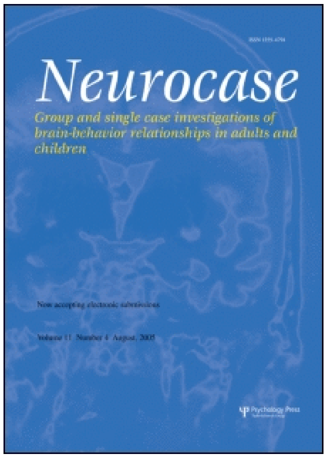

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Effect of the Cold Pressor Test on Memory and Cognitive Flexibility

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Cognitive flexibility is affected by stress. The cold pressor test is a known adrenergic stressor that impairs memory, but the effect on cognitive flexibility is unknown. Sixteen subjects were given cognitive flexibility and memory tasks with and without one hand immersed in cold water. Memory was impaired in the cold pressor condition but there was no effect on cognitive flexibility. The lack of a cold pressor effect on cognitive flexibility may result from an isolated effect on the peripheral noradrenergic system, whereas indirect effects due to nociception on memory may occur.

Keywords: Cognitive flexibility, pain, stress, noradrenergic, memory

Introduction

Testing in the setting of stressors has been shown to be associated with impaired cognitive flexibility, specifically flexibility of access to lexical/semantic and associative networks (Alexander, Hillier, Smith, Tivarus, & Beversdorf, 2007; Hillier, Alexander, & Beversdorf, 2006; Martindale & Greenough, 1973). This appears to be mediated by a noradrenergic mechanism, as propranolol, a central and peripheral beta-adrenergic antagonist, has been shown to reverse this effect (Alexander et al., 2007).

The cold pressor test, when used as a reversible stressor, has been shown to evoke an activation of the sympathetic nervous system peripherally, as demonstrated by an increase in the mean arterial pressure during administration (Zvan, Zaletel, Pretnar, Pogacnik, & Kiauta, 1998). The cold pressor has been shown to impair performance on some memory and attentional tasks (Datz & Echevarria, 2002; Kuhajda, Thorn, & Klinger, 1998; Kuhajda, Thorn, Klinger, & Rubin, 2002). However, as the effect of the noradrenergic system on cognitive flexibility appears to be mediated centrally (Beversdorf, White, Chever, Hughes, & Bornstein, 2002), it is uncertain whether the cold pressor, known for its effect of peripheral sympathetic activation, would affect cognitive flexibility. Therefore, we wished to examine the effect of the cold pressor condition on cognitive flexibility as well as memory. If the cold pressor test can affect the noradrenergic system centrally, we would predict that it would affect cognitive flexibility as measured by performance on the anagram task and the Compound Remote Associates task.

Materials and methods

Subjects

Eight females and eight males were recruited from the Ohio State University campus as subjects in this experiment. The average age was 23.8 ± 2.7 (standard deviation) years and the average educational level was 16.87 ± 0.5 (standard deviation) years. In compliance with the Institutional Review Board of The Ohio State University, all subjects gave signed consent and subjects with a history of cold intolerance, arrhythmias, or a reported history of learning disabilities such as dyslexia were excluded. English was a primary language for all subjects.

Procedures

Each subject participated in two test sessions performed on consecutive days. On one of the days, the session was performed with the cold pressor. Half of the subjects were tested with the cold pressor first, and half were tested without the

