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Guanfacine and Clonidine, Alpha2-Agonists, Improve Paired Associates Learning, but not Delayed Matching to Sample, in Humans

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The present study compares the effects of two alpha2-agonists, clonidine (0.5, 2, and 5 μg/kg, PO) and guanfacine (7 and 29 μg/kg, PO) in young healthy volunteers on their performance in visual paired associates learning (PAL) and delayed matching to sample (DMTS) visual short-term recognition memory tests. In the PAL test, clonidine 2 and guanfacine 29 μg/kg improved the subjects' performance. In the DMTS test, clonidine at 5 μg/kg delay-dependently impaired performance accuracy, and at 2 and 5 μg/kg it also slowed responses. Guanfacine had no effect on DMTS test performance. Clonidine 5 and guanfacine 29 μg/kg equally increased subjective feelings of sedation and reduced blood pressure. The results suggest that both clonidine and guanfacine facilitated PAL learning by improving "frontal strategies," but only clonidine disrupted "mnemonic processing" decreasing DMTS accuracy. The greater selectivity of guanfacine for alpha2A-adrenoceptor subtype may explain the different profile of action of the drugs. ***[Neuropsychopharmacology 20: 119–130, 1999]*** *© 1998 American College of Neuropsychopharmacology. Published by Elsevier Science Inc.*

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The locus coeruleus (LC) noradrenergic system plays an important role in arousal, vigilance, responses to novel, salient stimuli as well as several aspects of attentional functions (Foote and Morrison 1987; Harley 1987; Robbins and Everitt 1987; McCormick 1989; Aston-Jones et al. 1990; Jäkälä et al. 1992; Robbins and Everitt 1994). For example, in electrophysiological studies, noradrenaline regulates cortical desynchronization/synchronization (Riekkinen Jr. et al. 1990; Berridge and Foote 1991; Riekkinen Jr. et al. 1993), increases the signal-to-noise ratio (SNR) in the neocortex (Waterhouse et al. 1981; Morrison and Magistretti 1983), regulates the responsivity of thalamo-cortical relay neurons (Buzsáki et al. 1990; Riekkinen Jr. et al. 1991; Riekkinen Jr. et al. 1993), and facilitates excitatory and inhibitory responses in the limbic system (Segal and Bloom 1976; Sara and Bergis 1991).

The firing rate of LC noradrenergic neurons is regulated by alpha2-adrenergic autoreceptors (Aghajanian et al. 1977; Aghajanian and VanderMaelen 1982). Activation of these receptors by alpha2-agonists causes autoinhibition of noradrenergic neurons and a reduction in central noradrenergic activity (Cederbaum and Agha-

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janian 1976; Langer 1987). A major portion of alpha2-adrenoceptors is, however, localized on non-noradrenergic cells that receive a noradrenergic input, that is postsynaptic to LC neurons (U'Prichard et al. 1979; Aoki et al. 1994; Scheinin et al 1994; Rosin et al. 1996).

Three subtypes of alpha2-adrenoceptors (alpha2A, alpha2B, and alpha2C) have been cloned in humans (Kobilka et al. 1987; Regan et al. 1988; Lomasney et al. 1990). The anatomical distribution of the subtypes is unique (Scheinin et al. 1994; MacDonald et al. 1997), suggesting that modulation of these subtypes by subtype selective ligands might be of therapeutic importance. Unfortunately, no such subtype selective ligands are currently available. However, the adverse effects (sedation, hypotension) of unselective alpha2-agonists could be dissociated from their beneficial (cognition-enhancing) effects based on their relative affinities for each receptor subtype. Indeed, in the rat brain, alpha2B messanger (m) RNA is found exclusively in the thalamus (Scheinin et al. 1994), and an action at this receptor subtype could impair thalamocortical arousal mechanisms (Riekkinen, Jr. et al. 1993). The brainstem nucleus tractus solitarius contains alpha2A and alpha2C mRNA, and recently, action at the alpha2A adrenoceptor subtype was shown to mediate the hypotensive effects of alpha2-agonists (MacMillan et al. 1996). In the monkey prefrontal cortex, the alpha2A subtype has the densest distribution of all three alpha2-adrenoceptor subtypes (Aoki et al. 1994). Importantly, in monkeys, the ability of subtype nonselective alpha2-agonists, such as clonidine and guanfacine, to improve prefrontal cortical functions, such as spatial working memory performance, without causing adverse events were related to their relative selectivity for the alpha2A site (i.e., guanfacine > clonidine) (see Arnsten et al. 1996). It has been described in stable S115 mouse mammary tumor cell lines, expressing separately alpha2A-C10, alpha2B-C2, and alpha2C-C4 adrenoceptors that the affinities of clonidine and guanfacine at alpha2-adrenoceptor subtypes differed (Jansson et al. 1994). The alpha2A-C10/alpha2B-C2 Ki value ratios of clonidine and guanfacine were nearly equal. On the contrary, alpha2A-C10 versus alpha2C-C4 Ki value ratio of clonidine was 0.08 and that of guanfacine 0.04, indicating that guanfacine has a somewhat higher selectivity for alpha2A-adrenoceptor subtype than clonidine (Jansson et al. 1994).

