatial working memory, but clonidine dose-dependently disrupted performance. It is possible that the greater selectivity of guanfacine for α 2A-adrenoceptor subtype may underlie its differences from clonidine. [*Neuropsychopharmacology* 20:460–470, 1999] © 1999 American College of Neuropsychopharmacology. Published by Elsevier Science Inc.

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Defective executive functions, such as planning, working memory and attentional set-shifting, are characteristic features of several neurological disorders including Alzheimer disease, frontal lobe dementia, and basal ganglia disorders (Sahakian and Owen 1992; Robbins et al. 1994; Coull et al. 1996). Previous evidence has suggested that the prefrontal cortex is involved in the modulation of executive functions, and that dysfunction of

this region may result in specific cognitive defects (Luria 1969; Owen et al. 1990, 1995). For example, neuroimaging studies have revealed that discrete regions of the prefrontal cortex are activated by tasks that measure spatial working memory (Owen et al. 1996a), planning (Baker et al. 1996) or attention (Coull et al. 1996). Furthermore, Owen et al. (1991) compared the performance of patients with excision of frontal lobe or temporal lobe and patients who had undergone amygdalo-hippocampectomy in tests that measure executive functions. The frontal excision patients were impaired in measures of spatial working memory, planning [Tower of London (TOL)] and attentional set-shifting [Intra-dimensional/extra-dimensional set shifting, ID/ED]. The patients with temporal excision and selective amygdalo-hippocampectomy performed accurately in the TOL test, were slower to respond at the extra-dimensional set-shifting stage of the ID/ED test, and were selectively impaired at the most difficult 8-box problem level in a

From the Department of Neuroscience and Neurology, University and University Hospital of Kuopio, Kuopio, Finland.

Address correspondence to: Paavo Riekkinen, Jr., M.D., Ph.D., Department of Neuroscience and Neurology, University Hospital of Kuopio, Canthia Building, Kuopio, P.O. Box 70211, Finland.

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spatial working memory test (Owen et al. 1990, 1991, 1995). The frontal excision patients solved the TOL task less accurately and their speed of thinking was not as quick (Owen et al. 1990). In the ID/ED attentional test, the frontal patients exhibited deficits when they were confronted with the demanding extra-dimensional set-shifting stage of this test, but speed of responding remained normal (Owen et al. 1991). In contrast, all three groups of patients were impaired in a spatial working memory task (Owen et al. 1995). However, the nature of the performance defect differed in these groups, such that frontal excision patients had a poor search strategy whereas temporal lobe patients exhibited a mnemonic failure.

Pharmacological studies in animals have revealed that noradrenergic innervation is important for the functioning of the prefrontal cortex (Arnsten 1993; Berridge et al. 1993). Depletion of catecholamines by infusing 6-hydroxydopamine into the principal sulcus impairs the accuracy of young monkeys in a delayed response task (Brozoski et al. 1979) and the performance accuracy of these lesioned monkeys can be markedly improved by administration of α 2-agonists, such as clonidine or guanfacine (Arnsten et al. 1988). As monkeys age, their levels of central noradrenaline become depleted and a defect in working memory performance is also revealed. This age-related spatial working memory failure can also be alleviated by treatment with α 2-agonists (Arnsten and Contant 1992; Arnsten 1993; Arnsten and Cai 1993). Importantly, the improvement in working memory induced by α 2-agonists is blocked by an α 2-antagonist, but not by an α 1-antagonist (Arnsten and Cai 1993). Therefore, one could propose that post-synaptic stimulation of α 2-adrenoceptors enhances working memory performance and the efficiency of the sulcus principalis (Arnsten and Goldman-Rakic 1985). Unfortunately, the sedative and hypotensive side-effects associated with α 2-agonists, such as clonidine, limit their use in the treatment of disorders associated with frontal lobe dysfunction (Arnsten et al. 1988).

Three subtypes of α 2-adrenoceptors have now been cloned in humans: the α 2A, α 2B, and α 2C (Kobilka et al. 1987; Regan et al. 1988; Aoki et al. 1994). The anatomical distribution of all subtypes is unique, supporting the concept that adverse effects of α 2-agonists can be dissociated from beneficial drug effects (MacDonald and Scheinin 1995). Indeed, in the rat brain, α 2B messenger (m) RNA is found exclusively in the thalamus (Scheinin et al. 1994) and activation of this receptor subtype may impair functioning of thalamocortical arousal mechanisms (Riekkinen Jr. et al. 1993). The brainstem nucleus tractus solitarius, considered to be critical for the hypotensive effect of subtype non-selective α 2-agonists (Reis et al. 1984) contains α 2A and α 2C mRNA (MacDonald and Scheinin 1995). Importantly, in the prefrontal

cortex including the sulcus principalis region, the α 2A subtype predominates (Aoki et al. 1994). In monkeys, the beneficial effects of subtype non-selective α 2-agonists are related to their selectivity for the α 2A site (Arnsten et al. 1988; Arnsten and Leslie 1991). Furthermore, idazoxan, a non-subtype selective α 2-antagonist, blocked the beneficial effect of an α 2-agonist on working memory, but prazosin which in addition to its α 1-antagonist properties has quite high affinity for α 2B- and α 2C-adrenoceptors was ineffective in reversing the positive effects (Uhlen and Wikberg 1991; Marjamäki et al. 1993). These data suggest that actions at α 2A-adrenoceptors may be important in mediating the improvement in prefrontal functions in monkeys (Arnsten et al. 1996).

