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Cerebral Cortex, 2024, **34**, bhae159
https://doi.org/10.1093/cercor/bhae159
Advance access publication date 18 April 2024
Original Article

Consistently increased dorsolateral prefrontal cortex activity during the exposure to acute stressors

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Stress has a major impact on our mental health. Nonetheless, it is still not fully understood how the human brain responds to ongoing stressful events. Here, we aimed to determine the cortical dynamics during the exposure to ecologically valid, standardized stressors. To this end, we conducted 3 experiments in which healthy participants underwent the Trier Social Stress Test (experiments 1 and 2) and the Socially Evaluated Cold Pressor Test (experiment 3) or a respective control manipulation, while we measured their cortical activity using functional near-infrared spectroscopy. Increases in salivary cortisol and subjective stress levels confirmed the successful stress induction in all experiments. Results of experiment 1 showed significantly increased cortical activity, in particular in the dorsolateral prefrontal cortex, during the exposure to the Trier Social Stress Test. Experiment 2 replicated this finding and showed further that this stress-related increase in dorsolateral prefrontal cortex activity was transient and limited to the period of the Trier Social Stress Test. Experiment 3 demonstrated the increased dorsolateral prefrontal cortex activity during the Socially Evaluated Cold Pressor Test, suggesting that this increase is generalizable and not specific to the Trier Social Stress Test. Together, these data show consistently that dorsolateral prefrontal cortex activity is not reduced, as commonly assumed, but increased under stress, which may promote coping with the ongoing stressor.

Key words: stress; cortisol; dorsolateral prefrontal cortex; neural dynamics.

Introduction

Stressful events are ubiquitous in our everyday life. These stressors can have a major impact on how we think, feel, and act (Lupien et al. 2009; Sandi and Haller 2015). For instance, stress promotes memory formation for ongoing events and increases the reliance on established routines, while stress may impair memory retrieval or working memory (Sandi et al. 1997; de Quervain et al. 1998; Roozendaal 2002; Cahill et al. 2003; Schoofs et al. 2009; Shields et al. 2016; Wirz et al. 2018; Meier et al. 2022; Schwabe et al. 2022). These effects of stress are generally adaptive and enable the organism to cope with the ongoing stressor or prepare for similar situations in the future (Roozendaal 2000; de Kloet et al. 2005; Vogel et al. 2016). However, while being generally highly adaptive, these stress effects might also contribute to stress-related mental disorders in vulnerable individuals (McEwen 1998, 2002, 2000; de Quervain et al. 2017). Given the impact of stress on our health and well-being, decades of research aimed at elucidating the mechanisms involved in our response to stressful events. The physiological and endocrine stress responses are well established: the exposure to a stressor leads to a rapid activation of brainstem nuclei that initiate the release of multiple neurotransmitters in the brain. Moreover, stressful events trigger two major stress response systems, the autonomic nervous system (ANS) and the hypothalamus–pituitary–adrenal (HPA) axis (Ulrich-Lai and Herman 2009; Myers et al. 2017). Within seconds after stressor exposure, ANS activation leads to the release of adrenaline and noradrenaline from the adrenal medulla, which drive many of the well-known peripheral stress responses. The parallel activation of the HPA axis results in a delayed release of glucocorticoids (mainly cortisol in humans) from the adrenal cortex, which may exert rapid, nongenomic, and slow, genomic effects via binding to glucocorticoid and mineralocorticoid receptors (Joëls et al. 2008; Joëls and Baram 2009).

Although it is well known that stress mediators, such as noradrenaline and glucocorticoids, act directly or indirectly on brain areas critically implicated in affect and cognition (Joëls and Baram 2009), how the brain responds to acute stressors is not fully understood, in particular in humans. Neurophysiological studies in rodents suggested dynamic changes in prefrontal and limbic areas, including hippocampus and amygdala, dependent on the temporal profile of action of major stress mediators, in particular catecholamines and glucocorticoids (Bains et al. 2015; Karst and Joëls 2016; Joëls et al. 2018; Kim et al. 2019; Kim and Kim 2023). While these animal studies provided important insights into the neural mechanisms of the stress response, they lacked the temporal resolution to assess the neural dynamics that occur as the stressful event unfolds. Human studies employed primarily functional magnetic resonance imaging (fMRI) to elucidate how the brain responds to stressful events. One of the first neuroimaging studies on the influence of an ongoing stressor on human brain