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cold pressor first. During each test session, subjects were given one of two versions of a battery of tests. At each visit, to assess verbal memory, one of two versions of the California Verbal Learning Test, trials 1–5, list A (CVLT) (Delis, Kramer, Kaplan, & Ober, 1987) was given, and the number of words recalled on trial 5 as well as the total number of words recalled on all five trials were recorded. To assess spatial memory, one of two versions of the Rey Complex Figure (Corwin & Bylsma, 1993; Osterieth, 1944; Rey, 1941; Spreen & Strauss, 1998) was given, and the score on a 36-point scale for copy and recall as well as the time taken to copy and recall were recorded. In order to assess working memory, the n-back task was administered, and continued until subjects missed three in a row (Braver et al., 1997), with the maximum n achieved before failure recorded. To assess attention, the Stroop task was given (Lezak, 1995), with the response latencies recorded. To assess cognitive flexibility (flexibility of access to lexical/semantic and associative networks), one of two versions of the 5-letter anagram task was given, where subjects were asked to unscramble a set of letters to form a word (AADLS => SALAD), with the ln of solution latencies recorded as with our previous work (Beversdorf, Hughes, Steinberg, Lewis, & Heilman, 1999; Beversdorf et al., 2002), as well as the number of anagrams solved (15 items, maximum time allowed=45 s per problem). As a second measure of cognitive flexibility, one of two sets of items from the Compound Remote Association task (CRA) (Bowden & Jung-Beeman, 2003a,b) was given, where subjects were asked to find the single word that forms a compound with three given words (tree, cone, apple => PINE), and the number of correct items was recorded (30 items, maximum time allowed=7 s per problem). To assess spatial problem solving, alternating items from the Ravens Progressive Matrices were given, (Ravens) (Raven, 1938, 1996), with the number of correct items recorded.

Blood pressure, heart rate, and subjective measures of stress (subjects were asked to rank how stressed they were on a scale of 1–10, with 1 being the least stressed and 10 being the most stressed they could imagine), were assessed for all subjects before and at the end of testing to assess the stress response to the cold pressor test. For the cold pressor test, the water was kept between 2 and 4°C, with temperature confirmed before each period of hand immersion and adjusted with additional ice or water as needed. While performing cognitive tests during the cold pressor test, subjects were required to submerge their hand up to the wrist level for 3 min (selected from the maximum amount of time from previous research in which the stress effects of the cold pressor test did not attenuate (Montoya, Brody, Beck, Veit, & Rau, 1997)). Subjects then removed their hand from the cold water for 3 min; and the testing was paused until the next immersion. This procedure was then repeated until the subjects had completed all of the neuropsychological tests. In the control condition, the sequence of events was the same except that subjects placed their hands in an empty cooler up to the wrist level.

The order of testing was designed to accommodate the schedule of the cold pressor test, such that all tasks with handwritten responses could be performed during nondominant hand submersion: the Rey complex figure copy task and the alternating items from the Ravens progressive matrices were performed with the first hand submersion (nondominant hand submersed). The Rey complex figure task recall and trials 1–5 of list A of the CVLT were performed with the second hand submersion (nondominant hand). The third hand submersion (dominant hand) took place while subjects took the anagrams test, and the fourth hand submersion (nondominant hand) took place while subjects took the Stroop test and the n-back test. The CRA was administered during the final hand submersion (dominant hand).

The order of test condition (cold pressor vs. control) and test version administered were counterbalanced.

Analysis

Blood pressure and heart rate were compared between all conditions using paired *t*-tests. Performances on cognitive tests were adjusted for test order and test version (as with previous work, using the counterbalanced design to adjust scores on each task by a ratio accounting for the effects of variations in difficulty between the test versions for each task, as well as any learning effects for each task) and then compared between cold pressor and control conditions using paired *t*-tests.

Results

Physiologic parameters

In order to determine the hemodynamic impact of sympathetic effects of the cold pressor test, we compared blood pressure and heart rate before and after the cold pressor test. There was a significant increase in blood pressure during the cold pressor test (for systolic blood pressure, before = 124.9 ± 10.8, after = 132.5 ± 10.3, $t(15)=7.50$, $p = .000002$, diastolic blood pressure, before = 75.9 ± 9.4, after = 83.2 ± 8.2, $t(15) = 7.20$, $p = .000003$), but there was no change in heart rate with the cold pressor test (heart rate before=72.3 ± 10.1, heart rate after = 71.3 ± 9.4, $t(15) = 0.43$, $p = .68$). To confirm that this effect was specific to the cold pressor test and not a change due to the impact of the test session, we compared blood pressure at the end of the cold pressor test session with blood pressure and at the end of the control session, and found a similar effect of the cold pressor test (for systolic blood pressure, cold pressor condition=132.5 ± 10.3, control condition = 124.4 ± 12.7, $t(15) = 4.18$, $p = .001$, for diastolic blood pressure, cold pressor condition=83.2 ± 8.2, control condition = 78.4 ± 9.7, $t(15) = 2.40$, $p = .030$).