In humans, alpha2-adrenergic drugs can modulate several forms of attentional functions. In sustained attention tasks, clonidine impairs performance (Coull et al. 1995a; Jäkälä et al. in press). Furthermore, clonidine broadens the focus of attention (Clark et al. 1989; Coull et al. 1995c); whereas, an alpha2-antagonist, idazoxan, narrows its focusing (Smith and Nutt 1996). Clark et al. (1989) described clonidine as reducing the "cost of invalid cueing" in a covert orientation of attention test. On the contrary, idazoxan administration facilitated accuracy in a test of focused attention (Smith and Nutt 1996). Furthermore, a second alpha2-antagonist, atipamezole, improves focused attention and impairs behavioral and electrophysiological measures of divided attention (Mervaala et al. 1993); whereas, clonidine impairs focused attention, and this can be reversed by idazoxan (Smith and Nutt 1996).

There are fewer studies elucidating the role of alpha2-adrenoceptors in the modulation of human learning and memory functions than those examining modulation of attention. Coull et al. (1995a) reported some improvement in paired associates learning of nonverbal material in healthy volunteers by clonidine 2.5 μg/kg intravenously, but there are also studies conducted with healthy volunteers reporting no effect (Coull et al. 1997) or an impairment (Frith et al. 1985) in paired associates learning after clonidine. The difference in the effect of similar clonidine administration on nonverbal paired associates learning in the two studies of Coull et al. (1995a, 1997) may result from the variation in the experimental design. Indeed, in only the second study (Coull et al. 1997), the subjects were scanned with a positron emission tomography, and the battery of cognitive tests measured were also different in these two studies. Frith et al. (1985) reported that a fixed 200-μg dose of clonidine injected intravenously impaired paired associates learning of difficult, but not easy, word pairs in healthy volunteers. Therefore, it is possible that the effect of clonidine may be doubly dissociable depending upon the type of information processed (i.e., nonverbal vs. verbal). Idazoxan was reported to cause some improvement in delayed and logical memory performance in patients with dementia of the frontal type (Coull et al. 1996). Finally, spatial working memory and planning, functions thought to be dependent upon the "central executive" of the prefrontal cortex, were modulated by alpha2-adrenergic drugs (Coull et al. 1995b; Coull et al. 1996; Jäkälä et al. in press). Clonidine and guanfacine decreased errors in the spatial working memory test, but only guanfacine facilitated planning accuracy in the Tower of London Test.

We designed the present study to investigate the hypothesis that alpha2A-adrenoceptor activation is important for the beneficial effect of alpha2-agonists on frontal rather than temporal lobe functions in humans (Arnsten et al. 1996). We studied the actions of two alpha2-agonists, clonidine and guanfacine, on the performance of young, healthy volunteers in the paired associates learning (PAL) and delayed matching to sample (DMTS) visual short-term recognition memory tests in the visual memory battery of the Cambridge Neuropsychological Test Automated Battery (CANTAB) (Downes et al. 1989). The PAL test assesses simple visual pattern and visuospatial learning.

The PAL test assesses simple visual pattern and visuospatial associative learning, and contains aspects of

both a delayed response procedure and a conditional learning task, because the subject initially must remember the location of a single stimulus over a short delay, and then should learn the locations of up to eight different stimuli. Delayed response performance (Jacobsen et al. 1935) and conditional associative learning (Petrides 1982; Petrides 1985) are both impaired in patients and monkeys with frontal lobe damage. The PAL test also is sensitive to frontal lobe lesions in humans (Owen et al. 1995). Furthermore, PD patients are impaired in this test, possibly because of disruption of frontostriatal mechanisms (Sahakian and Owen 1992; Owen et al. 1993). Indeed, the ability to switch between the three dimensions (shape, color, and spatial location) in this test may be dependent upon efficient elaboration of "frontal strategies" and frontostriatal mechanisms. However, temporal lobe lesions and amygdalo-hippocampectomies (Owen et al. 1995), and early phases of AD (Sahakian et al. 1988; Sahakian and Owen 1992) also produce large-scale deficits in this test. Thus, successful performance in the present PAL test requires both elaboration of "frontal strategies" and medial temporal lobe "mnemonic processes." In line with this, in imaging studies using positron emission tomography (PET) the strongest task-induced activations in a PAL test using auditory verbal material have been found in the prefrontal and temporal cortical areas (Fletcher et al. 1995).

The DMTS test is based on the delayed matching to sample paradigm used by Mishkin and co-workers to define the neural substrates of visual memory in primates (Mishkin 1978; Murray and Mishkin 1984). The test primarily assesses the "mnemonic functions" of the inferotemporal cortex and medial temporal lobe structures, especially the perirhinal and entorhinal cortices (Zola-Morgan et al. 1989; Meunier et al. 1993; Murray et al. 1993; Mishkin and Murray 1994): lesions to these structures in monkeys produce delay-dependent deficits in accuracy in this task. In the human DMTS test, temporal lobe lesions and amygdalo-hippocampectomies produce similar delay-dependent deficits in performance accuracy (Owen et al. 1995). Furthermore, AD patients have a marked damage in their entorhinal cortex (Braak and Braak 1996), and show a sharp delay-dependent decline in performance accuracy (Sahakian et al. 1988; Sahakian and Owen 1992; Riekkinen et al. in press). In contrast, the performance accuracy of patients with frontal lobe lesions is at the level of controls (Owen et al. 1995), and the deficts in performance accuracy in patients with severe PD are delay-independent; that is, the performance accuracy deficits are present already at simultaneous presentation and 0 s delay, possibly reflecting impaired attentional set-shifting (Sahakian et al. 1988; Sahakian and Owen 1992; Owen et al. 1993). Thus, successful performance in this test may require more temporal lobe "mnemonic processess" in preference to elaboration of "frontal strategies."

