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Working memory-related frontal theta activity is decreased under acute stress

Matti Gärtner[a,b,*], Lea Rohde-Liebenau[a], Simone Grimm[a,b,c,1], Malek Bajbouj[a,b,1]

[a] Cluster of Excellence "Languages of Emotion", Freie Universität Berlin, 14195 Berlin, Germany
[b] Charité CBF, Klinik und Hochschulambulanz für Psychiatrie und Psychotherapie, 14050 Berlin, Germany
[c] Clinic for Affective Disorders and General Psychiatry, Psychiatric University Hospital Zurich, 8032 Zurich, Switzerland

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Summary Acute stress impairs prefrontal cortex (PFC) function and has detrimental effects on working memory (WM) performance. Converging evidence from electrophysiological studies suggests a close link between WM processes and frontal theta (FT) activity (4—8 Hz). However, the effect of stress on WM-related FT activity has not been investigated yet. To shed light on this topic we acquired EEG data from 31 healthy male subjects who underwent a stressful and a neutral control condition. In both conditions, they performed an n-back WM task at two different difficulty levels. Our results showed that WM-related FT activity was decreased under stress. Behaviorally, we found performance impairments under stress in the difficult task condition that were related to FT decreases. Increased cortisol levels indicated a successful moderate stress induction. These findings indicate that FT is a potential neurobiological marker for intact PFC functioning during WM and further supports the recently made assumption that FT acts in the PFC to optimize performance.

1. Introduction

It is well established that neurochemical changes that occur during stress markedly impair prefrontal cortex (PFC) function and disrupt PFC network connections (for review see Arnsten, 2009; McEwen and Morrison, 2013). Working memory (WM), i.e. the ability to temporally store and manipulate information in the absence of external stimulation (Baddeley, 2003), strongly depends on intact PFC functioning (Muller and Knight, 2006). Consistently, impaired WM performance under acute stress was found in several studies (Lupien et al., 1999; Oei et al., 2006; Schoofs et al., 2008). A precise understanding of how stress interferes with prefrontal functioning is of great importance for the treatment of stress disorders and for the development of novel therapeutic interventions.

The neuroendocrine response to stress includes a rapid response of the sympathetic nervous system (SNS) and a

* Corresponding author at: Cluster of Excellence "Languages of Emotion", Freie Universität Berlin, Habelschwerdter Allee 45, 14195 Berlin, Germany. Tel.: +49 030 838 57845; fax: +49 030 8445 8233.
E-mail address: matti.gaertner@fu-berlin.de (M. Gärtner).
[1] These authors contributed equally.

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somewhat slower response of the hypothalamus—pituitary—adrenal (HPA) axis (de Kloet et al., 2005). Sympathetic activation increases prefrontal catecholamine (Ca) levels, and the HPA response leads to increased prefrontal glucocorticoid (Gc) concentrations (Diorio et al., 1993; Finlay et al., 1995). Animal research has shown that PFC function is impaired by both, high Ca levels (Arnsten et al., 1999) and high Gc levels (de Quervain et al., 1998). Furthermore, it is assumed that the impairing effect of high Ca and Gc concentrations is mutually reinforced (Grundemann et al., 1998). Consistent with this assumption it has been shown that impairing effects of stress on WM performance are especially strong in a time range in which both stress systems (SNS and HPA) are activated (Elzinga and Roelofs, 2005; Schoofs et al., 2008). Another behavioral finding that has been reported several times is that detrimental effects of stress on WM are stronger at high workload levels (Lupien et al., 1999; Oei et al., 2006). An explanation that has been proposed for this finding is that demanding tasks act as an additional stressor in experimental settings (Matthews et al., 2006; Oei et al., 2006).

