

The Effect of α -2 Adrenergic Agonists on Memory and Cognitive Flexibility

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Background: The noradrenergic system modulates cognitive flexibility for insight-based problem solving in studies using β -adrenergic antagonists, which block noradrenergic neurotransmission postsynaptically. However, it is not known whether α -2-adrenergic agonists, that decrease noradrenergic neurotransmission by presynaptic inhibition, have the same effect.

Objectives: Therefore, we wished to test whether α -2-adrenergic agonists would have a similar effect on cognitive flexibility.

Methods: Eighteen normal adults were tested on cognitive flexibility, problem solving, verbal and spatial memory tasks after receiving clonidine (0.1 mg), an α -2-agonist, placebo, or ephedrine (25 mg), a noradrenergic stimulant.

Results: Three-way analysis of variance revealed no significant drug effect on cognitive flexibility or problem solving. There was also no significant effect of clonidine on memory.

Conclusions: Therefore, α -2-agonists do not influence cognitive flexibility in the same manner as β -antagonists. Better performance on memory with clonidine might be expected based on primate studies demonstrating benefits in working memory using clonidine. This benefit was not observed for the commonly used clinical memory tasks in our study. This may have implications for why clonidine has not demonstrated efficacy for cognitive disorders such as Alzheimer disease, despite its known benefit for working memory in animal models.

Key Words: α -2 agonists, cognitive flexibility, memory, noradrenergic, clonidine

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According to Cattell,¹ intelligence can be categorized as either fluid or crystallized intelligence. Crystallized intelligence concerns recall of declarative information, for example, a fact such as “a day is 24 hours.” Fluid

intelligence involves problem solving that requires further processing, including approaches such as trial and error, learned algorithms, and the use of cognitive flexibility. For the purposes of this study, cognitive flexibility will be assessed by performance on insight-based problem solving tasks, where a search must be done through a network of possible solutions to derive an answer.²

Earlier evidence suggested a role of the noradrenergic system in modulating cognitive flexibility and mediating some cognitive effects of stress. The noradrenergic system is an important component of anxiety and stress.^{3–6} Adolescents with cognitive impairment due to stress benefit from β -adrenergic antagonists on the Scholastic Achievement Test,⁷ supporting some effect of the noradrenergic system on cognition in subjects susceptible to the influence of stress. Furthermore, impairments in cognitive flexibility have been found during exposure to stress. Performance on the Remote Associates Test, which involves coming up with a word associated with a set of 3 presented words and is considered a measure of “creativity” that uses cognitive flexibility for insight-based problem solving,⁸ is decreased under conditions of stress whereas performance on other cognitive tasks improved.⁹ Therefore, the noradrenergic system seems a likely candidate for how stress affects cognitive flexibility. Noradrenergic changes also seem to account for changes in associative memory in sleep studies.¹⁰

The relationship between the noradrenergic system and cognitive flexibility has been further investigated using anagrams as a measure of cognitive flexibility. Performance on anagrams was found to be significantly better after propranolol, a β -adrenergic antagonist, than ephedrine, an adrenergic agonist.² A study comparing propranolol, a central and peripheral β -blocker, and nadolol, a peripheral β -blocker, suggested that modulation by the noradrenergic system occurs through a central mechanism.¹¹ A study comparing the effects of lorazepam, a GABAergic anxiolytic, and propranolol on cognitive flexibility suggested that cognitive flexibility is specifically modulated by the noradrenergic system rather than by a general effect of anxiety.¹² The tasks used in these studies involved a search through the semantic network to find a solution,² in contrast to other tasks that might be considered as “executive control” tasks, such as set-shifting, where subjects switch rules within a limited and fairly predictable set of options.

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In these previous studies implicating the noradrenergic system in modulation of cognitive flexibility, only drugs affecting the β -receptors were used. However, decrease in norepinephrine activity can occur due to blockage of β receptors or stimulation of α_2 presynaptic receptors. α_2 -agonists have also been used to treat anxiety.¹³ To test the receptor subtype specificity of the noradrenergic system's modulation of cognitive flexibility, we tested α_2 -adrenergic drugs in this study. Specifically, we investigated an α_2 -adrenergic agonist, clonidine, in comparison to the adrenergic agonist ephedrine to repeat the design of the original study comparing the β -adrenergic antagonist propranolol, placebo, and ephedrine,² while replacing the propranolol with clonidine. We also examined memory, which was shown to be affected by α_2 -receptor stimulation in previous studies in animal models.^{14,15}

The tasks used in this study were also derived from previous work demonstrating a modulatory effect of the noradrenergic system (using β -adrenergic agents) on cognitive flexibility,^{2,11} along with additional problem solving tasks. We also used commonly utilized clinical memory tasks that included verbal memory tasks that were impaired in cocaine withdrawal (due to presumed noradrenergic effects) and spatial memory tasks that were unimpaired in cocaine withdrawal.¹⁶

MATERIALS AND METHODS

Subjects

The study protocol was approved by The Ohio State University Institutional Review Board, and formal informed consent was received from all subjects before proceeding with the study. Eighteen normal right-handed subjects [11 male, 7 female, mean age 22.6 ± 2.8 (standard deviation)y, range 18 to 27 y] participated. All subjects were negative for a history of diabetes, asthma, narrow angle glaucoma, pulmonary or thyroid disease, depression, bradyarrhythmias, dyslexia or other learning disabilities, and previous adverse reactions to the study drugs. English was the primary language for all of the subjects.