We hypothesized that the beneficial effects of guanfacine on test performance, especially on the PAL performance, would be more apparent than those of clonidine, because it has a greater selectivity for alpha2A-adrenoceptor subtype (Uhlen and Wikberg 1991; Jansson et al. 1994; MacDonald and Scheinin 1995; Arnsten et al. 1996).

METHODS

Five separate groups of normal, healthy, young (aged 23 to 35 years of age, $n = 43$; 28 males and 15 females) volunteers took part in the drug study. All the subjects performed within the normal range in the WAIS-R Vocabulary Subtest and verbal fluency tests (Borkowski et al. 1967; Wechsler 1992). None of the volunteers was 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 a written informed consent. All subjects were covered by insurance. The number of test sessions was limited to two at the request of the local ethical committee.

Pharmacological Manipulations

Groups 1 (n = six; five males and one female), 2 (n = eight; seven males and one female) and 3 (n = eight; seven males and one female) received 0.5, 2.0, and 5.0 μg/kg, respectively, of clonidine hydrochloride (Catapressan®, Boehringer Ingelheim) PO in tablet form, or the appropriate oral placebo, 90 min before starting the test session. Groups 4 (n = nine; four males and five females) and 5 (n = 12; five males and seven females) received 7 and 29 μg/kg, respectively, of guanfacine hydrochloride (Estulic®, Sandoz Oy) PO in tablet form, or the appropriate oral placebo, 90 min before starting the test session. The doses were ± 3% accurate; for example, clonidine 5 ± 0.15 μg/kg.

Procedure and Experimental Design

Subjects from each group attended on two sessions (with at least 7 days between sessions), and received the relevant pharmacological manipulation on one occasion, and an appropriate placebo on the other in a counterbalanced order for each group (placebo-controlled double-blind crossover design) (Hills and Armitage 1979). Both the subject and the investigator were blind to the composition of the tablets. Experimental sessions were started at the same time of each testing day for each individual subject. The tests were given as a part

of our larger-scale project investigating the effects of alpha2-adrenergic drugs on executive, attentional, and memory functions. The entire session lasted 60 to 90 min for all the subjects, and the testing began 90 min postingestion of tablets for all the subjects.

Neuropsychological Tests

The paired associate learning (PAL) and delayed matching to sample (DMTS) tasks were part of the CANTAB battery (Downes et al. 1989) and were run on an IBM PS/2 Model 30 486 personal computer, with a high-resolution Taxan 770+ color monitor fitted with an Intasolve touch-sensitive screen.

Paired Associates Learning (PAL)

This is a test of visual pattern and visuospatial memory and learning, which contains aspects of conventional paired associates procedure and a conditional learning task. The subjects were presented with six white boxes arranged around the outside of the screen, which were then "opened up" by the computer to reveal six different colored patterns, one at a time. One of the six patterns was then displayed in the center of the screen, and the subjects were instructed to touch the box that had "contained" that particular shape. Without giving any feedback as to the accuracy of the response, the computer then presented another pattern and the subjects were asked to respond in the same way, until all six patterns had been placed. The test began at a very easy level with a single pattern in one of the boxes and then gradually become more difficult with two and three pattern sets before the test with six items. If the subjects had made no errors with the six-box problem, then the procedure was repeated with eight boxes and patterns. If however, at least one error had been made, then all six patterns were presented to the subjects in the same location as before, and subjects were not informed which shapes had been incorrectly placed. This was repeated until the subjects had placed all six patterns correctly, within a maximum of 10 trials. If the six-box problem was completed within 10 trials, then the eight-box problem was presented to the subjects. All the subjects in this study completed the six-box problem within 10 trials. The total number of trials needed to reach the criterion (i.e., all stimuli correctly located) with six- and eight-box problems are presented here, as in the study by Coull et al. 1995a) where clonidine at 2.5 μg/kg (IV) decreased the number of trials to reach the criterion.

Delayed Matching to Sample (DMTS)

A complex abstract pattern was presented in the center of the computer screen (the "sample") for a period of 4 to 5 s, and the subjects were instructed to remember what it looked like. Following a short delay, four other complex patterns then appeared along the bottom of the screen, and the subjects were required to match the sample to one of the four choices by touching the pattern they believed to be the correct match. One of the four choices was identical to the sample, one differed from the sample in shape only, one differed in color only, and one differed in both shape and color. If a subject chose incorrectly, the subject was instructed to try again until the correct choice was made, at which point the computer moved on to the next problem. Following three practice trials (one of each simultaneous, 0 and 12 s delay) 40 problems were presented, with three different lengths of delay (0 s, 4 s, 12 s), and also a simultaneous matching to sample condition to assess for perceptual deficits, in a pseudorandom order (10 trials in each of the four conditions). The number of correct responses made in each of these four conditions, and the time taken to respond for the first time in each of the four conditions are presented.

Visual Analog 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 afterward (i.e., just before beginning the test session), and after completion of the test session, which lasted for 60 to 90 min.