We designed the present study to investigate the hypothesis that α 2A-adrenoceptor activation is important for the beneficial effect of α 2-agonists on frontal lobe functions in humans (Arnsten et al. 1996). The theory of working memory that has been suggested by Baddeley (1986) includes an attentional co-ordinator, the "central executive," which controls the modality related slave systems of working memory. Dysfunction of the central executive located in the prefrontal cortex also disrupts performance in other tests measuring executive functions, such as TOL planning and ID/ED attentional set-shifting tests. Therefore, if α 2-adrenoceptors are important for the modulation of working memory, their role in other frontal functions, such as planning and attentional set-shifting, may also be important (Owen et al. 1990, 1991, 1995). We compared the actions of clonidine and guanfacine on spatial working memory, TOL and ID/ED attentional set-shifting tests in healthy volunteers. We hypothesized that the beneficial effects of guanfacine on frontal lobe functions would be more apparent than those of clonidine, as guanfacine has a greater α 2A-adrenoceptor selectivity.

MATERIALS AND METHODS

Subjects

Six separate groups of healthy and equally intelligent (as indicated by WAIS-R Vocabulary subtest and verbal fluency tests) (Borkowski et al. 1967; Wechsler 1992) young (23–35 years of age, $n = 55$) university educated volunteers took part in the study. None of the volunteers were receiving concurrent medication, nor had a history of psychiatric, neurologic, or cardiovascular illnesses, or other medical conditions that could interfere with central nervous system functions or interpretation of the results. The studies were approved by the local ethical committee and national drug regulatory authority, and all the subjects provided their informed consent in writing. All the subjects were covered by an insur-

ance. The number of test sessions was limited to two at the request of the local ethical committee.

Pharmacological Manipulations

Six different experimental groups were used. Five of the groups received once placebo and clonidine or guanfacine at one dose. Clonidine hydrochloride (Catapressan,[®] Boehringer Ingelheim, Germany) was administered PO 0.5 ($n = 6/\text{group}$), 2.0 ($n = 8/\text{group}$) or 5.0 ($n = 8/\text{group}$) $\mu\text{g}/\text{kg}$ in tablet form, or appropriate oral placebo, 90 min before starting the test session. Guanfacine hydrochloride (Estulic,[®] Sandoz Oy) was administered PO 7 ($n = 9/\text{group}$) and 29 ($n = 12/\text{group}$) $\mu\text{g}/\text{kg}$ in tablet form, or appropriate oral placebo, 90 min before starting the test session. The doses were $\pm 3\%$ accurate: e.g., $5 \pm 0.15 \mu\text{g}/\text{kg}$ clonidine. One group of 12 subjects received placebo before both of the two testing sessions.

Subjects from the clonidine or guanfacine treated groups attended on two occasions (at least seven days between sessions), and received the relevant pharmacological manipulation on one occasion, with an appropriate placebo on the other day in a counterbalanced order for each group (placebo-controlled double-blind cross over design). One of the groups was tested identically but placebo was administered before both testing sessions. Both the subject and the investigator were blinded to the composition of the tablets.

Procedure and Experimental Design

Experimental sessions were started at the same time of each testing day for each individual subject. The entire test session lasted 60–90 min for all the subjects, and the testing began 90 min post-ingestion of tablets for all the subjects.

Visual Analogue Scale

After completion of the test session, the subjects were asked to rate themselves for subjective feelings of "sedation/tiredness" by asking them to place a mark on a 100 mm line numbered from 1 to 10, with 1 representing "not at all" and 10 representing "exceedingly sedated/tired."

Monitoring of Blood Pressure

Blood pressure of the subjects was measured before they received the study drugs or matching placebo tablets, 90 min afterwards (i.e., just before the beginning of the test session), and after the completion of the test session which lasted for 60–90 min.

Tests

Spatial Working Memory (Owen et al. 1990). This is a self-ordered search test of working memory, which also incorporates a strategic search component to tax "central executive" (Owen et al. 1990). Subjects had to search through a number of "boxes" (4, 6 or 8) for a hidden "token" without returning to a box which they had already examined on the same trial (to avoid "within search" errors) or which had already contained a token in the previous trial (to avoid "between search" errors). Tokens were hidden one at a time, and were never hidden in the same box twice. The numbers of each type of error at each level of difficulty were measured. In addition, a measure of the use of an efficient search strategy was also derived from this test, defined as the total number of times a subject began a search with a different box on the 6- and 8-box problems. The lower this number, the greater the use of a strategy (Owen et al. 1990 for a fuller description). The results of 6- and 8-box levels were used in the analysis. The 4-box level was not included in the analysis, since it is too straightforward for healthy volunteers and a ceiling effect occurs.

Tower of London (Owen et al. 1990). This test of planning requires subjects to compare two different arrangements of "snooker or pool balls" in "socks or pockets" (one presented on the top half of the screen, the other on the bottom), and rearrange the balls in the lower half of the screen such that their positions match the goal arrangement in the upper half. Balls were moved by touching the ball to be moved, and then touching the space it was then to occupy. The number of moves required by the subject to rearrange the balls, as well as selection latencies for both the first and subsequent moves were recorded by the computer. These latencies were termed "initial" and "subsequent thinking times" respectively. For each test problem, a "yoked control" condition was employed to provide baseline measures of motor initiation and execution times. In this condition, the actual solutions that subject had generated for the two, three, four and five move problems were played back to the subject one move at a time, and he or she had simply to follow the movements that the computer made. In the analysis of results, these latencies were subtracted from the original selection latencies to give "purer" estimates of cognitive thinking time corrected for sensori-motor factors. The results of four and five move problems are shown here, as the ceiling effect blocks the ability to detect drug induced effects on performance on easier levels of the test.

