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Cortical hemodynamic changes during the Trier Social Stress Test: An fNIRS study

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A B S T R A C T

The study of the stress response has been of great interest in the last decades due to its relationship to physical and mental health. Along with the technological progress in the neurosciences, different methods of stress induction have been developed for the special requirements regarding the acquisition of neuroimaging data. However, these paradigms often differ from ecologically valid stress inductions such as the Trier Social Stress Test (TSST) in substantial ways.

In the study at hand, we used the rather robust optical imaging method of functional Near-infrared Spectroscopy (fNIRS) to assess brain activation during the TSST and two non-stressful control conditions. Additionally, we measured other stress parameters including the cortisol response and subjective stress ratings. As expected we found significant increases in subjective and physiological stress measures during the TSST in comparison to the baseline and control conditions. We found higher activation in parts of the cognitive control network (CCN) and dorsal attention network (DAN) – comprising the dorsolateral prefrontal cortex, the inferior frontal gyrus and superior parietal cortex – during the performance of the TSST in comparison to the control conditions. Further, calculation errors during the TSST as well as subjective and physiological stress parameters correlated significantly with the activation in the CCN. Our study confirms the validity of previous neuroimaging data obtained from adapted stress procedures by providing cortical activation data during a classical stress induction paradigm (i.e., the TSST) for the first time.

Introduction

The study of stress in humans is of great relevance because high levels of stress over long durations are considered to play a key role in the development of mental and physical health problems (Allen et al., 2017; Simeon et al., 2007b). For example, stress has been associated with depression and cardiovascular disorders (Grippo and Johnson, 2009; Rao et al., 2008), anxiety disorders – like social phobia (Krämer et al., 2012; Schmitz et al., 2011), PTSD (Simeon et al., 2007a), and panic disorder (Petrowski et al., 2013, 2010) – obesity (Laessle and Schulz, 2009) and psychosis (Pruessner et al., 2013). One of the most frequently used and validated methods for the induction of acute stress in a laboratory setting is the Trier Social Stress Test (TSST) which has a high ecological validity. During the TSST, which includes an anticipation phase and a test phase, subjects have to give a free speech and perform a mental arithmetic task in front of a committee (Kirschbaum et al., 1993). Although the neuro-endocrinological pathway of the stress response – the hypothalamic-pituitary-adrenal axis (HPAA) – is well studied, until today, only a few studies have tried to adapt stressful environments in a neuroimaging setup to examine cortical activation patterns during social stress, e.g. through the use of public speech, arithmetic or other mental tasks in fMRI. One paradigm used in neuroimaging is the Montreal

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Imaging Stress Test (MIST) in which an arithmetic challenge with negative feedback is used. Studies that used this task suggest decreased activity in the orbitofrontal cortex, deactivation of the limbic system and hippocampus as well as increased activity in the frontal lobes, the somatosensory and visual areas during the stress induction (Dedovic et al., 2009b, 2009a). Moreover, comparing stress responders and non-responders in an event-related MIST revealed increased activity in prefrontal, temporal and dorsolateral areas in stress responders (Dedovic et al., 2009c). Also other MRI studies that used arithmetic challenges reported positive associations of the cerebral blood flow (CBF) in the frontal cortex and subjective stress ratings (Wang et al., 2005). Consistently similar findings have been found with other stress induction tasks. With respect to public speech challenges, Tillfors et al. (2001) reported increased rCBF in the amygdala and decreased rCBF in orbitofrontal and temporal areas in social phobic subjects in comparison to non-phobic subjects as measured with PET (Tillfors et al., 2001). Other studies tried to provoke emotional stress, e.g. through the use of negative pictures (Sinha et al., 2004; Yanagisawa et al., 2011; Yang et al., 2007). In a study that used functional near-infrared spectroscopy (fNIRS), elevated activity within the frontal cortex during the exposure to negative pictures has been observed (Yang et al., 2007). Also activity of the ventrolateral PFC as assessed with fNIRS has been shown to have a regulative function on social pain during social exclusion (Yanagisawa et al., 2011). Similarly, Lee et al. (2014) observed in an adapted TSST fMRI paradigm, that watching video-recordings of oneself performing the TSST vs. another person increases activity in the bilateral IFG and insula. Further, cortical activation in the right IFG was higher and subjective stress was lower in males than in females (Lee et al., 2014). Usually, findings showing elevated activity within prefrontal cortex areas are thought to reflect top-down control processes over subcortical affective processing (Wager et al., 2008).

However, from a methodological perspective, many studies lack the ecological validity of the TSST. Due to the methodological restraints imposed by most neuroimaging methods, many studies resulted in designs that used only parts of the TSST (e.g., only the arithmetic challenge or public speech) or changed the environment of the measure in significant ways (e.g., by showing a videotaped interview while subjects lie in the fMRI or PET scanner instead of standing in front of a committee). These adaptations are usually implemented due to the specifics of the corresponding neurophysiological method, e.g., to avoid movement (critical for fMRI) or speech-related artefacts (critical for EEG and fMRI) in the original form of the TSST. With regards to the ecological validity, these settings might significantly differ from real-life stress situations, which might be a reason why some stress neuroimaging studies fail to show significant increases in stress indices (Dedovic et al., 2009c).

