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The effects of acute stress on human prefrontal working memory systems

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ABSTRACT

We examined the relationship between acute stress and prefrontal-cortex (PFC) based working memory (WM) systems using behavioral (Experiment 1) and functional magnetic resonance imaging (fMRI; Experiment 2) paradigms. Subjects performed a delayed-response item-recognition task, with alternating blocks of high and low WM demand trials. During scanning, participants performed this task under three stress conditions: cold stress (induced by cold-water hand-immersion), a room temperature water control (induced by tepid-water hand-immersion), and no-water control (no hand-immersion). Performance was affected by WM demand, but not stress. Cold stress elicited greater salivary cortisol readings in behavioral subjects, and greater PFC signal change in fMRI subjects, than control conditions. These results suggest that, under stress, increases in PFC activity may be necessary to mediate cognitive processes that maintain behavioral organization.

1. Introduction

Working memory (WM) may be defined as the retention and/or manipulation of to-be-remembered information over brief time intervals. It is believed to underlie many higher cognitive processes [6,59] including reasoning [51], planning [18] and problem solving [13,50]. Research indicates that the prefrontal cortex (PFC) is a vital neural substrate for WM functions [10,27]. Neuroimaging studies with humans have consistently demonstrated increased PFC activation during delayed-response tasks that require temporary storage of information [11,55]. In particular, event-related fMRI studies indicate that dorsolateral PFC mediates WM processes at high WM demands [55,57]. These results are consistent with primate WM studies showing sustained firing of PFC neurons during delay periods of WM tasks [19] and significant decreases in performance on delayed-response tasks following PFC lesions [17,26]. Primates also show performance decrements with stress induced PFC catecholaminergic changes [5].

Stress-regulation exerts influences on cognition and behavior. The presence of an acute environmental stressor can modify cognitive functions in humans, including WM systems [1,14,23,37,38,44,48]. Furthermore, WM processes may be particularly susceptible to the effects of acute stress under high memory loads [7,46] and during the resistance of interference from competing sources of information, especially for older adults [67]. Given the fundamental nature of relationships between WM and higher cognitive processes, delineating the underlying mechanisms of stress-related performance changes is critical, not only to a complete understanding of WM systems in particular, but to understanding the nature of stress–cognition relations generally.

Studies that have examined the effects of acute stress on WM have produced mixed results. Negative effects of acute stress on WM task performance have been observed in some studies [32,35,46,48,61]. Other studies, however, have not shown such effects [12,42,58]. Empirical discrepancies have been difficult to reconcile because, across studies, a variety of stress manipulations and WM measures have been used. Some stress manipulations may be more susceptible to individual reactivity differences than others [2,68]. Some performance measures may also be more susceptible to individual reactivity differences than others. For instance, some studies suggest that gender mediates stress–WM performance relationships [35,68]. Procedural differences between experiments may also lead to differences in

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results across studies. These include temporal relationships between stress-administration and cognitive assessment, cortisol collection methods, endogenous collection or exogenous cortisol administration, measured behavioral parameters (i.e., reaction time; RT and accuracy), and within- vs. between-subject stress manipulations.

Human and animal research suggests anatomic and neurochemical relationships between sub-cortical structures that respond to stress and affect PFC [21]. Rodent medial PFC is one target of the stress-related neurochemical response [8,15,16] via connections with amygdalar basolateral complex [41]. Additionally, lesions within these amygdalo–PFC pathways have been shown to attenuate catecholamine release within PFC [3,5]. Stress-related catecholaminergic changes may affect PFC-based WM processes in primates [5]. In one study, for instance, monkeys performed a spatial delayed-response task with varying delay intervals [3]. On some occasions, WM performance followed sustained exposure to loud noise (100–110 db wide-band frequency). Noise-related performance decrements were greater with longer delay intervals. Performance decrements were attributed to a "hyperdopaminergic" stress response in PFC because the behavioral stress response was mediated by administration of dopamine-receptor antagonists. In humans, excitation of the hypothalamic–pituitary–adrenal (HPA) axis leads to corticosteroid (e.g., cortisol) hypersecretion due to stress exposure. These hormones exert global effects on the brain and body and also affect mental states [20,22,45]. Results from multiple studies converge to indicate that increases in glucocorticoid levels exert a profound influence over PFC structure and functioning, in both animals and non-human primates. For example, corticosterone (the central cortisol analogue in rodents) has been associated with a reorganization of PFC dendritic fibers in rats [8]. Additionally, injections of hydrocortisone (a synthetic form of cortisol) have been linked to impairment of medial PFC-based behavioral inhibitory capabilities in non-human primates [39]. By impairing PFC function, excessive levels of cortisol also appear to disinhibit HPA activation thus increasing sympathetic nervous system activity.