ID/ED Attentional Set-Shifting Task (Owen et al. 1991). This is a test of attentional set-shifting based in part on the Wisconsin card sort test (WCST). There are nine stages in which a subject has to learn a visual discrimination performance to a set criterion (six consecu-

Table 1. Clonidine and Guanfacine at the Highest Doses Tested Increased Feelings of Sedation as Assessed with the Visual Analogue Scale

	Placebo	Drug
Clonidine (μg/kg)		
0.5	3.3 ± 1.1	3.0 ± 1.7
2	3.2 ± 1.4	3.3 ± 1.3
5	3.1 ± 1.5	5.0 ± 1.3 ^a
Guanfacine (μg/kg)		
7	3.0 ± 1.3	3.3 ± 1.4
29	3.2 ± 1.4	4.5 ± 1.3 ^a

Values (range 0–10; 1 representing not at all tired/sedated, and 10 representing exceedingly tired/sedated) represent ratings after completion of the test session (about 180 min after taking the study drug or matching placebo). Results are expressed as mean ± SD.

^a*p* < .05 vs. placebo.

tive trials correct). The first two stages required a simple visual discrimination (SD), followed by a reversal of this discrimination upon reaching the criterion (SDR). Another visual dimension is then introduced which the subject must learn is irrelevant [compound discrimination with stimuli separated (C_D) or superimposed (CD)], even in the situation of a reversal of the original discrimination [compound discrimination reversal (CDR)]. An intra-dimensional shift is then introduced, at which point new exemplars of the two dimensions are given, and the subject must now learn a new discrimination to criterion [intra-dimensional shift (IDS)] followed by a reversal of this rule [intra-dimensional reversal (IDR)]. The penultimate stage of the test introduces an extra-dimensional shift, where again new exemplars of the two dimensions are presented, but this time the subject must shift his or her attention to the dimension which was previously irrelevant [extra-dimensional shift (EDS)]; followed finally by a reversal of this rule [extra-

dimensional reversal (EDR)]. The EDS is akin to a category shift in the WCST. For each stage of the test, the computer calculates the number of trials to the criterion, number of errors made, and the latency to complete each stage.

Statistics

The repeated measures cross-over design may carry with it the problem of practice effects, which may confound the validity of the statistical interactions. To reveal possible practice effects in these tasks, we had beforehand tested a separate group (*n* = 12) of normal young healthy control subjects with the same test battery on two occasions with no less than 1 week between sessions. In the analysis of test data, a repeated measures analysis of variance (MANOVA) was used to analyze group (groups 1–6, see: pharmacological manipulations), repetition and difficulty level effects, and the appropriate interactions. A paired samples *t*-test was used also to compare drug-induced performance changes.

RESULTS

VAS Sedation Rating

The highest doses of clonidine and guanfacine (5 and 29 μg/kg, respectively) slightly increased the subjective feelings of sedation vs. placebo (*p* < .05 for both), whereas lower doses of the drugs had no effect (*p* > .01 for all) (Table 1).

Blood Pressure

Both clonidine (5 μg/kg) and guanfacine (29 μg/kg) at the highest doses used slightly reduced both systolic and diastolic blood pressures (*p* < .05 vs. placebo),

Table 2. Clonidine and Guanfacine at the Highest Doses Tested Decreased Blood Pressure

	Placebo			Drug		
	0 min	+90 min	+180 min	0 min	+90 min	+180 min
Clonidine (μg/kg)						
0.5	128/79	126/78	128/78	126/78	125/78	127/79
2	126/78	126/78	126/78	126/78	123/78	122/75
5	127/78	125/77	128/79	127/78	120/74 ^a	114/70 ^a
Guanfacine (μg/kg)						
7	125/78	124/78	125/78	124/79	126/78	128/80
29	127/77	129/78	126/78	129/77	122/78 ^a	117/75 ^a

Abbreviations: +90 min = 90 min after taking the study drug or matching placebo, i.e., just before starting the test session; +180 min = 180 min after taking the study drug or matching placebo, i.e., after completion of the test session.

Doses are expressed as μg/kg and blood pressure values (means of systolic/diastolic pressures) as mmHg.

^a*p* < .05 vs. placebo.

whereas the lower doses of the drugs had no significant effects on blood pressures ($p > .1$ for all) (Table 2).

Spatial Working Memory

The between or within search errors and strategy score of the placebo treated group did not differ during the first and second testing session (t -test: $p > .1$; for all comparisons).

Clonidine. A comparison of the between search errors of clonidine 0.5 $\mu\text{g}/\text{kg}$, clonidine 2 $\mu\text{g}/\text{kg}$, clonidine 5 $\mu\text{g}/\text{kg}$ with only placebo treated groups revealed a significant repetition ($F(1,29) = 7.9, p = .009$) effect and repetition \times group interaction ($F(3,29) = 4.22, p = .014$), indicating that 0.5, 2, or 5 $\mu\text{g}/\text{kg}$ of clonidine modulated performance (Figure 1, Part A). The 0.5 and 5 $\mu\text{g}/\text{kg}$ clonidine-treated groups made more between search errors after clonidine than after placebo treatment at 6- and 8-box levels (t -test: $p < .01$ for all comparisons). The medium dose of clonidine failed to affect the number of between search errors (t -test: $p > .4$; for both comparisons). In none of the groups were the number of within search errors or the strategy score affected by repetition ($(F(1,29)/(3,29) < 0.4, p > .55$; for all comparisons) (data not shown).

Guanfacine. Analysis of 7 $\mu\text{g}/\text{kg}$ or 29 $\mu\text{g}/\text{kg}$ of guanfacine- and placebo-treated groups showed a sig-

nificant repetition effect ($F(1,30) = 12.3, p = .001$) and repetition \times group interaction ($F(3,30) = 5.68, p = .008$) on the between search errors (Figure 1, panel B). Guanfacine 7 $\mu\text{g}/\text{kg}$ had no effect on between search errors (t -test: $p = .65$), but guanfacine 29 $\mu\text{g}/\text{kg}$ decreased between search errors at 6- and 8-box levels (t -test: $p < .01$; for both comparisons). In the contrast, within search errors and strategy score analysis revealed no repetition effects or repetition \times group interactions ($F(1,30)/(2,30) < 2.0, p > .2$, for all comparisons) (Data not shown).

