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Acute and past subjective stress influence working memory and related neural substrates

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ABSTRACT

Stress has been proposed to affect cognitive control capacities, including working memory (WM) maintenance. This effect may depend on variability in stress reactivity and past subjective stress. However, as most studies employed between-subjects designs, evidence for within-subject stress effects remains scarce. To understand the role of intra-individual stress effects on WM, we adopted a within-subject design to study how acute stress, variability in stress reactivity, and past subjective stress influence behavioral and neural WM mechanisms. Thirty-four healthy males performed a WM task during functional magnetic resonance imaging (fMRI) in a control versus acute stress condition following the Trier Social Stress Test, a validated psychosocial stressor method. We tested for stress effects on WM performance and related neural activation by associating them with individual acute stress responsivity and past subjective stress experience using retrospective self-report questionnaires. We found no evidence of an effect of acute stress or related stress-reactivity on intra-individual WM performance. However, past subjective stress negatively influenced acute stress-induced changes to WM. On the neural level, acute stress reduced WM-related activation in the dorsolateral prefrontal cortex (dlPFC). The observed negative influence of inter-individual variability in past subjective stress experience on changes in WM performance, suggests that past subjective stress might induce vulnerability for impairing effects of acute stress on cognitive functioning. Because acute stress reduced WM-related dlPFC activation while WM performance remained unaffected, acute stress might boost neural processing efficiency in this group of high performing healthy individuals. Our study suggests that measures of past subjective stress should be considered when studying and interpreting the effects of acute stress on cognition.

1. Introduction

When experiencing stress, it is essential to maintain cognitive control to successfully modulate thoughts and actions. For example, when arriving at a noisy crowded train station and the train is due to depart shortly, it is crucial to ascertain the correct platform of departure from the departure boards, despite experiencing stress. Stress is a psychophysiological process elicited by physical or psychosocial strains, leading to subjective evaluation of situations as stressful (Cohen et al., 2016; Rajesh et al., 2014) and triggering reactions via the sympathetic-adrenal-medullary(SAM)-system and hypothalamic-pituitary-adrenal (HPA)-axis (Calvo and Gutiérrez-García, 2016). Although stress responses alert the individual in life threathening situations, these reactions might be less functional in modern societies, for example due to a lack of natural predators. Stress can severely affect social, cognitive functioning and is crucially involved in the pathogenesis and maintainance of psychiatric disorders (Koob, 2008; Koob et al., 2014; McEwen, 2004). A deepened understanding of the behavioral and neural mechanisms of acute stress on cognitive abilities has major societal and clinical implications.

Studies suggest that acute stress, stress-induced increases of glucocorticoids, and catecholamines alter cognitive functioning such as (working) memory (Arnsten, 2009; Bogdanov and Schwabe, 2016; Cornelisse et al., 2011; Oei et al., 2007, 2006; Otto et al., 2013; Schoofs et al., 2013, 2008) or decision-making (Otto et al., 2013; Radenbach et al., 2015; Schwabe and Wolf, 2009). Working memory (WM)

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comprises the ability to maintain, manipulate, and update information as well as protecting it against distraction (Baddeley, 2003). Additionally, WM represents cognitive control and underlies goal-directed behavior (Otto et al., 2013). Neurally, WM functioning depends on fronto-parietal brain circuits (D'Esposito, 2007; D'Esposito and Postle, 2015; Owen et al., 2005). Within these circuits the dorsolateral prefrontal cortex (dlPFC) is thought to control which information will be maintained, depending on task relevance (D'Esposito, 2007; D'Esposito and Postle, 2015; Riley and Constantinidis, 2016).

Neuroimaging studies in humans have shown that acute stress decreases WM-related neural activation in the right dlPFC (Oei et al., 2012; Qin et al., 2009; Van Ast et al., 2016), emphasizing its stress susceptability (Bogdanov and Schwabe, 2016). However, the direction of stress effects on behavioral WM performance is less clear. While some studies have shown detrimental effects of acute stress on WM performance (e.g., Luethi et al., 2009; Schoofs et al., 2008), other studies point towards performance increases (e.g., Cornelisse et al., 2011; Schoofs et al., 2013) or no changes (Qin et al., 2009). A meta-analysis found that acute stress impairs WM, even though the overall effect is small and varies across studies (Shields et al., 2016). Moreover, the delay time between stress intervention and task performance seems to be an important moderator (Bendahan et al., 2017; Hermans et al., 2014; Margittai et al., 2015; Shields et al., 2016, 2015).