Statistics

The repeated measures crossover 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 without any drug treatment with the same test battery on two occasions with at least 7 days between sessions as in the study groups. No significant practice effects on the parameters analyzed in the present study were found (data not shown). In the analysis of DMTS test data, a multivariate analysis of variance (MANOVA) followed by paired samples t-test was used. Within-subject factors were drug condition (drug or placebo), and delay (i.e., simultaneous matching to sample, 0 s delay, 4 s delay, or 12 s delay), and interaction between the drug condition and

delay. In the analysis of PAL data, paired samples *t*-test was used. Values with $p < .05$ were considered significant.

RESULTS

Paired Associates Learning

Neither clonidine nor guanfacine affected the number of trials to reach the criterion with the easier six-box problem ($p > .1$ for all) (Figure 1A). However, in the more difficult stage of the test; that is, with the eight-box problem, clonidine 2.0 μg/kg and guanfacine 29 μg/kg improved the subjects' performance as compared to placebo in terms of trials required to reach criterion ($p < .005$ and $p < .02$, respectively) (Figure 1B). Other doses of clonidine and guanfacine had no effect on the number of trials to reach the criterion in the eight-box problem ($p > .1$ for all).

Delayed Matching to Sample

There was a significant delay effect on both the number of correct responses and latency to respond for each drug dose; that is, the longer the delay, the lower the number of correct responses made and the longer the latency to respond ($p < .05$ for all). Clonidine and guanfacine had no effect on the total number of responses made ($p > .05$, for all). Clonidine 0.5 μg/kg had no effect on the number of correct responses ($F_{1,5} = 1.52$, $p > .1$) (Figure 2A) or latency to respond ($F_{1,5} = 2.95$, $p > .1$) (Table 1). Clonidine 2 μg/kg had no effect on the number of correct responses ($F_{1,7} = 1.06$, $p > .1$) (Figure 2A), but slowed the latency to respond ($F_{1,7} = 7.29$, $p < .05$) (Table 1). The effect of clonidine 2 μg/kg to improve PAL accuracy did not correlate with the slowing of the latency to respond in the DMTS test ($r = 0.18$, $p > .05$). Clonidine 5 μg/kg decreased the number of correct responses ($F_{1,7} = 15.1$, $p < .01$) (Figure 2A). In addition, there was an interaction between drug and delay ($F_{3,21} = 4.22$, $p < .02$), so that clonidine 5 μg/kg impaired accuracy more where there were long delays. Furthermore, clonidine 5 μg/kg slowed latency to respond ($F_{1,7} = 30.9$, $p = .001$) (Table 1), and this effect was more prominent at the long delays (drug * delay interaction: ($F_{3,21} = 4.24$, $p < .02$). Guanfacine 7 or 29 μg/kg did not affect the number of correct responses ($F_{1,7} < 0.9$, $p > .4$ for both comparisons) (Figure 2B), or the latency to respond ($F_{1,7} < 1.1$, $p > .4$ for both comparisons) (Table 1).

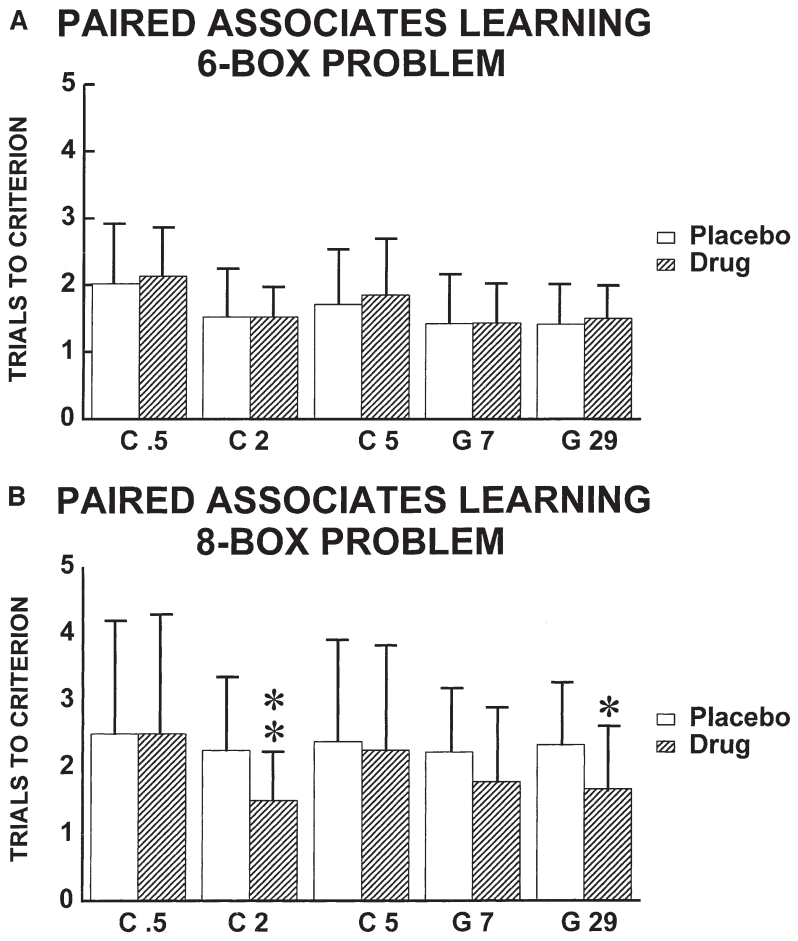

Figure 1. The effects of clonidine and guanfacine on the performance of the paired associates learning test. In the Y-axis, the trials needed to reach criterion (i.e., all stimuli correctly located) are shown for both the easier six-box problem (Part A) and for the more demanding eight-box problem (Part B). On the X-axis, different treatment groups are shown. Drug = C.5, 2, or 5, and G7 or 29 = clonidine 0.5, 2, or 5 μg/kg and guanfacine 7 or 29 μg/kg, respectively. **(A)** Neither clonidine nor guanfacine affected trials to reach the criterion with the easier six-box problem; **(B)** With the more demanding eight-box problem, clonidine at 2 μg/kg (*: treatment effect: $p < .005$) and guanfacine at 29 μg/kg (**: treatment effect: $p < .02$) improved performance as the total number of trials needed to reach the criterion decreased significantly.