Tower of London

The number of excess moves did not significantly decrease in the placebo treated group during the second testing session (t -test: $p = .28$), but the initial thinking times were significantly reduced (t -test: $p = .006$) with a similar trend in subsequent thinking times (t -test: $p = .071$).

Clonidine. The effect of repetition on the initial and subsequent thinking times varied between 0.5, 2, or 5 $\mu\text{g}/\text{kg}$ clonidine- and placebo-treated groups (repetition \times group interaction: $F(3,29) > 9.2, p < .001$; for both comparisons) (Table 3). A comparison of control treated group with 0.5 and 2 $\mu\text{g}/\text{kg}$ clonidine treatment revealed that clonidine decreased initial thinking times (treatment: $F(1,16)/(1,18) < 0.001, p < .008$; for both

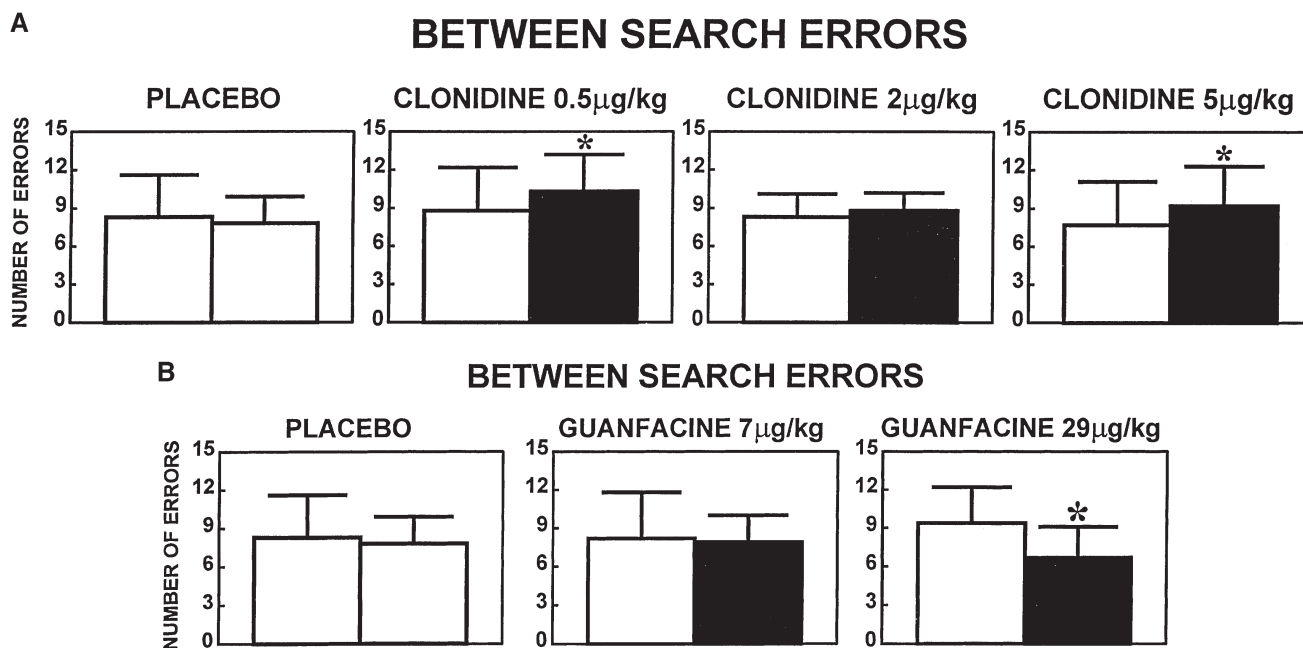


Figure 1. Effects of clonidine and guanfacine on between search errors in the spatial working memory test. On the Y-axis the number of errors made is shown. On the X-axis different treatments are shown. The values are expressed as mean \pm SD. (A) Clonidine 0.5 and 5 $\mu\text{g}/\text{kg}$ increased between search errors in the spatial working memory task, but clonidine 2 $\mu\text{g}/\text{kg}$ had no effect. Clonidine (solid bars) and placebo (open bars). (B) Guanfacine 29 $\mu\text{g}/\text{kg}$ decreased but guanfacine 7 $\mu\text{g}/\text{kg}$ had no effect on between search errors. Guanfacine (solid bars) and placebo (open bars). * $p < .05$ vs. own baseline values.

Table 3. Tower of London Test (Planning Ability)

Treatment Group	Initial Thinking Times (s)		Subsequent Thinking Times (s)	
	C	C	C	C
C + C	13.8 ± 4.8	12.1 ± 4.4**	6.5 ± 3.7	5.1 ± 2.2
	C	CLO	C	CLO
C + CLO 0.5	13.7 ± 2.7	7.7 ± 1.8*	7.8 ± 3.8	7.1 ± 2.9
C + CLO 2	15.6 ± 6.5	10.7 ± 3.0*	7.0 ± 3.5	5.8 ± 2.8
C + CLO 5	16.3 ± 5.6	19.7 ± 4.2*	7.1 ± 3.7	10.8 ± 2.6*
	C	G	C	G
C + G 7	14.1 ± 4.4	12.9 ± 4.3	7.0 ± 3.4	5.7 ± 2.1
C + G 29	13.6 ± 4.7	12.1 ± 4.6	6.1 ± 3.8	4.9 ± 2.2

Abbreviations: C + C = control group; C + CLO 0.5, 2, or 5 = 0.5, 2, or 5 µg/kg placebo + clonidine treated group; C + G 7 or 29 = 7 or 29 µg/kg placebo + guanfacine treated group.

In the Tower of London test of planning ability, control group had significantly shorter initial thinking times and nearly significantly shorter subsequent thinking times during the second session, respectively. 0.5 and 2 µg/kg clonidine further decreased initial thinking time and 5 µg/kg clonidine increased initial and subsequent thinking times. 7 and 29 µg/kg guanfacine failed to affect normal performance at initial or subsequent thinking time measures. The values (in seconds, s) are expressed as mean ± SD.

