

STRESS causes impaired performance on tests of creativity. Drugs that block β -adrenergic receptors improve test performance in patients with test anxiety. Furthermore, catecholamine precursors (L-DOPA) reduce the flexibility of semantic networks. Our study investigated the effect of noradrenergic system modulation on cognitive flexibility in problem solving. Eighteen normal subjects undertook three problem solving tasks (number series, shape manipulation and anagrams) 45 min after propranolol, placebo and ephedrine. On the task that appeared to rely most heavily on cognitive flexibility (anagrams), subjects who were most able to solve these problems demonstrated significantly shorter solution times (logarithmic scores) after propranolol than after ephedrine. This suggested that the noradrenergic system exerts a modulatory effect on cognitive flexibility in problem solving. *NeuroReport* 10:2763–2767 © 1999 Lippincott Williams & Wilkins.

Key words: β -Adrenergic antagonists; Cognition; Cognitive flexibility; Ephedrine; Catecholamines; Language; Norepinephrine; Problem solving; Propranolol

Noradrenergic modulation of cognitive flexibility in problem solving

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Introduction

Cattell [1] suggested that there may be two types of intelligence or ability to solve problems, fluid intelligence and crystallized intelligence. Crystallized intelligence includes declarative knowledge, for example knowing that Shakespeare wrote Hamlet, or knowing that $2 + 3 = 5$. Fluid intelligence is more important for solving problems that cannot be solved with declarative knowledge. These types of problems are believed to be solved by one or more of several methods, which include trial and error, learned algorithms, and use of cognitive flexibility.

Several lines of evidence have suggested a role for the noradrenergic system in the modulation of cognitive flexibility. Situational stressors are associated with a number of physiological responses, including an increase in activity of the noradrenergic system [2,3]. Furthermore, cognitive flexibility may be impaired by increased situational stress. For example, performance on the Remote Associates Test, in which subjects are required to produce a word that is associatively connected with three other words, decreases during high arousal conditions whereas performance on other cognitive tests improves with increased arousal [4]. This Remote

Associates Test is considered a measure of creative approaches to problem solving, in which utilization of a wider search for possible appropriate responses results in a better performance [4–6]. Anxiety has also been shown to impede remote responses but promote obvious responses on the Consequences Test, another test considered a measure of creative problem solving [7].

Electroencephalographic (EEG) data also provide support for the postulate that creative thinking most readily occurs in a setting of decreased arousal and stress. The dimensional complexity of frontocortical EEG activity during creative thinking is greater than during convergent thinking and resembles the activity detected during mental relaxation [8]. In the EEG experiments the creative thinking task involved asking subjects to think of as many unique consequences as possible to a hypothetical situation. The convergent thinking task involved asking subjects to give the solutions to arithmetical stories.

Studies in adolescents with known stress-induced cognitive dysfunction have shown that β -adrenergic blockade improved scores on the Scholastic Aptitude Test (SAT) [9]. Although the SAT is less likely to be a true measure of cognitive flexibility, the SAT findings suggest that the noradrenergic system can

play a modulatory role in some types of problem solving in certain individuals.

More recently, Kischka *et al.* [10] reported that administration of L-DOPA resulted in restriction of the semantic network in a priming experiment. Specifically, normal healthy subjects were asked to depress particular keys on a keyboard as quickly as possible indicating whether a particular group of letters formed a meaningful word or a meaningless letter string. Subjects were found to recognize words that were directly related and indirectly related to a previously seen word as meaningful more rapidly than unrelated words after taking placebo. After taking L-DOPA, only the directly related words and not the indirectly related words were recognized more rapidly than unrelated words. These results were interpreted as modulation of semantic networks by the dopaminergic system. However, L-DOPA is also converted into norepinephrine, thus a role for modulation of other catecholamines in producing this result cannot be excluded. Furthermore, studies of associative memory in sleep revealed changes in semantic priming more readily explained by alterations in the noradrenergic system than the dopaminergic system [11].

We investigated the hypothesis that noradrenergic modulation can influence neuronal networks by assessing normal subjects' ability to perform problem solving tasks during pharmacological treatments that increased or decreased noradrenergic activity.

Materials and Methods

The study protocol was approved by the University of Florida Institutional Review Board and all subjects signed written informed consent prior to entry into the study. Eighteen normal healthy subjects (nine male, nine female) mean age (\pm s.d.) 26.4 ± 6.0 years (median 27, range 18–37) participated in this randomized, double blind placebo controlled three-way crossover study. All subjects had a clinical interview and were found to have no symptoms or history of neurological disease or dyslexia or dyscalculia. English was a primary language for all subjects. Subjects with a history of cardiac disease, asthma, diabetes, thyroid disease and depression were excluded. Female subjects of childbearing potential were screened with a urine pregnancy test prior to participation. Each subject attended three test sessions each, one week apart. Forty-five minutes prior to the testing sessions, subjects received either oral propranolol (40 mg), oral ephedrine (25 mg) or placebo. At each test session, subjects were asked to solve sets of three types of tasks in a standardized order. Test session order (Test A, Test B, Test C; Fig. 1) and drug order were counterbalanced across equal numbers of male and