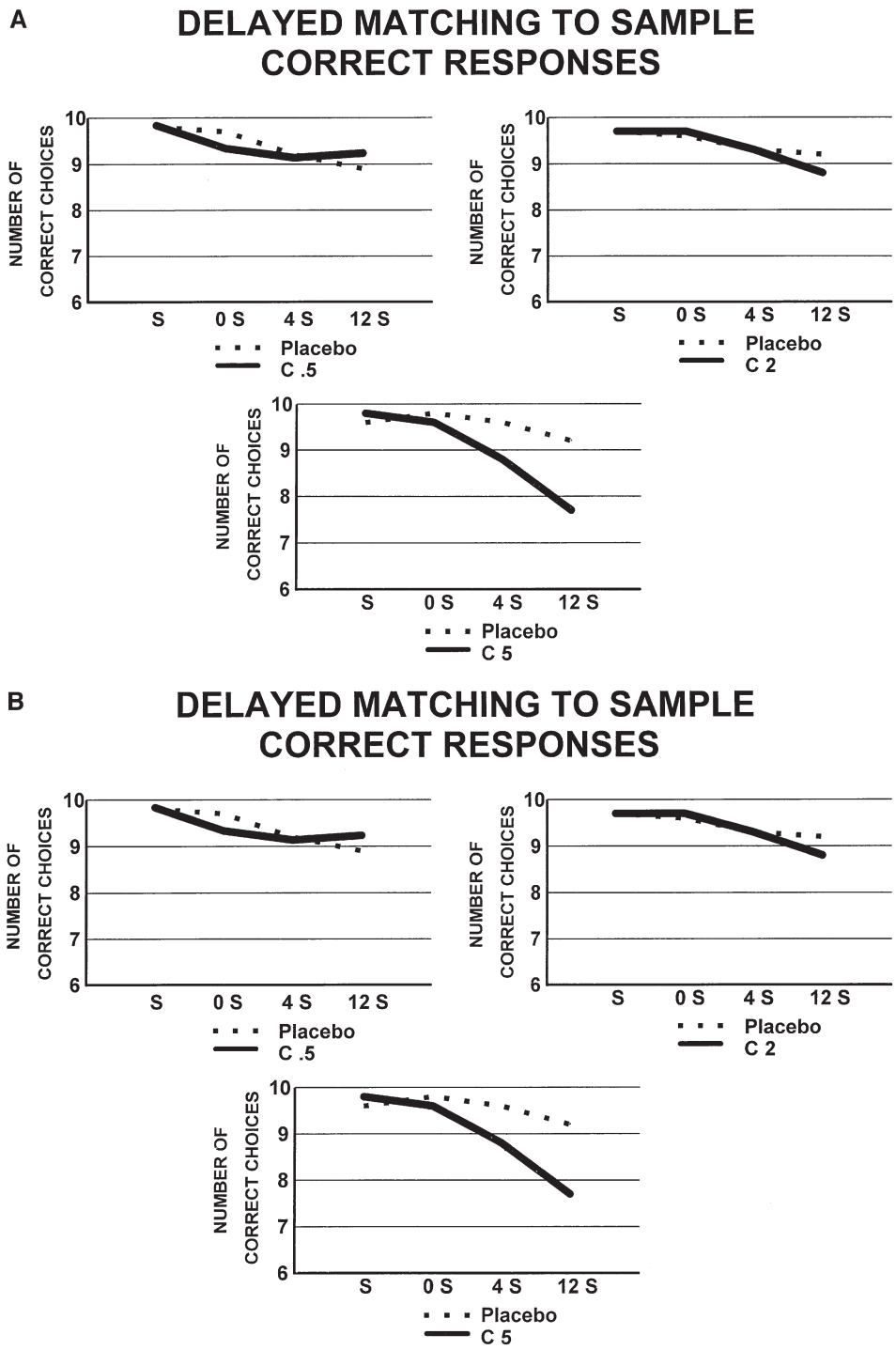

Figure 2. The effects of clonidine and guanfacine on the performance accuracy in the delayed matching to sample test. On the Y-axis, the number of correct responses made in simultaneous matching to sample and three different delay conditions are shown. On the X-axis, different delays are shown. S = simultaneous matching to sample condition; 0 S, 4 S, and 12 S = 0, 4, and 12 second delays, respectively; C.5, 2, or 5 and G7 or 29 = clonidine 0.5, 2, or 5 μg/kg and guanfacine 7 or 29 μg/kg, respectively. **(A)** Clonidine 5 μg/kg decreased the number of correct responses (*: treatment effect: $p < .01$), and this effect was more prominent at longer delays (**: treatment * delay interaction: $p < .05$); **(B)** Guanfacine had no effect on the number of correct responses.