**p* < .05 treatment group × repetition interaction, repeated measures analysis of variance.

***p* < .05 vs first session of the control group, *t*-test.

comparisons), but had no effect on the subsequent thinking times. In contrast, 5 µg/kg clonidine increased initial and subsequent thinking times (treatment: *F*(1,17) > 17.7, *p* < .001; for both comparisons). The analysis of excess moves made revealed no repetition effects or repe-

tition × group interaction (*F*(1,29)/(1,30) > 14.8, *p* < .001) (Figure 2, panel A).

Guanfacine. Analysis of 7 and 29 µg/kg placebo- and guanfacine-treated groups revealed a repetition effect

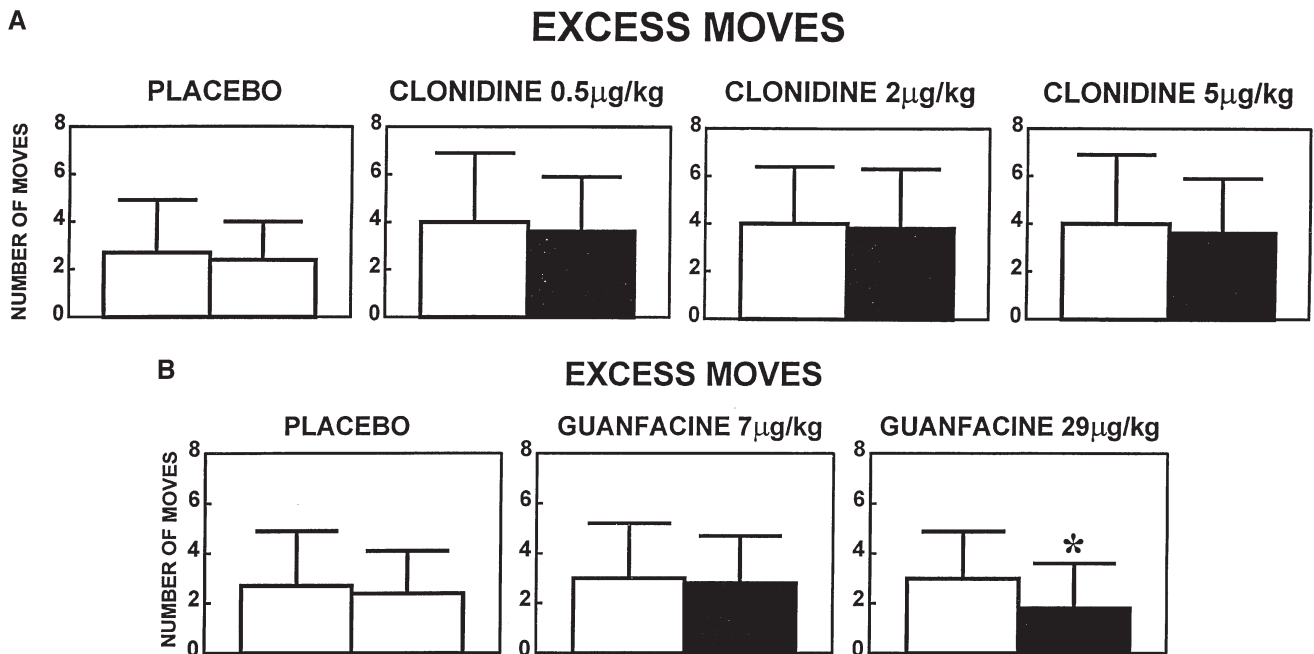


Figure 2. Effects of clonidine and guanfacine on the number of excess moves made in Tower of London planning test. On the Y-axis the number of errors made is shown. On the X-axis different treatments are shown. The values are expressed as mean ±SD. (A) Clonidine 0.5, 2 or 5 µg/kg had no effect on the number of excess moves made. Clonidine (solid bars) and placebo (open bars). (B) Guanfacine 29 µg/kg decreased and guanfacine 7 µg/kg had no effect on the number of excess moves made. Guanfacine (solid bars) and placebo (open bars). **p* < .05 vs. own baseline values.

($F(1,27) = 24.3, p < .001$) but no repetition \times group ($F(2,27) = 0.001, p = .998$) interaction, suggesting that guanfacine failed to modulate initial and subsequent thinking times (Table 3). In contrast, the number of excess moves showed a repetition effect ($F(1,30) = 10.7, p < 0.003$) and a nearly significant repetition \times group ($F(2,30) = 3.1, p = .06$) interaction. Post hoc comparison of the group 5 (29 $\mu\text{g}/\text{kg}$ guanfacine treated) with placebo-treated group revealed a repetition effect ($F(1,22) = 19.0, p > .001$) and a repetition \times group ($F(1,22) = 7.9, p < .01$) interaction on performance, indicating that 29 $\mu\text{g}/\text{kg}$ guanfacine significantly decreased the number of excess moves made (Figure 2, panel B).

ID/ED Set-Shifting

The placebo-treated subjects were faster at the ID and ED set-shifting stage during the second session than during the first session ($p < .05$ for all comparisons). However, no training effect was observed on the number of attempts needed to solve the ID set-shift stage ($p > .05$), but the training effect was significant at the ED set-shifting level ($p = .004$).

