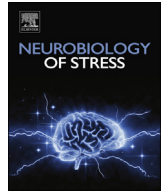




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## Neurobiology of Stress

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## Functional connectivity of resting-state, working memory and inhibition networks in perceived stress

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### ABSTRACT

Experimental imaging studies on the effects of acute stress have revealed functional changes in the amygdalae, hippocampi and medial frontal cortices. However, much less is known about the association between perceived stress and neurological function which may have implications for the development of stress related disorders. Participants completed a working-memory task and an inhibition task whilst undergoing a functional magnetic resonance imaging (fMRI) scan. Task related and resting-state fMRI data from 22 women and 24 men were analysed to investigate changes in task activations and functional connectivity associated with perceived stress over the past month. Analyses were stratified by gender due to gender differences in the stress response. Stress was associated with faster working memory response time in women, but not men. Stress was not associated with any differences in task activations in either gender. There were many significant associations between stress and connectivity: findings in women were consistent with increased emotional regulation; men exhibited decreases in connectivity between affective processing areas during the tasks and showed no relation between perceived stress and resting-state connectivity; very few of the within gender differences were significantly different between gender. Dysregulated connectivity between areas involved in the neural stress response and self-referential thoughts (e.g. the default mode network) suggests that perceived stress may have a subtle impact on cognitive processing and neural correlates.

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## 1. Introduction

### 1.1. Stress & cognitive function

Stress can be interpreted as appraising a situation as beyond the organism's resources (Lazarus and Folkman, 1984). The acute stress response involves the release of adrenocorticotrophin hormone (ACTH) and culminates in the release of glucocorticoids (cortisol in humans) from the adrenal cortex. The release of cortisol results in temporary changes to the metabolic, immune and nervous systems. In the short-term this stress response could be adaptive, but

prolonged exposure to high levels of stress has been associated with poorer health and cognitive impairment (Lucassen et al., 2014; S. J. Lupien et al., 2009; Steptoe and Kivimaki, 2013).

Stress has been shown to impact on the function of many regions of the limbic system, including the medial prefrontal cortex (mePFC), anterior cingulate (ACC), hippocampus, amygdalae and insulae (Dedovic et al., 2009; Heimer and Van Hoesen, 2006). The most consistent areas associated with stress appear to be in the hippocampus and amygdala, followed by the cingulate (Dedovic et al., 2009) in keeping with the neuroendocrinological process of the stress response (Pruessner et al., 2010). However, more recently the role of the frontal lobes in stress regulation (Dedovic et al., 2009) and the impact of stress on frontal lobe function has become apparent (Lataster et al., 2011; Lucassen et al., 2014; S. J. Lupien et al., 2009). Whilst chronic stress (over many years) has long been associated with smaller hippocampal volume,

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**Non-standard abbreviations**

SAT	Spatial addition task
HL	High Load
LL	Low Load
HM	High Maintenance
LM	Low Maintenance
I	Incongruent
C	Congruent

dysregulated function and poorer hippocampal dependent memory (Gianaros et al., 2007; S. J. Lupien et al., 1998) the indication that stress impacts on frontal lobe function has implications for many executive functions (Sonia J Lupien et al., 2007; Mika et al., 2012). For instance, studies have shown that frontal dependent working memory is more sensitive to the effects of cortisol administration than hippocampal dependent declarative memory (Sonia J Lupien et al., 2007).

### 1.2. Stress, WM and inhibition

The relationship between stress and cognitive function depends not only on the task, but also the type, stage and intensity of stress (Sandi and Pinelo-Nava, 2007). Interestingly, a meta-analysis showed that for the first 75 min after cortisol administration, working memory is impaired, but after 75 min the administration results in improved working memory (Shields et al., 2015). The reverse was true for inhibition; whereby for the first 135 min after cortisol administration inhibition performance was improved, but after 135 min cortisol administration was associated with impaired inhibition performance (Shields et al., 2015). There was no association between cortisol administration and set-shifting performance (Shields et al., 2015).