Cognitive tests

As expected, subjects recalled fewer words on the CVLT during the cold pressor test than in the control condition.

Subjects also took less time to copy and recall the Rey complex figure but recalled fewer items on the Rey complex figure test during the cold pressor test. The effects on the Rey complex figure recall and the effects on the total number of words on the CVLT remained after Bonferroni correction. However, there was no significant difference between conditions for the other cognitive tasks including all tests of cognitive flexibility (see table 1). Performance did not differ between conditions for either the number of problems solved or the rate of solving problems on the cognitive flexibility tasks.

As a subjective measure of stress, the subjects' reported level of stress was examined and found to be significantly higher after the cold pressor test session as compared to after the control condition (before cold pressor test = 3.31 ± 1.62, after cold pressor test = 4.06 ± 1.44, $t(15) = 2.54$, $p = .023$). There was no such effect on reported level of stress at baseline (before cold pressor test = 3.56 ± 1.67, before control = 3.31 ± 1.67, $t(15) = 0.67$, $p = 1.51$). There was no significant correlation detected between stress reported during the cold pressor test and memory performance or Rey recall time during the cold pressor test (stress vs. CVLT trial 5: $r = .05$, $p = .85$; stress vs. CVLT total: $r = .009$; $p = .97$; stress vs. Rey recall time: $r = -.22$, $p = .40$; stress vs. Rey recall: $r = .31$, $p = .24$).

Discussion

Peripheral indices of adrenergic stress were increased during administration of the cold pressor test as evidenced by the increase in blood pressure. There was also an increase in the subjective measure of stress. Performance on tests of verbal and spatial memory (CVLT and Rey complex figure recall) were decreased with the cold pressor test, as expected given previous researchers' findings of impaired memory during the cold pressor test (Datz & Echevarria, 2002). Therefore, the cold pressor test was sufficient to induce sympathetic and cognitive responses. The changes in blood pressure were similar in magnitude to what was observed in our previous work demonstrating an effect of a public speaking stressor on cognitive flexibility (Alexander et al., 2007), with a similar sample size. However, we did not find a significant difference between the control and the cold pressor conditions on either cognitive flexibility task (the anagrams task or the CRA).

The activity of the hand area of the primary somatosensory cortex (S1) strongly correlates with activity in the insula and orbitofrontal cortex bilaterally during pain (Petrovic, Petersson, Hansson, & Ingvar, 2002), suggesting impact of stimuli such as the cold pressor test on areas distant from the primary S1 areas. Furthermore, the cold pressor test decreases alpha waves in the posterior leads on electroencephalography (EEG), believed to be the effect of the nociceptive input on attentional processing (Chang, Arendt-Nielsen, & Chen, 2002), and delta, theta and beta waves increased during the cold pressor test, believed to relate to modulation of motivation (Chang et al., 2002). Perhaps these remote effects relate to why the memory impairment occurs with such painful stimuli (Datz & Echevarria, 2002; Kudajda et al., 1998). The specificity of the effect on memory in the apparent presence of no effect on other demanding tasks in our study may suggest against the proposed hypothesis that such stimuli impair memory due to decreased attentional resources in general, causing impaired performance on demanding tasks (Datz & Echevarria, 2002; Kudajda et al., 1998, 2002). However, the attentional tasks of our study involved the naming tasks during the Stroop, whereas in the previous research, attentional resources were assessed in a semantic categorization task, which may be differentially affected by stress. The reason for

Table 1. Comparison of scores on different neuropsychological tests between experimental and control conditions