Clonidine. Analysis of the number of trials required by the subjects of 0.5, 2, or 5 $\mu\text{g}/\text{kg}$ clonidine and placebo-treated groups to solve the ID/ED set-shifting problem showed a significant repetition effect ($F(1,29) = 32.3, p < .001$), indicating that practice improved performance (Table 4). Clonidine 0.5, 2, or 5 $\mu\text{g}/\text{kg}$ did not affect accuracy of performance at any level of the test

Table 4. Intra-Dimensional and Extra-Dimensional Attentional Set-Shifting Test

Treatment Group	Intradimensional Shift Errors		Extradimensional Shift Errors	
	C	C	C	C
C + C	0.7 \pm 0.9	0.6 \pm 0.4	4.9 \pm 3.7	4.1 \pm 3.5
	C	CLO	C	CLO
C + CLO 0.5	0.9 \pm 0.7	0.7 \pm 1.0	4.7 \pm 3.8	4.2 \pm 3.9
C + CLO 2	0.8 \pm 0.5	0.7 \pm 0.8	4.4 \pm 3.7	3.8 \pm 3.8
C + CLO 5	0.7 \pm 0.7	0.7 \pm 0.6	5.1 \pm 3.9	4.5 \pm 4.6
	C	G	C	G
C + G 7	0.8 \pm 1.0	0.9 \pm 0.7	5.1 \pm 4.4	4.5 \pm 4.1
C + G 29	0.9 \pm 0.8	0.8 \pm 0.6	5.3 \pm 3.8	4.9 \pm 2.2

Abbreviations: C + C = control group; C + CLO 0.5, 2, or 5 = 0.5, 2, or 5 $\mu\text{g}/\text{kg}$ placebo + clonidine treated group; C + G 7 or 29 = 7 or 29 $\mu\text{g}/\text{kg}$ placebo + guanfacine treated group.

The control group solved the ID/ED attentional set-shifting test with less errors during the second session. 0.5, 2, or 5 $\mu\text{g}/\text{kg}$ clonidine and 7 or 29 $\mu\text{g}/\text{kg}$ guanfacine failed to affect the number of errors made during the ID/ED testing. The number of errors made at intradimensional and extradimensional shifting stage is shown (mean \pm SD).

(group \times repetition \times difficulty level interaction: $F(24,232) = 0.63, p = .91$). However, response latency after 5 $\mu\text{g}/\text{kg}$ clonidine treatment was increased at the ED shift stage, but not at the ID shift stage (group \times repetition \times difficulty level interaction: $F(3,29) = 6.95, p < .001$ (Table 5).

Guanfacine. In contrast, guanfacine treatment failed to affect accuracy or speed of responses at ID or ED shift stage of the test ($F(15,240) = 0.4, p > .6$; for all comparisons) (Tables 4 and 5).

DISCUSSION

Clonidine and guanfacine induced qualitatively different effects on performance in tests measuring spatial working memory, planning and attentional set-shifting. Guanfacine enhanced performance in the spatial working memory and planning tests at the higher dose tested, but had no effect on ID/ED attentional set-shifting performance, whereas clonidine did not produce any reliable improvement of spatial working memory or planning performance. First, the deleterious effect of clonidine on spatial working memory followed an inverted U-shaped dose response curve. Second, 0.5 and 2 $\mu\text{g}/\text{kg}$ clonidine increased impulsivity in the planning test. Third, the highest clonidine dose retarded re-

Table 5. Intra-Dimensional and Extra-Dimensional Attentional Set-Shifting Test Response Latencies

Treatment Group	Intradimensional Shift Latency		Extradimensional Shift Latency	
	C	C	C	C
C + C	1.6 \pm 0.3	1.4 \pm 0.2	1.5 \pm 0.3	1.3 \pm 0.2
	C	CLO	C	CLO
C + CLO 0.5	1.5 \pm 0.3	1.4 \pm 0.3	1.5 \pm 0.3	1.4 \pm 0.4
C + CLO 2	1.7 \pm 0.3	1.5 \pm 0.3	1.5 \pm 0.3	1.3 \pm 0.3
C + CLO 5	1.5 \pm 0.2	1.3 \pm 0.2	1.5 \pm 0.3	1.7 \pm 0.2*
	C	G	C	G
C + G 7	1.5 \pm 0.3	1.3 \pm 0.4	1.7 \pm 0.4	1.5 \pm 0.5
C + G 29	1.7 \pm 0.8	1.4 \pm 0.6	1.5 \pm 0.8	1.3 \pm 0.6

Abbreviations: C + C = control group; C + CLO 0.5, 2, or 5 = 0.5, 2, or 5 $\mu\text{g}/\text{kg}$ placebo + clonidine treated group; C + G 7 or 29 = 7 or 29 $\mu\text{g}/\text{kg}$ placebo + guanfacine treated group.

The control group solved the ID/ED attentional set-shifting test faster during the second session. 0.5 or 2 $\mu\text{g}/\text{kg}$ clonidine and 7 or 29 $\mu\text{g}/\text{kg}$ guanfacine failed to affect the speed of responding during the ID/ED testing. In contrast, 5 $\mu\text{g}/\text{kg}$ clonidine slowed responding at the difficult extra-dimensional sifting stage. The latency (in seconds, s) to respond at the intra-dimensional and extra-dimensional sifting stage is shown (mean \pm SD).

* $p = .06$ vs. own placebo (t -test) + $p = .001$ Group \times Repetition \times Difficulty Level interaction.

sponse speed at the difficult test levels of planning and attentional set-shifting. These data showing that guanfacine was more effective in stimulating working memory and planning than clonidine in humans are in principle similar to those reported by Arnsten and collaborators in monkeys (Arnsten et al. 1996). Our results suggest that the effect of guanfacine is not limited to a single function mediated by the central executive system (Baddeley 1986), since spatial working memory and planning were both improved. However, ID/ED attentional set shifting, which is also considered to be dependent on the central executive was insensitive to guanfacine treatment. Furthermore, we observed beneficial effects with a slightly sedating and hypotensive dose of guanfacine, indicating that in neurologically healthy humans, its dose range for inducing side-effects and improvement of frontal functions may overlap.

