

Central β -adrenergic modulation of cognitive flexibility

David Q. Beversdorf,^{CA} Dawn M. White,¹ Daquesha C. Chever,² John D. Hughes³ and Robert A. Bornstein

Departments of Neurology and Psychiatry, The Ohio State University Medical Center, Means Hall 469, 1654 Upham Drive, Columbus, OH 43210;

¹Department of Psychiatry, University of Colorado Health Science Center, Denver, CO 80262; ²Ohio University, Athens, OH 45701;

³Department of Neurology, National Naval Medical Center, Bethesda, MD 20889, USA

^{CA}Corresponding Author: beversdorf-l@medctr.osu.edu

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Situational stressors and anxiety impede performance on creativity tests requiring cognitive flexibility. Preliminary research revealed better performance on a task requiring cognitive flexibility, the anagram task, after propranolol (β -adrenergic antagonist) than after ephedrine (β -adrenergic agonist). However, propranolol and ephedrine have both peripheral and central β -adrenergic effects. In order to determine whether noradrenergic modulation of cognitive flexibility is a centrally or peripherally mediated

phenomenon, we compared the effects of propranolol (peripheral and central β -blocker), nadolol (peripheral β -blocker), and placebo on anagram task performance. Solution latency scores for each subject were compared across the drug conditions. Anagram solution latency scores after propranolol were significantly lower than after nadolol. This suggests a centrally mediated modulatory influence of the noradrenergic system on cognitive flexibility. *NeuroReport* 13:2505–2507 © 2002 Lippincott Williams & Wilkins.

Key words: β -Adrenergic; Cognitive flexibility; Executive function; Norepinephrine; Problem solving

INTRODUCTION

Early theories of intelligence proposed that there are two types of intelligence or ability to solve problems, fluid intelligence and crystallized intelligence [1]. Crystallized intelligence includes declarative knowledge such as knowing that Annapolis is the capital of Maryland, whereas fluid intelligence is utilized for problems that cannot be solved with knowledge alone. Problem solving in complex situations involves selecting a sequence of actions that move one from the initial problem to a solution. At each point in problem solving multiple action sequences are available and at times it is necessary to inhibit selection of dominant but inappropriate actions in order to discover the optimal path to a solution. Cognitive flexibility, a form of fluid intelligence, encompasses the ability to inhibit strong preferences in order to explore alternative solution paths [2].

Research involving adolescents with stress-induced cognitive impairment demonstrated that treatment with β -adrenergic antagonists, such as propranolol, significantly improved scores on the scholastic aptitude test (SAT) [3]. Furthermore, situational stressors and anxiety are known to impede performance on creativity tests requiring cognitive flexibility [4]. An increase in activity of the noradrenergic system is known to occur in the setting of stress [5,6]. These findings suggest a role of the noradrenergic system in stress-related modulation of performance in some types of problem solving in certain individuals. Administration of L-dopa, which is converted into both dopamine and

norepinephrine, has resulted in restriction of the semantic network in a priming experiment in normal individuals [7]. Specifically, normal subjects were asked to press a button as soon as they knew whether a string of letters formed a meaningful word or a non-word. Subjects recognized words as meaningful more quickly if they were directly or indirectly related to a previously seen word, and more slowly if no related word was seen previously. After taking L-dopa, the more rapid response only occurred with directly, and not indirectly related words. This was interpreted as a restriction of the semantic network due to action of the dopaminergic system. However, in light of the conversion of L-dopa into norepinephrine, as well as the aforementioned interrelation between stress, cognitive flexibility, and the noradrenergic system, we propose that the noradrenergic system modulates the solution network and is, therefore, involved in stress-related modulation of cognitive flexibility in problem solving.

In a pilot investigation, 18 normal subjects were given three problem solving tasks (number series, shape manipulation, and anagrams) 45 min after taking propranolol (a central and peripheral β -adrenergic antagonist), placebo, or ephedrine (a central and peripheral β -adrenergic agonist). On the task predicted to be most dependent on cognitive flexibility, the anagrams task, subjects best able to solve the problems had significantly shorter solution times (logarithmic scores) after propranolol than after ephedrine [2], suggesting noradrenergic modulation of cognitive flexibility.