Received: December 1, 2023. **Revised:** March 15, 2024. **Accepted:** March 17, 2024

activity indicated that acute psychosocial stress is associated with a deactivation of the anterior cingulate cortex (ACC), medial orbitofrontal cortex or limbic areas such as the hippocampus, (Pruessner et al. 2008). A recent meta-analysis of fMRI studies further revealed that stressor exposure may be accompanied by activation in the claustrum, insula, and inferior frontal cortex but reduced activation in the parahippocampal cortex (Berretz et al. 2021). Beyond changes in individual brain areas, fMRI studies demonstrated that stress may induce a reconfiguration of large-scale neural networks (Hermans et al. 2014; van Oort et al. 2017). Specifically, stress has been suggested to favor the salience network, including areas such as the amygdala, insula, or ACC, at the expense of a central executive network, including the dorsolateral prefrontal cortex (dlPFC) or the dorsal posterior parietal cortex (dPPC; Hermans et al. 2011; van Oort et al. 2017). Experimental stress induction in the MRI scanner, however, turned out to be challenging due to the immobilization and supine position of the participants. Specific stress protocols were developed to overcome these challenges. These stress protocols differed both from each other and from established stress protocols. For example, in some tasks, participants were passively viewing highly disturbing film scenes of violence (Henckens et al. 2009), whereas other tasks were designed to resemble psychosocial stress protocols such as the Trier Social Stress Test (TSST; Kirschbaum et al. 1993) and provided uncontrollable negative feedback while participants were performing cognitive tasks (Pruessner et al. 2008; Lederbogen et al. 2011; Streit et al. 2014). However, the developed protocols were typically associated with more subtle stress responses compared to established stress protocols, such as the TSST (Kirschbaum et al. 1993), a mock job interview that mimics relevant stressful events in everyday life and is considered to be a gold standard in human stress research. Thus, how the human brain responds to more naturalistic stressors remained largely elusive.

In the present series of experiments, we leveraged functional near-infrared spectroscopy (fNIRS) to examine how the human brain responds to ecologically valid stressors. Although fNIRS has a lower spatial resolution than fMRI, fNIRS has the great advantage that it allows the measurement of cortical activity during less artificial, real-life situations and it has been used during stressful encounters in recent studies already (Rosenbaum et al. 2018; Henze et al. 2023). In a first experiment, we measured cortical activity during the standard TSST (or a control manipulation). A second experiment aimed to test whether the results of the first experiment can be replicated, when participants are exposed to the TSST at a different time of the day, and to what extent observed neural changes linger after the offset of the stressful event. Finally, we tested in a third experiment whether the results of the first experiments generalize to a different stressor that contains more physical stress elements (Socially Evaluated Cold Pressor Test, SECPT; Schwabe, Haddad & Schächinger 2008). In all of these experiments, we focused on cortical areas of the salience, default mode, and central executive networks and tested whether stress-related neural changes were correlated with subjective and endocrine stress responses.

Materials and methods

Experiment 1

Experiment 1 served to test the cortical activation dynamics during a well-established psychosocial stressor that mimics moderately stressful events in everyday life.

Participants and design

Forty-six healthy volunteers (25 women) participated in this experiment [age range: 18 to 36 years, mean (M) age = 24.41, standard error of the mean (SEM) = 0.63]. Exclusion criteria were checked in a standardized interview before participation and comprised any current or chronic mental or physical disorders, medication intake, or drug abuse. Further, smokers and women taking hormonal contraceptives were excluded from participation. In addition, participants were asked to refrain from food intake, caffeine, and physical activity for 2 h before testing. All participants gave written informed consent before entering the study and received a monetary compensation. The study was approved by the local ethics committee and part of a larger project on stress and cognition (Kalbe et al. 2020). In a between-subjects design, participants were randomly assigned to the stress (13 women, 10 men) or control group (12 women, 11 men). All testing took place in the afternoon to control for the diurnal rhythm of the stress hormone cortisol.

Experimental procedure

After participants had given written informed consent and answered a German mood questionnaire (*Mehrdimensionaler Befindlichkeitsfragebogen, MDBF*; Steyer et al. 1994), fNIRS optodes were mounted and a first saliva sample using Salivette collection devices (Sarstedt, Germany) was collected. Next, we recorded an initial fNIRS baseline period of 5 min, during which participants were standing in a quiet room. Importantly, participants had no information about group assignment at this stage. Thereafter, participants underwent the TSST, a standardized stress protocol known to reliably elicit both subjective and physiological stress responses (Kirschbaum et al. 1993; Allen et al. 2014), or a nonstressful control manipulation. Briefly, the TSST consisted of a mock job interview during which participants were asked to give a 5-min free speech about why they are the ideal candidate for a job tailored to their interests, followed by a 5-min mental arithmetic task (counting backwards in steps of 17 from 2043 as fast and accurate as possible; upon a mistake, they had to stop and start again from 2043). Both, the free speech and the mental arithmetic task were performed in front of 2 nonreinforcing experimenters (1 male, 1 female), dressed in white lab coats and introduced as experts in behavioral analysis, while being audio- and videotaped. Furthermore, participants could see themselves on a large screen placed next to the panel of the 2 experimenters.