The beneficial effects of guanfacine occurred at 29 μ g/kg in spatial working memory and planning tests, suggesting that guanfacine may produce its effects on working memory and planning via the same neurochemical mechanism(s). Interestingly, the previous pharmacological studies conducted with different animal cognition models suggest that post-synaptic α 2A-adrenoceptors mediate the beneficial effect of guanfacine on working memory (Arnsten et al. 1996). Therefore, the present results supplement previous animal data in suggesting that guanfacine may stimulate the function of prefrontal cortical areas involved in the "central executive" (Baddeley 1986) component of working memory and planning tasks via post-synaptic α 2A-adrenoceptors in different mammalian species (Arnsten et al. 1996). However, it is possible that guanfacine may modulate these two functions via different anatomical subregions of the prefrontal cortex.

The dose response of clonidine to modulate performance in different tests was not unidirectional, but this is possibly explained by assuming that the drug acted on both pre- and postsynaptic α 2-adrenoceptors. However, it is equally possible that the non-linear dose response curves of clonidine results from activation of α 2-adrenoceptor subtypes located in characteristic anatomical regions (MacDonald and Scheinin 1995) or the highest dose of clonidine may have caused stimulation of α 1-adrenoceptors (Arnsten and Leslie 1991).

It is difficult to assign mechanisms of action to systematically administered drugs when they affect cognition, but comparisons with previous data describing the effects of more focal brain insults may be of help in elucidating the sites of action of α 2-agonists. Therefore, it is relevant to compare the action of clonidine and guanfacine on spatial working memory, planning and attentional set-shifting function with the performance failure induced by temporal or frontal lobe lesions, and Parkinson's disease (Owen et al. 1990, 1991, 1993).

The beneficial effect of guanfacine on between search errors at the 6- and 8-box levels in a spatial working

memory test is the opposite of that seen in patients with frontal lobe excisions who are more error-prone in these tests (Owen et al. 1990) and is further support for the theory that α 2-adrenoceptors located in the frontal cortex can mediate the effect of guanfacine on working memory (Arnsten 1997). However, frontal lobe excisions not only increased errors at the 6- and 8-box level, but also impaired the strategy measure. Indeed, it is possible that guanfacine stimulates selectively prefrontal areas involved in the processing of the working memory component of the paradigm, as this treatment had no effect on the strategy measure. Alternatively, it could be argued that guanfacine stimulates the accuracy of spatial working memory performance via temporal lobe structures, since temporal lobe excision impaired accuracy but had no effect on the strategy measure. However, Owen et al. (1996a, 1996b) revealed that a temporal lobe lesion disrupted accuracy selectively at the 8-box level. Therefore, it is less likely that guanfacine acts via temporal lobe structures, since an improvement in spatial working memory was observed at the 6- and 8-box levels.

Clonidine produced a profile that is not easily interpreted in terms of dysfunction of frontal or temporal regions, since treatment lessened accuracy at the 6- and 8-box levels but had no effect on strategy score. The action of 0.5 and 5 μ g/kg clonidine to increase between search spatial working memory errors at the 6- and 8-box levels cannot be explained in terms of a single behavioral factor, such as sedation. Indeed, 5 μ g/kg clonidine impaired but 29 μ g/kg guanfacine improved working memory, though at these doses both compounds induced similar subjective feelings of sedation. Furthermore, 0.5 μ g/kg clonidine had no effect on subjective feelings of sedation, but still impaired working memory. It is possible that 0.5 μ g/kg clonidine decreases the LC firing rate and noradrenaline release in the prefrontal cortex and on its own this is enough to disrupt working memory (Aghajanian et al. 1977; Cedarbaum and Aghajanian 1977; Aghajanian 1978). Furthermore, clonidine 2 μ g/kg may have masked the working memory defect induced by presynaptic suppression of LC activity by stimulating a sufficient number of postsynaptic α 2-adrenoceptors in the frontal cortex (Arnsten and Goldman-Rakic 1985). Finally, 5 μ g/kg clonidine may also act via additional forebrain structures, such as basal ganglia or thalamus, all of which contain a characteristic distribution pattern of α 2-adrenoceptor subtypes (Aantaa et al. 1995). Interestingly, patients with Parkinson's disease have a reduction of dopaminergic activity in the striatum and demonstrate a qualitatively similar failure as that induced by clonidine on spatial working memory behavior. Indeed, the spatial working memory behavior of Parkinson's disease patients is also characterized by an increase in number of errors at the 6- and 8-box levels, but an adequate strategy (Owen et

al. 1993). Therefore, it is possible that the adverse effects of clonidine on spatial working memory is mediated via a decrease in dopaminergic activity or directly at the basal ganglia level (MacDonald and Scheinin 1995).

The 29 $\mu\text{g}/\text{kg}$ dose of guanfacine decreased excess moves but had no effect on thinking times in the TOL test, revealing that administration of this α_2 -agonist can also improve planning abilities. Again, this partly mirrors the effect of frontal lobe excision in humans, as Owen et al. (1990) described that excess moves and thinking times were increased in patients with frontal lobe excisions. It is tempting to speculate that guanfacine may facilitate functioning of the prefrontal cortex and improve planning, and that α_2 -adrenoceptors more effectively modulate this frontal mechanism underlying accuracy than having any effect on thinking times. In addition, our results agree with those of Coull et al. (1995) showing that 0.5 and 2 $\mu\text{g}/\text{kg}$ clonidine increased impulsivity, as indicated in decreased initial responding latency in TOL, but did not affect subsequent thinking times or the number of excess moves made. It is relevant to note here that a previous positron emission tomography study suggested that an increase in rostral prefrontal activity was important for the components of executive functions comprising of response selection and evaluation (Owen et al. 1996a). Clonidine may act to suppress this frontal activation and thus increase impulsivity. However, as indicated earlier, the most characteristic change observed in subjects with frontal dysfunction is an increase in the excess moves in the TOL test (Owen et al. 1990). This raises an alternative possibility, i.e., clonidine acts via other brain structures that are important for suppressing impulsivity and are inhibited by α_2 -adrenoceptor activation, such as brainstem serotonin projections (MacDonald and Scheinin, 1995; Robbins, 1997).