These studies are consistent with the notion that WM systems are especially susceptible to the deleterious effects of acute stress. They illustrate a plausible mechanism through which stress could affect PFC-dependent WM processes, through PFC–amygdala interactions. To observe this mechanism in humans, we had subjects perform a delayed-response WM task during behavioral performance and fMRI scanning. In behavioral (Experiment 1) and fMRI (Experiment 2) studies we periodically immersed subjects' hands in ice-cold water (4 °C) to induce acute stress. For Experiment 1, we hypothesized that there would be a significant difference in salivary cortisol levels during cold stress compared to control conditions. Specifically, we hypothesized that salivary cortisol levels would be higher when subjects' hands were immersed in cold water than when they were immersed in room temperature water. For Experiment 2, we predicted that PFC activity would be most affected by the application of cold stress, relative to non-cold stress conditions. It is our hypothesis that the cold press experience results in increased cortisol levels, and that these higher cortisol levels disrupt typical prefrontal functioning. Additionally we predicted that this increase, if present, may be mediated by amygdalar activity. Because behavioral results from studies of acute stress have been mixed [35,42,46,49,58], we were less certain about predictions regarding behavioral performance. By convolving the presence or absence of acute cold-pressor stress with high and low WM demand we sought to clarify the manner in which these factors interact with PFC activity, amygdala activity and WM performance. The current study sheds new light on the nature of the interaction of PFC areas underlying WM processes and the amygdala, and how these neural regions interact to regulate the effects of acute stress in order to maintain organized and goal-directed behavior.

2. Experiment 1

2.1. Method

2.1.1. Participants

Eighteen healthy young volunteers (mean age=20.4; 6 men) were recruited from the undergraduate and medical campus of Rutgers University — Newark and UMDNJ. Participants were excluded if they had any medical (including type I or type II diabetes, hypertension, cardiac condition, significant weight loss or major surgery within the last 6 months), psychiatric (including depression, anxiety or substance abuse), or neurological (including epilepsy and migraine syndrome) conditions. Participants were also excluded if they were pregnant or taking oral contraceptives, currently on psychotropic medication, presently menstruating, smoked more than ten cigarettes per day or if they consumed more than fifteen drinks of alcohol per week. Participants were prohibited from consuming a large meal 60 min prior to the experiment, dairy products at least 30 min prior to the experiment and smoking or consuming alcohol 24 h prior to the study. All participants provided informed consent.

2.1.2. Procedure

In order to control for circadian fluctuations in cortisol levels, all sessions took place between 11 am and 1 pm. This choice of an earlier time in the day was made to enable subjects to easily follow the dietary guidelines necessary for accurate salivary cortisol collection (i.e. no eating or drinking for about 1 to 1.5 h prior to sample collection). Participants were greeted by an experimenter upon arrival to the laboratory and told that they would be involved in a study of memory. They were told that they would be taking several computerized cognitive tasks in addition to having their hands immersed in water intermittently. After signing IRB-approved consent forms, participants were escorted to an isolated experiment room, which maintained pleasantly neutral lighting so that subjects could acclimate to the lab environment. They were asked to settle in for about 20 min, provided with neutral reading material, and told that the experimenter would return shortly with instructions.

Following this acclimation period, the experimenter returned with a bucket of either chilled water or room temperature water for the hand-immersion procedure (see Section 2.1.2.2 below for description) immediately prior to the cognitive task. After the completion of the first run of the WM task (see Section 2.1.2.1), the participant was told to relax, continue reading until the experimenter returned with further instructions. After a 20-minute period, the experimenter returned with the bucket of either chilled water or room temperature water. The participant began the second run of the WM task. Salivary cortisol samples were obtained at baseline (immediately after acclimation period and prior to beginning the cognitive task), 20 min after task I and 20 min after task II (see Section 2.1.2.3). These time-delays permitted us to capture the effects of the room temperature and cold-pressor stress on salivary cortisol levels, as it generally takes 15–20 min for task-related changes in unbound cortisol levels to be expressed in the saliva.

2.1.2.1. Working memory assessment. The WM task was a modified version of the Sternberg Item Recognition Task. Subjects were presented sequentially with blocks of 1 letter (low WM demand condition) or 6 letter (high WM demand condition) trials. There were 5 trials per block. Subjects received 2 runs of the Sternberg Item Recognition Task, each consisting of a total of 60 trials with an ITI of 1 s. On each trial, either 1 or 6 letters appeared on the computer screen for 4 s. At the end of this period, the letters disappeared and a 5 s delay period ensued (fixation). Then a probe letter appeared for 3.5 s and the subject indicated whether the letter was part of the previously presented string of letters or not.

2.1.2.2. Cold-pressor task (CPT). A bucket of ice water chilled to a temperature of 4 °C was used. Temperature was assessed intermittently