In electrophysiological studies, frontal theta (FT) activity (4—8 Hz) has been closely linked to WM processes (for review see Mitchell et al., 2008; Hsieh and Ranganath, 2013). Increases in FT during WM have been robustly observed across tasks (Gevins et al., 1997; Jensen and Tesche, 2002) and modalities (Bastiaansen et al., 2002; Sauseng et al., 2007). An often-reported relationship is that increases in WM load are coincided with increases of FT activity (Jensen and Tesche, 2002; Onton et al., 2005; Sauseng et al., 2007). Additionally, a positive relationship between FT and behavioral performance has been reported several times (Gevins et al., 1997; Smith et al., 1999; Itthipuripat et al., 2013). A few studies attempted to separate different WM components in the theta band (Missonnier et al., 2006; Deiber et al., 2007). Deiber et al. (2007) showed that an early transient FT response (0—1000 ms after stimulus presentation) is related to attentional processes, while a later sustained response (1000—2500 ms after stimulus presentation) is more directly related to WM processes such as maintenance, updating and manipulation.

Besides the close link to WM processes, FT activity has been observed in other cognitive tasks such as error processing (Luu et al., 2003), attention (Makeig et al., 2002) and episodic memory (Nyhus and Curran, 2010). Because of this broad range of higher-order cognitive functions, it has recently been proposed that FT may be the putative "language" of a prefrontal network, in which action monitoring and top-down control mechanisms functionally interact to optimize performance (Cohen, 2011; van Driel et al., 2012).

In several source localization studies the medial prefrontal cortex (mPFC) and the anterior cingulate cortex (ACC) have been identified as possible sources for FT (Gevins et al., 1997; Raghavachari et al., 2001; Onton et al., 2005). Both structures have been implicated in processes related to WM, such as attentional control and performance monitoring (for review see Duncan and Owen, 2000; Ridderinkhof et al., 2004). Moreover, a negative relationship between FT and default mode network (DMN; Raichle et al., 2001) activity has been reported (for review see Hsieh and Ranganath, 2013). The DMN is a set of brain regions, including the mPFC that are related to internal attention and stimulus independent thought (Buckner et al., 2008). Its suppression has been related to performance during WM tasks (Hampson et al., 2006), and the inability to suppress DMN activity during tasks has been proposed as a cognitive risk factor for various mental disorders (Broyd et al., 2009). Using stress induction, Qin et al. (2009) showed that suppression of DMN activity was disrupted during a stressful WM condition when compared to a neutral condition. Establishing FT as a marker of DMN suppression during cognitive tasks could proof to be a useful tool during the diagnosis and treatment of mental disorders that have been related to impaired DMN suppression.

Given these findings, an interesting research question is whether and how WM-related FT activity is modulated under acute stress. There are several reasons to expect decreased FT activity during stress. First, synchronized activity in the theta band is a putative mechanism by which the PFC forms network connections (Anderson et al., 2010; Cohen, 2011), and PFC network connections are impaired under stress (Arnsten, 2009). Therefore, it can be expected that stress-related impairments of PFC network connections lead to less synchronization in the theta band, i.e. decreased FT activity under stress. Second, FT activity has been linked to stages of good performance during WM tasks (Gevins et al., 1997; Itthipuripat et al., 2013). Since WM performance during stress is impaired (Lupien et al., 1999; Schoofs et al., 2008), decreased FT activity can be expected. Third, FT activity is negatively correlated to DMN activity (Hsieh and Ranganath, 2013), which is less suppressed under stress (Qin et al., 2009). Thus, a third argument for stress-related FT decreases is provided. Despite the strong support for FT decreases under stress, we would like to point out that in another line of argument stress-related FT increases could be expected: FT increases with increasing task demands (Jensen and Tesche, 2002), and high task demands can act as an additional stressor in experimental settings (Oei et al., 2006). It is possible that FT is related to the stress that comes with high task demands, and therefore might increase under stress.

To investigate the above question empirically, we recruited 31 healthy male subjects that underwent a stressful and a neutral condition in which they performed a WM task at two difficulty levels. The difficulty levels were applied to investigate whether the expected effects of stress on WM performance and FT activity differ between a medium and a high workload condition. In the analysis of FT activity, we additionally tested whether stress modulates FT differently in two separate time windows that have been related to attentional- and maintenance processes during WM. Furthermore, we tested in an explorative analysis whether the detrimental effects of stress show variation in the time course after stress induction. We suspected stronger stress-effects in a time range in which concurrent SNS—HPA activation can be expected.

2. Methods

2.1. Subjects

31 healthy men (ages: 20—50) participated in the study. Only men were selected because fluctuations across the hormonal cycle and the use of hormonal contraceptives influence the