During the control condition, 2 experimenters interacted with the participants in a nonstressful manner. First, the participants had a 5-min conversation with the experimenters about a topic of their choice (e.g. their last holiday). Then, the experimenters and the participants played a simple 5-min counting game (counting forward but excluding numbers that can be divided by 7). Throughout the control manipulation, the experimenters interacted with the participant in a normal, friendly way and no video recordings were taken. To assess subjective stress responses, participants rated the stressfulness, difficulty, and unpleasantness of the previous experience on a scale from 0 ("not at all") to 100 ("very much") immediately after the TSST or control manipulation and a second saliva sample was collected. The fNIRS signal was recorded during the entire stress and control manipulation, respectively.

To quantify cortisol concentrations after the stress or control manipulation, we collected further saliva samples 30 and 45 min after task onset. Saliva samples were stored at −20 °C until the end of the study. At the end of data collection, we determined

the concentration of the free fraction of the stress hormone cortisol from the saliva samples using a luminescence assay (IBL, Germany).

Experiment 2

Experiment 2 served to replicate the findings of experiment 1 and to extend these by examining the cortical dynamics in the 30 min after a stressful event, when cortisol concentrations were expected to reach peak levels.

Participants and design

In experiment 2, we tested 56 healthy volunteers (29 women; age range: 18 to 39 years, M = 26.04, SEM = 0.66). Exclusion criteria were similar to those of the first experiment and were again checked in a standardized interview before participation. None of the participants of experiment 1 participated in experiment 2. All participants gave written informed consent before entering the study and received a monetary compensation. The study was approved by the local ethics committee. Again, participants were randomly assigned to the stress (14 women, 14 men) or control group (15 women, 13 men). To control for the diurnal rhythm of cortisol but further test whether the findings of experiment 1 were related to the time of testing, all testing took place in the morning.

Experimental procedure

Upon participants' arrival at the laboratory and after providing written informed consent, the fNIRS setup was prepared, a first saliva sample was collected, and participants answered the MDBF mood questionnaire. Afterwards, we recorded a 5-min fNIRS baseline measurement, during which participants were sitting in a quiet room. During the baseline period, participants were unaware of their group assignment. Subsequently, as in experiment 1, participants underwent the TSST or a nonstressful control manipulation (see Experimental Procedure section for experiment 1 for details). Thereafter, participants rated the stressfulness, difficulty, and unpleasantness of the previous experience and another saliva sample was collected. Again, we recorded the fNIRS signal during the TSST and the control procedure, respectively. Importantly, to additionally assess the temporal dynamics of cortical activity in the after stress offset, we also recorded the fNIRS signal for 30 min after the end of the TSST or control manipulation. During this post-stress phase, participants were not engaged in any task but were asked to rest and keep their eyes open. Furthermore, saliva samples for later cortisol analysis were collected every 10 min (i.e. 20, 30, and 40 min after task onset).

Experiment 3

Experiment 3 tested to what extent the findings of experiments 1 and 2 can be translated to a different stressor that combines psychosocial and physical elements.

Participants and design

Fifty-four healthy volunteers (28 women) participated in the third experiment (age range: 19 to 38 years, M = 25.70, SEM = 0.64). Exclusion criteria were identical to those of the first 2 experiments and checked in a standardized interview before participation. None of the participants of experiment 1 or 2 participated in experiment 3. All participants gave written informed consent before entering the study and received a monetary compensation. The study was approved by the local ethics committee. In a between-subjects design, participants were randomly assigned to the stress (13 women, 13 men) or control group (15 women, 13 men). All testing took place in the morning.

Experimental procedure

After participants' arrival at the laboratory and their written informed consent, the fNIRS setup was prepared and a first saliva sample was collected. Subsequently, we recorded a 5-min baseline fNIRS period, during which participants were sitting (same as during the task) in a quiet room. As in experiments 1 and 2, participants in experiment 3 did not have any information about which group they belonged to during the baseline recording.

Participants in the stress condition then underwent the SECPT (Schwabe, Haddad & Schächinger 2008), a standardized stress protocol known to elicit both subjective and physiological stress responses (Schwabe and Schächinger 2018). In brief, participants were requested to immerse their left hand, including the wrist, for 3 min into ice water (0 to 2 °C), while being videotaped and evaluated by a rather cold and nonreinforcing experimenter dressed in a white lab coat. In the control condition, participants were asked to immerse their left hand, including the wrist, for 3 min into warm water (35 to 37 °C), without being videotaped or evaluated.