In the current study, we tried to verify the usage of an optical neuroimaging method in this context that is relatively robust with regards to movement and speech artefacts: functional Near-infrared Spectroscopy (fNIRS). For fNIRS measurements, a set of optodes is used to emit light in the near-infrared spectrum into the human brain. In these wavelengths, light is capable to penetrate the human skull and brain up to 2–3 cm (Cui et al., 2011; Haeussinger et al., 2014, 2011). In the brain, this light is absorbed to different degrees by oxygenated and deoxygenated blood, which results in changes in the amount of reflected light that can be measured on the head with receiver optodes. Most importantly for our case, the method can be applied in mobile settings (Ehlis et al., 2014) and has been shown to be reliable (Plichta et al., 2006; Schecklmann et al., 2008) and valid (Huppert et al., 2006; Plichta et al., 2007) when compared to other imaging methods. Due to its relative robustness, fNIRS might be suitable to measure cortical activation in the ecologically valid TSST environment.

In the study at hand, we attempted to implement fNIRS measurements in the TSST by only changing subtle aspects of the TSST protocol to preserve its high ecological validity. We implemented two non-stressful control conditions where subjects were asked to (1) read numbers and (2) do calculations without any social or time pressure, in order to isolate the specific effects of the stress component on, e.g., the fNIRS data. Also, we changed the arithmetic task of the TSST into a block design to measure the hemodynamic response. All other aspects of the TSST remained unchanged. Stress induction was validated by subjective ratings on visual analog scales (VAS) as well as with salivary cortisol and heart rate measurements.

From the above outlined prior neuroimaging studies (Dedovic et al., 2009c; Tillfors et al., 2001; Wang et al., 2005; Yanagisawa et al., 2011), we hypothesized an increase of cortical activity in parts of the cognitive control network (CCN) and dorsal attention network (DAN) during the TSST as compared to the non-stressful control conditions. The CCN, which includes areas of the dorsolateral prefrontal cortex (dlPFC), inferior frontal gyrus (pars opercularis) (IFG) and inferior anterior parietal lobule, is thought to be a mediator between the DAN and the default mode network (Spreng et al., 2010). During stress-induction, the subjects are forced to adapt to the higher demands of the situation by using attention regulation and emotion regulation, which should be neurally accompanied by higher activation of the CCN and DAN (Kogler et al., 2015; Kohn et al., 2014). As subjects who are more stressed by the TSST – due to higher discrepancies between the resources and demands of the task – would need to activate regions of cognitive control more strongly to fulfill the task, we expected a positive relationship between activation in areas of the CCN during stress and other physiological and subjective stress indices.

Materials and methods

Participants

32 healthy and unmedicated (with the exception of contraceptive medication) participants were recruited at the University of Tübingen. This study was approved by the ethics committee at the University Hospital and University of Tübingen. All procedures were in line with the Declaration of Helsinki in its latest version and all participants gave their written informed consent. Exclusion criteria of the study comprised: A history of or an acute mental disorder as assessed by a structured clinical interview for DSM-IV (SCID), a history of or an acute neurological disorder, diabetes, kidney failure, arterial hypertension, Cushing syndrome, cortisone medication, and smoking of more than 3 cigarettes per week. The mean age of the sample was 21.44 years (SD = 2.93), 26 subjects were female of which 18 took contraceptive medication. 8 females did not take contraceptive medication, two of which were at the end of their menstrual cycle (>28 days since beginning) and one at the beginning (<7 days since beginning). Most subjects (56%) performed sports activities 1 to 2 times per week. However, subjects were told not to perform any sort of physical training at the day of the measurement, to sleep the night before as long as they usually do and not to drink alcohol the day before the measurement. Further, subjects were instructed not to drink and eat 30 min before the measurement started.

Procedures

At the day of their measurement, subjects completed the basis documentation (including demographic variables and sports habits) together with the experimenter in a separate room. Afterwards, they were led to the fNIRS laboratory where the preparation for the fNIRS measurement was done. fNIRS was assessed during all control conditions and all parts of the TSST. However, due to methodological considerations (total measurement time, possibility of controlling task performance, artificial neural activity through movement artefacts) only the TSST arithmetic task was formally analyzed with regards to the fNIRS data and compared to the control conditions (CTL1, CTL2) specifically designed for this part of the paradigm. The fNIRS laboratory was adapted for the purposes of the TSST: The fNIRS machine was positioned behind the subjects who were seated at a table. After the preparation, a 7-min resting-state measurement was performed, followed by the first salivary