female subjects. The first type of task was a group of number series problems. During this test subjects were given a list of numbers, and were asked to derive the next few numbers in the series (Fig. 1). The maximum time allowed to answer each problem was 3 min. The second type of task was a series of shape rearrangement tasks. These tasks resemble the Matchstick Test of Cognitive Flexibility [12]. In the original Matchstick task, the subjects are given a figure representing a geometric shape made by matchsticks and are asked to remove a given number of matches to derive a new geometric shape. The task used in our study was made more difficult by asking the subject to remove the matches and relocate them within the figure to make a new geometric shape (maximum time allowed: 4 min per problem; Fig. 1). The third type of task was a group of word-unscrambling (anagram) tests. In this test, subjects were given a group of letters that did not form a word, but when rearranged could form a particular word. Subjects were asked to unscramble or reorganize the letters and find the word (maximum time allowed: 2 min per problem, all times < 5 s were rounded up to 5 s; Fig. 1).

The time taken to complete each test was recorded. At the end of the test period, heart rates were also measured in order to determine the peripheral autonomic effects of the administered drugs or placebo.

The primary comparison for each type of task was performance after noradrenergic stimulation *vs* noradrenergic blockade. In order to normalize variance among the longer task times, the natural logarithm of the time to completion of each type of test (number series, spatial rearrangement, and anagram) were compared between the drug treatments (such that the difference between 110 s and 120 s would not be treated the same as the difference between 10 and 20 s). Since many subjects were unable to solve a large number of spatial and anagram problems, we suspected that a floor effect might influence the results. Therefore, the comparison was repeated for those subjects best able to solve the problems (defined as subjects solving the problems more rapidly than the mean) for the spatial ($n=9$) and anagram ($n=7$) tasks. All completion time scores were adjusted for test order (since subjects would be expected to improve with each week of testing) and test booklet (since individual tests might vary in difficulty).

The logarithmic scores, adjusted for test order and test booklet, for each test type for all subjects as well as best performers were compared between the conditions of maximal noradrenergic activation (post-ephedrine) and minimal noradrenergic activation (post-propranolol) using analysis of variance (ANOVA). A three-way comparison of adjusted

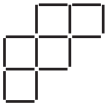

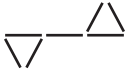






Test A		MHBTU
0,2,5,9,14,20,27,__,__,__	Move 4 lines to make 4 small squares	
1,1,2,3,5,8,13,21,__,__,__		RPPEA
0,1,3,7,15,__,__,__	Move 5 lines to make 4 small squares	RNFGEI
1,0,4,1,7,2,10,3,13,4,__,__,__,__		CNLPIE
	Move 3 lines to make 3 small triangles	RLTNNEA
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Test B		HTRSI
1,3,7,13,21,31,__,__,__	Move 2 lines to make 3 small triangles	TRSIA
0,3,8,15,24,35,__,__,__		SRREEA
3,5,9,17,33,65,__,__,__	Move 3 lines to make 5 small squares	KPNNIA
0,1,5,14,30,55,__,__,__		LMRFAUO
	Move 3 lines to make 3 small squares	
<hr/>		
Test C		DSLEI
2,4,7,11,16,22,__,__,__	Move 2 lines to make 6 small squares	TMLAE
3,6,11,18,27,38,__,__,__		NHDLEA
1,3,4,7,11,18,29,__,__,__	Move 3 lines to make 7 small squares	KSTBEA
0,2,1,5,3,9,6,14,10,20,__,__,__,__		LNHPDIO
	Move 4 lines to make 6 small squares	

FIG. 1. Sample problem solving items from one test session in the preliminary study. For the calculation test (left), subjects were asked to give the next numbers in the number series in the spaces provided. For the spatial task (center), subjects were asked to pretend that each shape was made up of toothpicks and to move the requested number of toothpicks to a new location within the same drawing to make the requested new shape. For the word unscrambling (anagram) task (right), subjects were asked to rearrange the letters to form an English word.

logarithmic scores for all drugs (ephedrine, placebo and propranolol) using repeated measures ANOVA was also performed. A similar analysis was performed on the heart rate data.

Results

A trend towards a difference between completion times of the number series tasks was detected using the three-way repeated measures ANOVA compari-

son between all drug conditions ($F(1, 16) = 2.989$, $p = 0.079$). However, no difference existed on the index measure following oral ephedrine or oral propranolol using repeated measures ANOVA ($F(1, 17) = 2.012$, $p = 0.174$). Similarly, no difference existed between completion times of the spatial task following oral ephedrine or oral propranolol for all subjects ($F(1, 16) = 0.159$, $p = 0.854$ for the three-way comparison including placebo; $F(1, 17) = 0.218$, $p = 0.646$ for ephedrine *vs* propranolol) or for the best problem solvers ($F(1, 7) = 0.017$, $p = 0.983$ for the three-way comparison; $F(1, 8) = 0.000$, $p = 0.998$ for ephedrine *vs* propranolol). Comparison of completion times for the anagram task following oral ephedrine and oral propranolol revealed no significant difference between groups when all subjects were analyzed ($F(1, 16) = 0.339$, $p = 0.717$ for the three-way comparison; $F(1, 17) = 0.486$, $p = 0.495$ for ephedrine *vs* propranolol). When, however, the best problem solvers were selected to avoid the floor effect, the performance was significantly better following oral propranolol than following oral ephedrine ($F(1, 6) = 8.598$, $p = 0.026$), with a trend also observed on the three-way comparison ($F(1, 5) = 5.053$, $p = 0.063$).