Visual Analog Scale

Clonidine 5 μg/kg and guanfacine 29 μg/kg slightly increased the subjective feelings of sedation versus placebo ($p < .05$ for both); whereas, lower doses of the drugs had no effect ($p > .1$ for all) (Table 2). Comparisons of the high dose of clonidine (5 μg/kg) and guanfacine (29 μg/kg) groups revealed no differences in the values of subjective feelings of sedation measured after placebo or drug (clonidine 5 μg/kg vs. guanfacine 29 μg/kg) treatments, or in the increase in subjective feelings of sedation induced by clonidine 5 μg/kg and guanfacine 29 μg/kg (i.e., [clonidine 5 μg/kg - placebo] vs. [guanfacine 29 μg/kg - placebo] $p > .1$ for all).

Blood Pressure

Clonidine 5 μg/kg and guanfacine 29 μg/kg slightly reduced both systolic and diastolic blood pressures ($p <$

Table 1. Effects of Clonidine and Guanfacine on the Latency to Respond in the Delayed Matching to Sample Test

	C.5	C 2[a]	C 5[a,b]	G 7	G 29
Simultaneous matching to sample	2.57 ± 0.82 (2.61 ± 0.70)	2.70 ± 0.71 (2.60 ± 0.80)	2.50 ± 0.71 (2.41 ± 0.80)	2.54 ± 0.71 (2.61 ± 0.70)	2.57 ± 0.86 (2.66 ± 0.82)
0-s delay	2.71 ± 0.99 (2.88 ± 1.34)	2.80 ± 0.81 (2.69 ± 1.11)	2.77 ± 0.99 (2.76 ± 1.24)	2.80 ± 0.87 (2.77 ± 1.29)	2.79 ± 0.81 (2.72 ± 0.71)
4-s delay	2.91 ± 0.77 (2.99 ± 0.88)	3.10 ± 0.89 (2.93 ± 1.00)	3.21 ± 0.52 (2.92 ± 0.58)	2.88 ± 0.89 (2.90 ± 0.78)	3.00 ± 0.89 (2.90 ± 0.89)
12-s delay	3.12 ± 1.23 (3.21 ± 0.81)	3.21 ± 1.10 (3.14 ± 0.90)	3.51 ± 1.11 (3.15 ± 0.71)	3.21 ± 1.10 (3.11 ± 0.72)	3.01 ± 0.77 (3.18 ±0.77)

The latency to respond in seconds in simultaneous matching to sample and three different delay conditions are shown. Drug values are given first, with corresponding placebo values in parenthesis below. Abbreviations: C = clonidine; G = guanfacine. Doses are expressed as μg/kg. Results are expressed as means ± SD. In all drug treatment conditions, the delay effect was significant.

[a]= treatment effect: $p < .05$;

[b]= treatment *delay interaction: $p < .05$.

.05 vs. placebo); whereas, lower doses of the drugs had no significant effects on blood pressure values ($p > .1$ for all) (Table 3).

DISCUSSION

The alpha2-agonists used in the present study, clonidine and guanfacine, induced qualitatively partly similar and partly distinct effects on performance in tests measuring visual paired associates learning (PAL) and visual short-term recognition memory (DMTS). In the PAL test, both drugs improved performance, because the subjects treated with clonidine 2 μg/kg and guanfacine 29 μg/kg made fewer memory errors at the most demanding level of the test. In the DMTS test, clonidine, but not guanfacine, impaired performance, because clonidine at 5 μg/kg delay-dependently decreased performance accuracy and at 2 and 5 μg/kg slowed responses.

Clonidine 5 μg/kg and guanfacine 29 μg/kg lowered systolic and diastolic blood pressures equally. This hypotensive response to clonidine and guanfacine is thought to result from a centrally mediated effect upon autonomic activity (Bousquet et al. 1992; Ernsberger et al. 1992). It is more difficult to define the mechanisms of action of systemically administered drugs to affect cognition. However, comparison with previous studies describing the effects of focal brain pathology may help to elucidate the sites of action of systemically administered alpha2-agonists. In Table 4, the performance profiles in different patient groups with frontal and/or temporal lobe damage in PAL and DMTS tests are summarized and compared to the effects produced by clonidine and guanfacine. We suggest that the improvement in PAL by guanfacine and clonidine may have resulted from more efficient elaboration of "frontal strategies;" whereas, the delay-dependent performance accuracy deficit in DMTS seen with clonidine may have resulted from an impairment in temporal lobe "mnemonic processing."

The PAL performance was improved by both clonidine 2 μg/kg and guanfacine 29 μg/kg, as indicated by the lower number of trials needed to reach the learning criterion at the most demanding level of the test. Neither the lower (0.5 μg/kg) nor higher (5 μg/kg) doses of clonidine had any effect on performance. The nonlinear dose-response curve of clonidine to modulate PAL performance may be explained by assuming that the drug acted on both pre- and postsynaptic alpha2-adrenoceptors. It is generally assumed that the 0.5 μg/kg dose acts presynaptically in humans to reduce LC noradrenergic activity (Frith et al. 1985; Coull et al. 1995b). This is less clear for the higher doses (2 and 5 μg/kg), which probably have additional postsynaptic actions, especially the highest 5 μg/kg dose (Coull et al. 1995b). An equally plausible theory is that the nonlinear dose-response curve of clonidine in PAL results from activation of alpha2-adrenoceptor subtypes located in distinct anatomical regions (Scheinin et al. 1994; MacDonald et al. 1997). Indeed, because successful performance in

Table 2. The Effects of Clonidine and Guanfacine on Subjective Ratings for Sedation on a Visual Analog Scale

	Placebo	Drug
C.5	3.3 ± 1.1	3.0 ± 1.7
C 2	3.2 ± 1.4	3.3 ± 1.3
C 5	3.1 ± 1.5	5.0 ± 1.3*
G7	3.0 ± 1.3	3.3 ± 1.4
G29	3.2 ± 1.4	4.5 ± 1.3*

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). Abbreviations: C = clonidine; G = guanfacine. Doses are expressed as μg/kg. Results are expressed as means ± SD. *:$p < .05$ versus placebo.