Procedure

Subjects were required to attend 3 test sessions, each 1 week apart. The test sessions were counterbalanced for drug order and test version, as 3 parallel test versions, equal in difficulty, were used. At one session, subjects received oral clonidine (0.1 mg) 2 hours before testing (dose selected as the recommended safe starting dose for initiation of hypertension treatment, as was done to select the propranolol dose for previous studies^{2,11,12}). During the 2 other sessions, subjects received either oral ephedrine (25 mg) or placebo 45 minutes before testing. The time intervals selected for each drug were based on the earliest time of peak effect for that drug. Subjects and test administrators were blinded to drug condition (individuals administering tests were not aware of which drug matched with which drug administration-test inter-

val). Heart rate and blood pressure were measured before consumption of the medication and just before the testing session.

At each testing session, subjects were given 1 of 3 sets of 20 anagrams (fourteen 5-letter words and six 7-letter words) to assess cognitive flexibility. As with previous research,^{2,12} a maximum of 2 minutes was allowed for unscrambling each word. The time taken to solve each problem was recorded; unsolved problems were recorded as 120 seconds. As an alternate task for assessing cognitive flexibility for insight-based problem solving, 1 of 3 sets of a 30 item Compound Remote Associates test was administered as well.⁸ Subjects were presented with a set of 3 words; the task was to come up with a fourth word that was associated with each of the 3 words (eg, "cheese" for the following 3 words: "cottage," "Swiss," and "cake"). As with previous research⁸ a maximum of 7 seconds was allotted for each set of 3 words. The time taken to solve each problem was recorded for this task; unsolved problems were recorded as 7 seconds.

For assessment of problem solving in the spatial domain, subjects were given the Raven Progressive Matrices.¹⁷ The Matrices (parts A–E) were divided into 3 equivalent sets of 20 problems, with 1 set given per session. The task required the subject to complete a pattern by choosing the missing piece from 6 or 8 possibilities, where the strategy required to determine the appropriate pattern must be implied.

To assess visuospatial memory, 1 of 3 versions of the Rey-Osterrieth Complex Figure task—copying and 30-minute recall—were given.^{18,19} To examine verbal memory, the California Verbal Learning Test, 2nd ed (CVLT)—standard and alternate forms,²⁰ and an equivalent third list of words were given during the 3 test sessions.

The duration of testing was approximately 1 hour for all conditions. The tests were presented in a fixed order, with encoding and immediate recall tasks at the beginning, followed by cognitive flexibility, problem solving, and delayed recall tasks.

Analysis

As with previous research,² natural logarithms of completion times were taken for the anagram task. For this task, the latency score used in analysis was the sum of the natural logarithms of the completion times of each problem. The sum of the latency scores were also derived for the Compound Remote Associates tests. The score on the Rey-Osterrieth Complex Figure for 30-minute recall on a 36 point scale, the total free immediate recall for trials 1 to 5 from list A (for verbal learning) and the sum of trial 1 from list A and B (for immediate recall) from the CVLTs, and the number of correct answers on the Raven Progressive Matrices were also analyzed.

All scores from these counterbalanced sessions were adjusted for test order and test version (divided by the factors proportional to the relative performance of that particular place in order and that test version), to account

for a learning effect and for any potential differences in problem difficulty between test sets. A 3-way analysis of variance (ANOVA) was conducted to compare the scores after clonidine, placebo, and ephedrine test conditions. Individual paired *t* tests were then examined to specify the effects when significant differences were found with ANOVA. Postmedication heart rate, systolic blood pressure, and diastolic blood pressure for the 3 test sessions were also compared using within subject *t* tests as well.

RESULTS

As expected, clonidine resulted in significantly lower blood pressure compared with ephedrine [$t(17) = 4.75$, $P = 0.0002$ for systolic blood pressure, $t(17) = 2.55$, $P = 0.02$ for diastolic blood pressure], and as compared with placebo [$t(17) = 2.73$, $P = 0.01$ and $t(17) = 2.84$, $P = 0.01$ for systolic and diastolic blood pressure, respectively]. There was no difference in systolic and diastolic blood pressure between placebo and ephedrine [$t(17) = 1.28$, $P = 0.22$ and $t(17) = 0.05$, $P = 0.96$, respectively]. There was a trend toward a heart rate effect as well with ephedrine versus clonidine [$t(17) = 2.05$, $P = 0.06$]. Heart rate was not significantly greater for ephedrine compared with placebo [$t(17) = 1.71$, $P = 0.11$], and no difference was found between clonidine and placebo [$t(17) = 0.54$, $P = 0.59$].