Importantly, beyond the effects of delay, stress-induced changes in cognitive abilities depend on individual variability of trait anxiety (Goette et al., 2015), catecholamine-related arousal-responses (Arnsten, 2009; Arnsten and Li, 2005; Berridge and Arnsten, 2013; Radenbach et al., 2015), and cortisol levels (Oei et al., 2006; Radenbach et al., 2015; Van Ast et al., 2016). Qin and colleagues found that performance reductions in an *n*-back WM task scaled with increases of cortisol and heart rate (Qin et al., 2009). Consistently, Oei and colleagues observed an association between slowed reaction times in a Sternberg WM task under acute stress and higher levels of cortisol (Oei et al., 2006). Additionally, acute stress-induced impairments of WM performance are associated with self-reported previous stress exposure (Shields et al., 2017). Past stress experiences might render individuals more vulnerable to impairing effects of acute stress on cognitive processing, consistent with psychological stress theories claiming that repeated coping is taxing and depletes individual coping resources (Calvo and Gutiérrez-García, 2016; Lazarus and Folkman, 1984). Indeed, converging evidence from studies in animals and humans shows that decision-making capacities are predicted by levels of past stress (Dias-Ferreira et al., 2009; Radenbach et al., 2015), and past stress is negatively related to spatial WM in children with autism spectrum disorder (Ogawa et al., 2017). These results suggest that the interplay of past and acute stress might have detrimental influences on cognitive functioning.

However, virtually all presented studies employed between-subject designs. The inherent inability to dissociate within- from between-subject effects in those designs precludes any statements about modulation of intra-individual acute stress effects on WM and its neural correlates by stress responsivity or past subjective stress. It remains elusive whether changes in WM performance due to acute stress can truly be attributed to within-subject changes in cortisol levels. This knowledge gap implicates an urgent need of investigation using within-subject designs.

Additionally, the existing literature has focused on cortisol as a marker of stress responsivity, widely ignoring the fact that stress is more than an increase of circulating cortisol (Calvo and Gutiérrez-García, 2016; Shields et al., 2016), as stress changes the subjective stress experience of the individual (Calvo and Gutiérrez-García, 2016). According to psychological stress theories, determination of stressful events should be based on the subjective evaluation of situations as being stressful (Calvo and Gutiérrez-García, 2016; Lazarus, 1966; Lazarus and Folkman, 1984). It is currently unknown how changes to subjective stress response are related to WM performance and its neural correlates under acute stress.

In the present within-subject study, we investigated the effects of acute psychosocial stress, related individual stress reactivity, and past subjective stress experiences on intra-individual changes of WM performance and its neural signatures using functional magnetic resonance imaging (fMRI). We hypothesized that intra-individual WM performance and its neural signatures would be negatively affected by acute stress, that stress effects would be related to individual cortisol reactivity and subjective stress responses, and that past subjective stress would be associated with acute stress-induced changes to WM on both the behavioral and neural level.

2. Methods

2.1. Participants

Thirty-four healthy male participants completed the study (see Power Analysis in the Supplement). Participants were recruited from the database of the Max Planck Institute for Human Cognitive and Brain Sciences in Leipzig, Germany and from the local community through advertising. Only males were included in the study to avoid confounding effects of hormonal cycles that might interact with stress responsivity (Cornelisse et al., 2011; Schoofs et al., 2013).

Exclusion cirteria were medical, neurological disorders, and any current or lifetime psychiatric disorder assessed using the German Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders (SCID-IV, Wittchen et al., 1997). Participants reporting chronic intake of any medication known to interact with the central nervous system or endocrine responses were excluded.

The study was approved by the ethics committee of the medical faculty at the University of Leipzig and was conducted in accordance with the Declaration of Helsinki. All participants provided written informed consent before participation and were fully debriefed about the aims of the study after completing the entire protocol.

2.2. Design

The study entailed a within-subjects design, where participants performed an *n*-back WM task (e.g., Deserno et al., 2012) during fMRI in two separate test sessions. One session involved acute stress intervention (stress condition), and the other session involved no stress (control condition). The two sessions took place seven days apart, and the order of sessions was counterbalanced across participants. Each test session started in the afternoon between 1.30 and 4.30 pm to control for natural effects of circadian rhythms on cortisol (Kudielka et al., 2004; Radenbach et al., 2015; Starcke et al., 2013). Each participant's control and stress session were scheduled at the same time (e.g., a participant's stress condition started at 1.30 p.m. on a Monday and his control condition started at 1.30 p.m. on the Monday one week later). Acute stress reactivation in the form of saliva samples (cortisol response) and mood questionnaires (subjective acute stress experience) were assessed at six time-points during each test session (see Fig. 1).

2.3. Acute stress induction

During the stress condition participants were subjected to the standardized Trier Social Stress Test (TSST, Kirschbaum et al., 1993), which is known to increase endocrine, autonomous, and subjective markers of stress (Kirschbaum et al., 1993; Kudielka et al., 2004) more reliably than other stress induction paradigms (Dickerson and Kemeny, 2004; Giles et al., 2014). The test includes an interview and arithmetics in front of an emotionally neutral committee in white laboratary coats (see Supplement for detailed description). During the control condition, participants read a neutral piece of text without the presence of a committee (Radenbach et al., 2015). Importantly, both interventions were performed in different rooms, assuring no crossover effects due to location context. They were located at approximately the same distance