Longer term perceived stress (last two weeks) has been associated with improved working memory performance (Lewis et al., 2008; Vedhara et al., 2000), but poorer attention (Vedhara et al., 2000), consistent with the delayed effects of acute stress (Shields et al., 2015). Similarly, chronic stress was associated with slower interference inhibition in a sample of caregivers (Oken et al., 2011). However, long term work-stress related sick leave has also been associated with poorer performance in verbal working memory and digit span tasks (Jovanovic et al., 2011), suggesting that whilst acute stress improves working memory, prolonger stress may result in impaired working memory. Nonetheless, this finding may be related to the effects of stress related illness, rather than the impact of stress.

### 1.3. Stress and imaging

A meta-analysis reported acute intrinsic stress resulted in greater activation of the right superior temporal gyrus, inferior frontal gyrus and insula (Kogler et al., 2015), but fewer studies have investigated the neural correlates of extrinsic stress on cognitive function. Two studies have investigated the effect of stress on inhibition (Liston et al., 2009; Rahdar and Galvan, 2014) in mixed gender groups. Self-reported high state stress (on the day of testing) was associated with poorer inhibition performance and greater mePFC activation during the task, compared to participants who reported average state stress (Rahdar and Galvan, 2014). Similarly, one month of higher perceived stress was associated with impaired attention shifting and decreased neural coupling between

the dorsolateral prefrontal cortex and many areas of the fronto-parietal attention network employed in the task, but greater coupling between the left dorsolateral prefrontal cortex and middle temporal gyrus (Liston et al., 2009).

### 1.4. Gender differences in the stress response

Many studies have shown a gender difference in the cognitive, endocrine and neural stress response (Kogler et al., 2016; Lighthall et al., 2012; McLaughlin et al., 2009; Wang et al., 2007) and further gender differences depending on the type of stress (Wang et al., 2007). There are gender differences in the stress hormone response to psychosocial stress (Kirschbaum et al., 1999). In addition, women are thought to be more sensitive to social stress, whereas men are considered to be more sensitive to achievement related stressors (Kudielka et al., 2009; Wang et al., 2007). Wang and colleagues (2007) reported acute stress was associated with greater activations in the right prefrontal cortex in men and deactivated the left orbitofrontal cortex and inferior frontal cortex. However, in women, stress ratings were associated with more limbic activations; in the insulae and ventral striatum during the task and the anterior cingulate (ACC) and posterior cingulate cortex (PCC) one hour after the task. The authors speculated that men respond to stress with a fight or flight, whereas women employ emotional coping strategies. Others have supported the notion that women cope with stress using more emotionally focused strategies, but propose men to be more reward oriented when stressed (Kogler et al., 2016; Lighthall et al., 2012). There is some support for this hypothesis from a study indicating basal cortisol level is positively associated with greater connectivity between the amygdala and emotion related areas (e.g. PCC and inferior frontal gyrus, IFG) in women and between the amygdala and reward areas (e.g. striatum) in men (Kogler et al., 2016). Given these gender differences, it is not surprising that many studies investigating the neural effects of stress focus on single gender samples.

#### 1.4.1. Women

Relatively few studies investigating stress and cognition have focused on women; one study demonstrated no association between basal cortisol and inhibition task performance in a small sample of women (Tops et al., 2006); two studies have demonstrated associations between stress and altered resting-state neural connectivity from the amygdala. The first study demonstrated an enhanced coupling between the amygdala and ACC and insula after acutely induced stress (van Marle et al., 2009), conversely, chronic stress was associated with decreased coupling between the amygdala and ACC (Jovanovic et al., 2011).

#### 1.4.2. Men

High perceived stress did not impair inhibition performance in a sample of 60 men (Wu et al., 2014). However, one study reported decreased working memory accuracy after induced stress (Qin et al., 2012), but another study reported improved recall the next day (Henckens et al., 2009). Other studies reported no association between acute stress and working memory (Weerda et al., 2010) or cognitive flexibility (Ohira et al., 2011). Imaging studies have reported decreased memory task related activity (Qin et al., 2012; Weerda et al., 2010). However, acute stress was associated with less middle temporal lobe deactivation in one study – where there was also poorer performance in the stressed group (Qin et al., 2012), but the other study reported decreased middle temporal lobe activity, but only during the maintenance phase – with no relationship between stress and performance (Weerda et al., 2010), suggesting that the phases of memory and performance may contribute to differences in imaging findings.

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