Table 3. The Effects of Clonidine and Guanfacine on Blood Pressure

	Placebo			Drug		
	0 min	**+90 min**	**+180 min**	**0 min**	**+90 min**	**+180 min**
C.5	128/79	126/78	128/78	126/78	125/78	127/79
C 2	126/78	126/78	126/78	126/78	123/78	122/75
C 5	127/78	125/77	128/79	127/78	120/74*	114/70*
G 7	125/78	124/78	125/78	124/79	126/78	128/80
G 29	127/77	129/78	126/78	129/77	122/78*	117/75*

Abbreviations: +90 min = 90 min after taking the study drug or matching placebo, that is just before starting the test session; +180 min = 180 min after taking the study drug or matching placebo; that is after completion of the test session; C = clonidine; G = guanfacine. Doses are expressed as μg/kg and blood pressure values (means of systolic/diastolic pressures) as mmHg. *:$p < .05$ versus placebo.

this test requires both frontal and temporal lobe processing (see above), the lack of PAL improvement by the highest 5.0 μg/kg dose may have resulted from the disruption of temporal lobe "mnemonic processing," as suggested by the delay-dependent performance accuracy impairment in the DMTS test produced by clonidine 5 μg/kg (see discussion below). Finally, the nonlinear dose-response curve of clonidine to modulate PAL could also result from additional stimulation of alpha1-adrenoceptors, which may become a factor with the highest, 5 μg/kg, dose (Arnsten et al. 1996). The beneficial effects of guanfacine on PAL were observed at 29 μg/kg dose that induced slight hypotension and subjective feelings of sedation, indicating that in neurologically intact healthy humans, there may be an overlap in the dosage ranges for inducing minor side-effects an PAL improvement.

The improvement in PAL by guanfacine 29 μg/kg and clonidine 2 μg/kg may have resulted form more efficient elaboration of "frontal strategies." Indeed, in a study by Coull et al. (1995b), clonidine at 2.5 μg/kg (IV), but not at 1.5 μg/kg (IV), improved performance in a spatial working memory test that is sensitive to frontal rather than temporal lobe damage in humans (Owen et al. 1995; Owen et al. 1996b). Furthermore, in our previous study, guanfacine 29 μg/kg (PO) improved spatial working memory performance (Jäkälä et al. in press). On the other hand, clonidine had no effect on performance accuracy in the Tower of London planning test at 1.5 and 2.5 μg/kg (IV) (Coull et al. 1995b) or at 0.5, 2.0 and 5.0 μg/kg (PO) (Jäkälä et al. in press); whereas, guanfacine 29 μg/kg (PO) improved planning (Jäkälä et al. in press). Finally, attentional set-shifting was not affected by either clonidine (0.5, 2.0, and 5.0 μg/kg, PO) or guanfacine (7 and 29 μg/kg, PO) (Jäkälä et al. in press). The data showing that guanfacine is more effective than clonidine in stimulating some of the functions that are dependent on successful elaboration of "frontal strategies" are, in principle, similar to those reported by Arnsten et al. (1996) in monkeys and may be related to the greater selectivity ratio of guanfacine for alpha2A- versus nonalpha2A-adrenoceptors (Uhlen and Wikberg 1991; Jansson et al. 1994; MacDonald and Scheinin 1995; Arnsten et al. 1996). Furthermore, performance in different cognitive tests that require elaboration of "frontal strategies" (Baddeley 1996) seem to be differentially sensitive to clonidine and guanfacine treatments. Interestingly, the prefrontal areas involved in spatial working memory, planning, and attentional set-shifting may be partly distinct (Baker et al. 1996; Owen et al. 1996a). This is also supported by neuroimaging studies in humans showing a partly unique activation of different parts of the prefrontal lobe during spatial working memory performance and planning (Baker et al. 1996; Owen et al. 1996a). It is possible that these areas differ in their sensitivity to treatment with guanfacine and clonidine.

The proposal that the PAL-improving effects of clonidine and guanfacine are mediated by means of an improvement in spatial working memory processes is also supported by earlier experimental data (see Arnsten

Table 4. The performance profile of different patient groups with frontal and/or temporal lobe damage and the effects of clonidine and guanfacine in paired associates learning and delayed matching to sample tests

	PAL	**DMTS**
Frontal lobe lesion	$\downarrow^{a}$	$\leftrightarrow^{a}$
Temporal lobe lesion	$\downarrow^{a}$	$\downarrow^{a}$
Amygdalo-hippocampectomy	$\downarrow^{a}$	$\downarrow^{a}$
Alzheimer's disease	$\downarrow^{b,c}$	$\downarrow^{b,c,f}$
Parkinson's disease	$\downarrow^{b,c,d}$	$\leftrightarrow^{b,c,d}$
Cloindine	$\uparrow^{e}$	$\downarrow^{e}$
Guanfacine	$\uparrow^{e}$	$\leftrightarrow^{e}$