Three-way ANOVA revealed no significant difference between the 3 drug conditions for any of the cognitive flexibility and problem solving measures [natural log of anagrams: $F(2, 17) = 2.34$, $P = 0.13$; Compound Remote Associates problems: $F(2, 17) = 0.02$, $P = 0.98$; Raven Progressive Matrices: $F(2, 17) = 0.20$, $P = 0.82$].

Significant differences were found on 3-way ANOVA for the memory tests. Verbal memory significantly differed between groups [$F(2, 17) = 5.90$, $P = 0.01$ for total of trials 1 to 5 from list A and $F(2, 17) = 3.83$, $P = 0.04$ for the sum of trial 1 from list A and B in the CVLTs]. Spatial memory also significantly differed between groups [$F(2, 17) = 4.61$, $P = 0.03$ for Rey-Osterrieth Complex Figure 30-minute recall]. However, the pattern of significant findings and trends on paired *t* tests suggested that this effect was primarily driven by impaired performance on ephedrine on verbal memory [$t(17) = 1.84$, $P = 0.08$ for ephedrine vs. placebo and $t(17) = 3.13$, $P = 0.006$ for ephedrine vs. clonidine for total of trials 1 to 5 from list A of the CVLT; $t(17) = 2.35$,

$P = 0.03$ for ephedrine vs. placebo, and ephedrine vs. clonidine did not reach significance for the sum of trial 1 recall for list A plus list B of the CVLT ($t(17) = 1.72$, $P = 0.10$]. *t* tests also suggested that ephedrine improved performance on the spatial memory task [$t(17) = 1.89$, $P = 0.08$ for ephedrine vs. placebo, $t(17) = 2.95$, $P = 0.009$ for ephedrine vs. clonidine].

Results are summarized in the Table 1.

DISCUSSION

The intent of this study was to investigate the effect of an α_2 -adrenergic agonist (clonidine) on cognitive flexibility for insight-based problem solving, in contrast to previous studies which involved β -adrenergic antagonists. Because both agents decrease noradrenergic neurotransmission at the synapse, the question was whether the α_2 -agonist also had the same modulatory effect as β -antagonists on cognitive flexibility. A 3-way ANOVA across the drug conditions revealed no significant effect on cognitive flexibility or problem solving, despite a significant hemodynamic effect comparable to that achieved in the previous β -adrenergic studies.¹¹ Therefore, α_2 -agonists do not behave in a similar manner to β -antagonists in modulation of cognitive flexibility or problem solving.

High-dose clonidine has been shown to improve immediate spatial memory in aged monkeys,¹⁴ an effect also found in younger monkeys,²¹ believed to be mediated by action at the prefrontal cortex.²² Research using the lower doses of clonidine that are typically used in humans (as in our study) demonstrate varying results at varying doses, including impaired visual working memory, varying effects on spatial working memory, and impulsive responses on planning tasks.^{23,24} However, our finding does not demonstrate to any α_2 -adrenergic effect on clinical tests of spatial and verbal memory, as opposed to the working memory tasks used in the previous research. The small sample size in our study, though, may be a limitation. Therefore, further work examining varying doses and larger sample sizes may be instructive.

In summary, clinical doses of α_2 -adrenergic agonists do not behave in the same manner as β -adrenergic antagonists² in modulating cognitive flexibility, and do not have a significant effect on commonly used clinical tests of memory in normal individuals. This may relate to why research on clonidine has not yet revealed a consistent finding of benefit for cognitive disorders such

TABLE 1. Summary of Results, Mean \pm Standard Deviation Scores Per Subject, Adjusted for Test Order and Test Version

	Clonidine (0.1 mg)	Placebo	Ephedrine (25 mg)	3-way ANOVA (<i>P</i>)
Anagram solution latency (sum of ln)	47.2 \pm 11.6	47.6 \pm 13.1	42.8 \pm 14.8	NS
Compound Remote Associates latency	160.9 \pm 17.4	161.5 \pm 17.5	161.5 \pm 15.4	NS
Ravens Progressive Matrices	18.2 \pm 1.5	18.2 \pm 1.1	18.4 \pm 1.5	NS
CVLT trials 1-5	64.1 \pm 7.0	62.5 \pm 6.8	59.7 \pm 7.8	0.01
CVLT trial 1 A + B	15.8 \pm 2.6	15.9 \pm 3.1	14.5 \pm 3.1	0.04
Rey figure recall	25.1 \pm 5.2	25.6 \pm 6.1	28.1 \pm 4.9	0.03

as Alzheimer disease^{25,26} or Korsakoff syndrome,^{27,28} despite reports of improvement on memory in animal models.^{14,21} However, effects due to task order within each session and variability in duration of drug effect could have contributed to our results. Due to the wide range of differences in methodologies inherent in previous research using α -2-adrenergic agents in primate and human studies, further work will be necessary to fully understand the clinical implications of these lines of research.

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