Anagram Test 1	Anagram Test 2	Anagram Test 3
5 Letter Words	5 Letter Words	5 Letter Words
1. IRBCK	1. SLAGS	1. ZAZPI
2. NYOME	2. NEHOY	2. TMOEL
3. OSEOG	3. ITAPO	3. OPNHE
4. AADLS	4. THETE	4. MOBOR
5. EKRCE	5. NECFE	5. MHBTU
6. HTRSI	6. EIYDL	6. GLAEE
6 Letter Words	6 Letter Words	6 Letter Words
7. ROYEMM	7. WOERLF	7. PPLEUR
8. NHDLEA	8. CERCOS	8. IARTGU
9. GERUBR	9. KSTBEA	9. KPNNIA
10. SRREEA	10. OPCILE	10. NNIEAC
11. NECICS	11. CNLPIE	11. SNIIOV
12. ATESTE	12. AOGRNE	12. RBELRA
7 Letter Words	7 Letter Words	7 Letter Words
13. ORYCTAF	13. DUNTERH	13. KNECIHC
14. LETKLIS	14. WEEJYLR	14. ILOADHY
15. CLEHIVE	15. LEGLOCE	15. NENTAAN

Fig. 1. Anagram test sets utilized in the experiment.

However, propranolol and ephedrine exert action on the noradrenergic system both through peripheral receptors and CNS receptors. Either mechanism has been postulated to modulate cognition. A central-only mechanism is supported by the modulatory effect of norepinephrine on the signal-to-noise ratio of neuronal activity within the cortex [8]. However, others have proposed that the cognitive effects of the noradrenergic system are mediated by central responses to feedback from the adrenergic effects on the peripheral autonomic nervous system [9]. Therefore, we tested whether noradrenergic modulation of cognitive flexibility occurs by a central or peripheral feedback mechanism. To accomplish this, we compared performance on anagrams (Fig. 1) after administration of propranolol (a central and peripheral β -adrenergic antagonist), nadolol (a peripheral-only β -adrenergic antagonist), and placebo.

MATERIALS AND METHODS

Subjects: The study protocol was approved by The Ohio State University Office of Research Risks Protection and all subjects signed informed consent prior to entry into the study. Eighteen normal subjects (nine male, nine female, mean (\pm s.d.) age 23.8 ± 1.2 years, range 22–27 years) recruited from the college campus attended three test sessions each, one week apart. Subjects with histories of dyslexia, cardiac disease, asthma, diabetes, thyroid disease,

and depression were excluded. Patients taking medications that affect the noradrenergic system were excluded. English was a primary language for all subjects. Female subjects of childbearing potential were screened with a urine pregnancy test prior to participation.

Procedures: At one of the sessions, subjects were given propranolol (40 mg) 60 min prior to testing in order to block central and peripheral noradrenergic receptors. At another session they were given placebo 90 min prior to testing. At the other they were given nadolol (50 mg) 120 min prior to testing in order to block peripheral-only noradrenergic receptors. At each test session, subjects were given a group of letters that when rearranged formed a particular word (anagrams, maximum time allowed 2 min/problem; Fig. 1). Subjects were asked to unscramble the letters and find the word. Problems not solved within 2 min were recorded as 120 s. The order of drug administration and the order of test booklet administration (a different test set was used for each drug condition) was counterbalanced across all subjects.

Analysis: Logarithmic scores of time taken to complete each test item were recorded, in addition to heart rates at the time of testing (to assess the degree of autonomic effects of the drugs). As in previous research, each subject's solution latency score for each drug condition was computed from the sum of natural logs of solution latencies for each problem [2]. All solution latency scores were adjusted for test order (for learning effect) and test booklet (for variability in difficulty of individual test sets). The solution latency scores were compared across subjects between the three drug conditions (nadolol, placebo, and propranolol) using repeated measures analysis of variance (ANOVA). The number of unsolved anagrams, adjusted for test order and test booklet, was also compared between drug conditions using repeated measures ANOVA. Heart rates were then compared across subjects between the three drug conditions using repeated measures ANOVA.

RESULTS

Both propranolol and nadolol were associated with a significantly slower heart rate at the time of testing compared with placebo (nadolol *vs* placebo $F(1,17) = 5.420$, $p > 0.033$; propranolol *vs* placebo $F(1,16) = 10.981$, $p = 0.004$), indicating that doses of both drugs were adequate to result in peripheral adrenergic blockade. Furthermore, direct comparison between propranolol and nadolol demonstrated the same degree of peripheral adrenergic blockade ($F(1,16) = 0$, $p = 1$).