Abbreviations: PAL = paired associates learning, DMTS = delayed matching to sample, ↓ = impairment, ↑= improvement, ↔ = no effect. In PAL, the number of trails to reach criterion and in DMTS, the delay-dependent performance accuracy are referred to. References (see list of references):

[a]Owen et al. 1995;
[b]Sahakian et al. 1988;
[c]Sahakian and Owen 1992;
[d]Owen et al. 1993;
[e]the present study;
[f]Riekkinen et al. in press.

et al. 1996). Lesioning and pharmacological studies in monkeys by Arnsten and colleagues have revealed that normal noradrenergic function of the prefrontal cortex is important for successful performance in spatial working memory and delayed response tests (Arnsten 1993; Berridge et al. 1993). For example, catecholamine depletion in the sulcus principalis region of the prefrontal cortex renders young monkeys unable to perform a delayed response task (Brozoski et al. 1979), and a normal level of performance can be reinstated by the administration of clonidine or guanfacine (Arnsten et al. 1988). Furthermore, in aged monkeys with naturally occurring noradrenaline depletion, alpha2-agonists alleviate spatial working memory failure (Arnsten and Contant 1992; Arnsten 1993; Arnsten and Cai 1993). These effects of alpha2-agonists may be mediated by means of their actions at postsynaptic alpha2-adrenoceptors in the prefrontal cortex (see Arnsten et al. 1996). Interestingly, in electron microscopic studies, alpha2A-immunoreactivity has been localized to postsynaptic sites in the monkey prefrontal cortex (Aoki et al. 1994). Thus, at least in monkeys, the beneficial effects of alpha2-agonists on spatial working memory are likely to be mediated by their actions at postsynaptic prefrontal cortical alpha2A-adrenoceptors.

In contrast to the delay-dependent impairing effects of the highest dose of clonidine on memory accuracy in DMTS test, guanfacine, which is a more selective agonist at alpha2A-adrenoceptors than clonidine, had no deleterious effects on DMTS performance accuracy. Thus, the memory accuracy impairing effects of clonidine 5 μg/kg could be mediated by means of more extensive stimulation of alpha2B- or alpha2C-adrenoceptors than can be obtained with guanfacine (Jansson et al. 1994; MacDonald and Scheinin 1995).

The slowing of responding induced by clonidine 2 μg/kg and 5 μg/kg in the DMTS test could be interpreted in terms of a decrease in effortful information processing capacity. Indeed, it is unlikely that the slowed response latencies by clonidine were simply attributable to sedation, because a sedating dose of guanfacine (29 μg/kg) had no effect on response latency. Indeed, clonidine 2 μg/kg only decreased speed of information processing capacity, clonidine 5 μg/kg both decreased speed of information processing capacity and increased subjective feelings of sedation, and guanfacine 29 μg/kg only increased subjective feelings of sedation. The slowing of effortful information processing capacity by clonidine, but not by guanfacine, could be mediated by means of stronger binding (Jansson et al. 1994) to striatal alpha2C-adrenoceptors located on striatal interneurons (Rosin et al. 1996) that control the excitability of striatal output neurons. On the other hand, the decrease in resting state vigilance by clonidine 5 μg/kg and guanfacine 29 μg/kg may be at least partly attributable to impaired thalamocortical activation (Buzsáki et al. 1990; Riekkinen, Jr. et al. 1993). This is also supported by a recent paper by Coull et al. (1997), which demonstrated that engagement in a sustained attention test reduced the decrease in thalamic flow induced by clonidine, as assessed by PET. We have observed an enhanced sedative action of an alpha2-agonist, dexmedetomidine, on cortical EEG arousal in mice lacking alpha2C-adrenoceptors (knock out mice) (Puoliväli et al. 1997); whereas, overexpression of alpha2C-adrenoceptors in transgenic mice did not alter the effects of dexmedetomidine on cortical EEG arousal (Björklund et al. 1996). Thus, alpha2C-adrenoceptors are unlikely to play a major role in the sedative actions of alpha2-agonists. On the contrary, in the rat brain, alpha2B mRNA is found exclusively in the thalamus (Scheinin et al. 1994), and this receptor subtype could, to some extent, mediate the sedative actions of alpha2-agonists.

In conclusion, both guanfacine and clonidine improved visual pattern and visuospatial paired associates learning, possibly because of more efficient elaboration of "frontal strategies" (Coull et al. 1995b; Jäkälä et al. in press), but only clonidine impaired visual pattern short-term recognition memory, possibly because of disruption of temporal lobe "mnemonic processes." The differences in the actions of guanfacine and clonidine may be related to the greater selectivity ratio of alpha2A- versus nonalpha2A-adrenoceptors of guanfacine as compared with clonidine (Uhlen and Wikberg 1991; Jansson et al. 1994; MacDonald and Scheinin 1995; Arnsten et al. 1996). These data may also be of some clinical relevance, suggesting that alpha2A-adrenoceptor subtype specific drugs might have therapeutic potential in the treatment of executive dysfunctions related to a number of clinical disorders including attention-deficit hyperactivity disorder, frontal lobe dementia, AD, and such basal ganglia disorders as PD (Sahakian and Owen 1992; Arnsten et al. 1996; Coull et al. 1996).

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