Since the three types of problem sets that we gave the normal healthy subjects attempted to assess fluid intelligence, a *post-hoc* analysis was performed. These problems may be solved by one or more of three methods: trial and error, pre-existing algorithms, and cognitive flexibility. We attempted to learn which type of strategy each subject used by examining their test booklets. The trial and error or algorithmic strategies, unlike utilization of cognitive flexibility, may require the temporary storage of more information than can be held in a subject's working memory. Therefore, if a subject uses a trial and error or algorithmic strategy to solve these problems then that person may be more likely to write in the booklet. Writing in the booklets suggesting algorithmic or trial and error approaches was present for a significantly greater number of test items per subject for the number series problems than for the anagram task ($t(17) = 4.345$, $p < 0.0005$) and similarly for significantly greater numbers of items per subject for the spatial task *vs* the anagram task ($t(17) = 7.124$, $p < 0.0005$).

Heart rate comparisons between the testing days following oral propranolol or oral ephedrine revealed that heart rate showed a trend towards being greater following receipt of ephedrine than placebo ($F(1, 14) = 3.543$, $p = 0.081$), and significantly lower following receipt of propranolol than placebo ($F(1, 14) = 15.114$, $p = 0.002$). The three-way comparison of ephedrine, placebo and propranolol revealed a significant difference in heart rate across conditions

of noradrenergic modulation ($F(1, 12) = 11.361$, $p = 0.002$).

Discussion

This study investigated the effects of noradrenergic modulation on cognitive flexibility in problem solving. The results of this study showed that the task which most utilized cognitive flexibility appeared to be the anagram task. The range of reasonable possible solutions that must be searched through for the anagram task is greater than for the other tasks (the number of words of a given length is greater than the number of simple number series or shapes that could be utilized in our study). Anagram solution when measured shows speed-accuracy decomposition more consistent with all-or-none processing rather than piecemeal processing [13,14], as would be expected for a true cognitive flexibility task. Our data show that this task was also the only task we studied that was significantly influenced by modulation of the noradrenergic system. These results support the hypothesis that the effect of anxiety and arousal on cognitive flexibility may be mediated, at least in part, by the noradrenergic system. If this is true, then this may have important implications as to the mechanisms of test anxiety. It also suggests that one mechanism contributing to the previously reported effect of L-DOPA on the semantic network could be as a result of its conversion to norepinephrine. However, our study is limited by the small number of test items of each type that could be presented per session (Fig. 1) due to the limited duration of peak activity of the administered drugs.

Whether the noradrenergic modulation occurs in the central nervous system or is mediated by peripheral feedback is unknown. Both ephedrine and propranolol have effects on central as well as peripheral adrenergic receptors. Peripheral feedback of adrenergic tone has been proposed to play an important role in modulation of cognitive processes [15]. However, another possibility is that noradrenergic modulation of cognition is mediated by direct modulation of the signal-to-noise ratio within the cortex [16].

We propose that utilizing cognitive flexibility in problem sets such as the anagram task may be mediated by 'search of the possible solution network', much as a search of the semantic network is required to identify or produce a word. We also suggest that frontal brain regions guide the search by selective engagement of the posterior regions relevant to the type of problem being solved. Frontal regions are well known to be crucial for optimal performance on tasks involving cognitive

flexibility [17–20]. EEG data are supportive of a strong frontal–posterior network in performance in cognitive flexibility, as evidenced by the strong coherence of tracings of these regions during creative tasks in various modalities [21]. Further evidence in favor of this hypothesis is that patients with right frontal lesions are impaired in strategy shifting ability whereas patients with parietal lesions have a general visuospatial information processing impairment using a spatial task also derived from the Matchstick Test of Cognitive Flexibility [12,22]. Examination of this phenomenon may be helpful in the study of conditions such as dementia of the Alzheimer type, in which early impairments referable to the frontal lobe occur without significant frontal pathology [23,24], possibly resulting from disruptions of the frontal–posterior networks [24]. Our results may also explain the ‘moment of insight’ experiences where a difficult problem is repeatedly approached with effort, only to have the solution come later at a moment of rest, such as just before falling asleep. These moments of insight would therefore occur when arousal and noradrenergic activation are known to be at their nadir [25].

Conclusion

This study supports the hypothesis that the noradrenergic system has a modulatory effect on cognitive flexibility. Follow-up studies using expanded prob-

lem sets of a single type will be needed to further test this hypothesis. Future research will be required to further elucidate the mechanism by which this phenomenon occurs.

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