Guanfacine did not facilitate all forms of cognitive processes dependent on the integrity of the prefrontal cortex, since it had no effect on the ID/ED attentional set-shifting performance. Similarly, clonidine failed to stimulate ID/ED attentional set-shifting performance in agreement with earlier data (Coull et al. 1995). Thus, the ability to deduce rules on the basis of reinforcing feedback and to use them to solve discrimination tasks was not promoted by α_2 -adrenoceptor activation. A previous study of Owen et al. (1990) reported that frontal excision disrupted accuracy of performance at the ED stage in this test, in addition to causing defects in TOL and spatial working memory measures. However, the prefrontal areas involved in working memory, planning, and attentional set-shifting are partly distinct (Baker et al. 1996; Owen et al. 1996a) and it is possible that those areas differ in their sensitivity to guanfacine treatment. Indeed, neuroimaging studies in humans have shown a characteristic activation of different parts of prefrontal lobe during planning and spatial working memory

performance (Baker et al. 1996; Owen et al. 1996a). Furthermore, in monkeys, lesions to the orbital and lateral prefrontal cortex impair affective processing and attentional set-shifting, respectively (Dias et al. 1996).

In contrast to the effects of guanfacine, 5 $\mu\text{g}/\text{kg}$ clonidine impaired not only working memory, but also slowed initial and subsequent responding in the TOL and decreased speed of responding in the ID/ED attentional set-shifting test at the ED stage. This may not result simply from sedation, since an equally sedative dose of guanfacine (29 $\mu\text{g}/\text{kg}$) had no effect on speed of responding. This shows that 5 $\mu\text{g}/\text{kg}$ clonidine decreased the speed of effortful processing as well as vigilance, but 29 $\mu\text{g}/\text{kg}$ guanfacine decreased only vigilance. The decrease in resting state vigilance induced by these two α_2 -agonists may be, at least partly, due to impaired thalamocortical activation (Riekkinen Jr et al. 1993; Aantaa et al. 1995; MacDonald and Scheinin 1995), as supported by a recent PET study (Coull et al. 1997).

It is possible that during 5 $\mu\text{g}/\text{kg}$ clonidine treatment, subjects have adopted an alternative strategy and traded speed for maintenance of higher accuracy of responding in TOL and ID/ED tests. However, it is difficult to pinpoint the site of action for clonidine to impair speed of effortful processing, though it may involve the temporal lobe, and areas of the "fronto-striatal" loops at the cortical and basal ganglia levels (Lange et al. 1992; Owen et al. 1993; Robbins et al. 1994). First, 5 $\mu\text{g}/\text{kg}$ clonidine had no effect on the accuracy of ID/ED test but slowed responding at the ED stage, a finding mimicking closely the defect induced by temporal excision in humans (Owen et al. 1991). Thus, temporal lobe areas may mediate the action of clonidine on attentional set-shifting behavior. Second, the increase in initial and subsequent thinking times in TOL test induced by clonidine is not paralleled by excision of the frontal and temporal lobes, or Parkinson's disease (Owen et al. 1990; Owen et al. 1991; Owen et al. 1993). Indeed, Parkinson's disease slows only the initial movements, whereas frontal excisions decrease selectively the pace of subsequent responses (Owen et al. 1990; Owen et al. 1993). Therefore, it is theoretically possible that clonidine slows responding in TOL test via α_2 -adrenoceptors located both at cortical and subcortical levels of the fronto-striatal systems (Aantaa et al. 1995; MacDonald and Scheinin 1995).

It is relevant to note here that the activity decreasing (Hunter et al. 1997) and hypotensive (MacMillan et al. 1996) effects of α_2 -agonists are attenuated in α_2 -adrenoceptor mutant mice. Therefore, our result showing that 5 $\mu\text{g}/\text{kg}$ clonidine and 29 $\mu\text{g}/\text{kg}$ guanfacine had equal hypotensive and sedating action in resting subjects may indicate that these drugs at these doses had equal efficacy in stimulating α_2 -adrenoceptors (MacMillan et al. 1996). Interestingly, we have observed that mice overexpressing $\alpha_2\text{C}$ -adrenoceptors were re-

tarded in developing an effective escape strategy in the water maze, and the involvement of α 2C-adrenoceptors was supported by altered dose response relationships to an α 2-antagonist (Björklund et al. 1996). Therefore, the increase in working memory errors and slowing of effortful mental processing by clonidine at the highest dose tested may be related to stronger activation of α 2C-adrenoceptors by 5 μ g/kg clonidine than that attained with 29 μ g/kg guanfacine (Jansson et al. 1994). Furthermore, an additional possibility is that at the doses used in this study clonidine increases the activity of thalamic α 2B-adrenoceptors more strongly than guanfacine (Jansson et al. 1994; Aantaa et al. 1995) and thus is more capable of depressing the speed of effortful information processing.

CONCLUSION

In conclusion, our data shows that guanfacine can stimulate spatial working memory and planning in humans, but has no effect on attentional set-shifting. This suggests that performance in those cognitive tests that utilize the central executive (Baddeley 1986) and are dependent on partly distinct prefrontal areas (Owen et al. 1996a, 1996b) is differentially sensitive to guanfacine. In contrast, clonidine produced many actions that may not be mediated via the prefrontal cortex and had no reliable effect in improving any measures of executive function. In fact, at a low dose it impaired working memory and increased impulsivity, and at a high dose, it impaired speed of effortful mental processing. The qualitatively different actions of guanfacine and clonidine may be related to greater selectivity ratio of guanfacine for α 2A vs. non- α 2A adrenoceptors compared with clonidine (Arnsten et al. 1996).

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