The average (\pm s.d.) solution latency score across subjects for propranolol was 35.18 ± 10.99 , for placebo 36.29 ± 9.24 and for nadolol 38.11 ± 10.56 . Patients performed significantly better on propranolol than on nadolol ($F(1,17) = 5.773$, $p = 0.028$). Comparisons between each drug and placebo did not reach significance (placebo *vs* nadolol $F(1,17) = 2.069$, $p = 0.168$; placebo *vs* propranolol $F(1,17) = 0.481$, $p = 0.497$). A trend towards significance was detected in a three-drug comparison ($F(1,16) = 3.227$, $p = 0.066$). Comparison of the number of unsolved anagrams, a less sensitive measure of performance, did not significantly differ between conditions (propranolol *vs*

nadolol $F(1,17) = 0.32$, $p = 0.861$; placebo *vs* nadolol $F(1,17) = 0.260$, $p = 0.617$; placebo *vs* propranolol $F(1,17) = 0.098$, $p = 0.758$.

DISCUSSION

Previous research has demonstrated better performance on a cognitive flexibility task, the anagram task, after propranolol (β -adrenergic antagonist) than after ephedrine (β -adrenergic agonist). However, since propranolol and ephedrine have both central and peripheral effects, the question remained whether noradrenergic modulation of cognitive flexibility is a centrally or peripherally mediated phenomenon.

The current results demonstrate that central and peripheral β -adrenergic blockade results in better performance on anagrams than peripheral-only β -adrenergic blockade. Heart rate data suggests that doses of the two β -blockers had equivalent systemic effect. These results support a central mechanism of noradrenergic modulation of cognitive flexibility. This provides supportive evidence for the hypothesis that arousal influences cognitive flexibility, related to creativity in earlier literature [4,10–12], through the action of the central noradrenergic system. However, an interaction between central and peripheral effects may offer an alternative explanation to the results. This could be addressed by future research such as comparing the effects of propranolol combined with a peripheral-only β -agonist to placebo, thus isolating the cognitive effect of central β -blockade. Our findings also raise the possibility that the L-dopa induced restriction of the semantic network in the aforementioned priming experiment [7] may have in part resulted from conversion of L-dopa into norepinephrine.

The proposed centrally mediated mechanism of noradrenergic modulation of cognitive flexibility may be related to the modulatory effect of norepinephrine on the signal-to-noise ratio of neuronal activity within the cortex [8,13]. Electronic coupling of noradrenergic neurons in the monkey cortex has been shown to correlate with proportions of goal-directed versus exploratory behaviors [13].

The anagram task has been utilized in the past as a method of assessing creativity [14–16]. This task has also been widely utilized in studies of anxiety, demonstrating a decrement in performance in anxious subjects [17–19], and has furthermore been proposed as a marker of anxiety [20]. This finding may therefore be relevant to the understanding of anxiety disorders, as is evidenced by the benefit adolescents with test anxiety receive with propranolol [3].

This may also have relevance to conditions such as autism spectrum disorder, where restricted semantic network flexibility is observed [21]. This may also be important in withdrawal from cocaine and opiates due to the noradrenergic upregulation and associated symptomatology observed in these conditions [22,23], and the suggestion of benefit from propranolol in cocaine withdrawal [24].

This finding begins to reveal how the ability to solve problems can be state dependent, with situations upregulating the noradrenergic system impairing cognitive flexibility

and situations downregulating the noradrenergic system aiding cognitive flexibility. Furthermore, this begins to reveal the regulation of one component of how the brain carries out creative processes.

The neural mechanisms underlying cognitive flexibility are not yet fully understood, but it appears that the frontal lobes play an important role. Patients with right frontal lesions have been found to be impaired in strategy shifting ability whereas patients with parietal lesions have a general visuospatial processing impairment using a visuospatial task which requires cognitive flexibility [25]. Further research will be needed to clarify the mechanisms by which the noradrenergic system affects this process and to more precisely define the pharmacology of this process. Further research will also be needed to determine the range of cognitive tasks modulated by the noradrenergic system. The lack of a significant difference between the propranolol and placebo conditions could result from variability in ambient noradrenergic tone in the placebo condition being sufficient to interfere with comparisons to the drug conditions. Further investigation will be needed with larger sample sizes in order to further address this question.

CONCLUSION

This study supports the hypothesis that the noradrenergic system modulates cognitive flexibility through a central mechanism. Further research will be required to further elucidate the mechanism of action of this phenomenon, and to determine the range of cognitive tasks modulated by the noradrenergic system.

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