Test	Measured parameter	Mean ± sdev. while stressed	Mean ± sdev. during control	$t(15) =$	$p =$
CRA	Items Correct (out of 30)	8.13 ± 4.27	8.50 ± 5.19	0.41	0.69
n-back	Highest n achieved	8.06 ± 3.87	8.13 ± 2.92	0.54	0.60
Stroop	Words (seconds)	16.81 ± 10.82	14.38 ± 5.32	1.09	0.29
	Colors (seconds)	18.38 ± 5.30	19.63 ± 5.32	1.42	0.18
Anagram	LnANA	31.51 ± 6.33	31.65 ± 5.79	0.07	0.94
	Items correct (out of 15)	11.94 ± 2.14	11.69 ± 2.27	0.66	0.52
CVLT	Items on free recall of trial 5	11.31 ± 2.65	12.94 ± 2.02	2.82	0.013
	Items on free recall of total of trials 1–5	46.19 ± 10.17	51.00 ± 8.73	3.47	0.003
Rey Complex Figure	Time to copy item (sec)	70.63 ± 24.41	81.94 ± 31.63	2.08	0.055
	Score on copy item (out of 36)	35.34 ± 1.01	35.38 ± 0.96	0.096	0.93
	Time to recall item (sec)	65.69 ± 32.38	92.38 ± 42.29	3.71	0.002
	Score on recall item	17.97 ± 6.31	22.94 ± 5.66	3.53	0.003
Ravens	Overall score	22.50 ± 4.02	23.44 ± 2.53	0.74	0.47

t-Tests are preformed on scores adjusted for variations in test set difficulty and test order (sdev, standard deviation; CRA, Compound Remote Association; CVLT, California Verbal Learning Test; lnANA, sum of natural logs of times to solve each anagram).

the apparent specificity of the memory impairment in this setting warrants further investigation. The possibility must also be considered that the apparent selective memory impairments resulted from the encoding phase of the memory tests being presented at the beginning of the cold pressor test session, despite our efforts to minimize habituation to the cold pressor test. Furthermore, the need to perform handwritten responses during nondominant hand submersion may have biased the results. All cognitive flexibility tasks, as a result of their verbal response, were performed during dominant hand immersion. Comparison of performance on these tasks would need to be performed during immersion of each hand to resolve this confound. Future studies should also monitor other markers of sympathetic activity as well as cortisol and other stress markers.

Psychological stress has been shown to impair performance on tests of cognitive flexibility (Martindale & Greenough, 1973), presumably mediated by an effect of the central noradrenergic system (Alexander et al., 2007; Beversdorf et al., 2002). However, the stressor in the present study did not affect cognitive flexibility presumably due to its effect primarily on the peripheral autonomic system, much as peripheral adrenergic drugs do not modulate cognitive flexibility (Beversdorf et al., 2002). This conclusion, though, must be considered preliminary given the small sample size. Consistent with this, recent research has shown that the decrease in baroreceptor loading while lying down, resulting in decreased stimulation of the locus coeruleus–noradrenergic system, improves cognitive flexibility as compared to standing (Lipnicki & Byrne, 2005). Similarly, vagus nerve stimulation also decreases cognitive flexibility, presumably due to increased locus coeruleus–noradrenergic activity (Ghacibeh, Shenker, Shenal, Uthman, & Heilman, 2006). In our study, the effects of this peripheral stressor, which has been shown to increase peripheral resistance as part of its increase in blood pressure (Montoya et al., 1997), would not affect cognitive flexibility, whereas the increase in blood pressure associated with cognitive stressors (such as mental arithmetic stress) are not associated with changes in peripheral resistance (Montoya et al., 1997), and do affect cognitive flexibility (Alexander et al., 2007). The cold pressor test would not then appear to be an ideal model for the interaction between stress and cognition in conditions such as test anxiety (Faigel, 1991). It is thus important to carefully discern the physiological impact of various stressors in order to properly model their cognitive effects. Further research will be necessary to complete this picture.

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