Immediately thereafter, participants rated the stressfulness, unpleasantness, and painfulness of the task on a scale from 0 ("not at all") to 100 ("very much") and another saliva sample was collected. As in experiments 1 and 2, we recorded the fNIRS signal during the entire stress exposure. Like in experiment 2, we were additionally interested in the temporal dynamics after the utilized stress protocol. Thus, we again implemented a post-stress-phase after the task offset, in which participants were not engaged in any task and were asked to keep their eyes open, while the fNIRS signal was recorded. Taking the different durations of the TSST in experiment 2 and SECPT in experiment 3 into account, the post-stress-phase lasted 40 min in experiment 3, compared to 30 min in experiment 2. Thereby, time windows relative to the respective stress onset were comparable between experiment 2 and experiment 3. To quantify cortisol concentrations during the post-phase, we also collected saliva samples after 10, 20, 30, and 40 min after stressor onset.

Control variables

In all experiments, participants completed the German version of the Beck Depression Inventory (BDI; Beck et al. 1996), the Trier Inventory for the Assessment of Chronic Stress (TICS; Schulz and Schlotz 1999), and the State-Trait Anxiety Inventory (STAI; Spielberger 1983) to control for potential group differences in depressive mood, subjective chronic stress, and anxiety. In addition, participants completed a German mood questionnaire (MDBF; Steyer et al. 1994) that measures subjective feeling on 3 dimensions (elevated vs. depressed mood, wakefulness vs. sleepiness, and calmness vs. restlessness) at the beginning of all experiments.

Statistical analysis

To assess the effectiveness of the experimental stress manipulation, differences in subjective stress ratings between the stress and control group after the experimental manipulation were analyzed by means of *t*-tests for independent samples. Cortisol changes were analyzed using mixed-design ANOVAs with the within-subject factor time point of measurement (experiment 1: −5, 10, 30, and 45 min after task onset; experiment 2: −5, 10, 20, 30, and 40 min after task onset; experiment 3: −5, 5, 10, 20, 30, and 40 min after task onset) and the between-subjects factor group (stress vs. control). We further calculated the baseline-to-peak difference (e.g. the difference between baseline and peak cortisol), which reflects an established cortisol index for stress

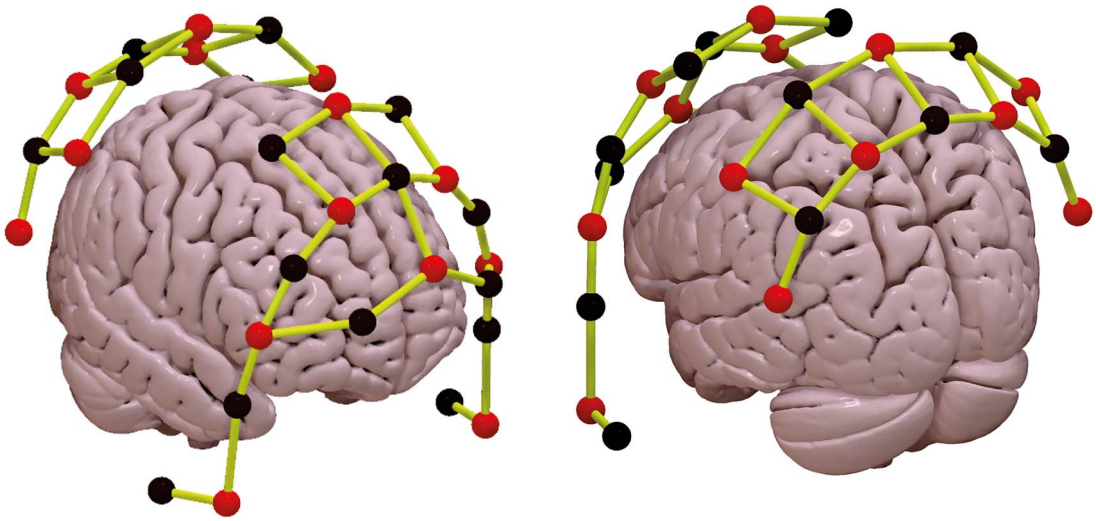

Fig. 1. fNIRS montage used in all 3 experiments. Our fNIRS montage covered the dlPFC, FEF, pre-SMA, FFA, IT, TPJ, and dPPC.

reactivity. Peak cortisol was defined as the (individual) maximum concentration of cortisol regardless of the time point of measurement. Due to experimenter error in experiment 1, the saliva samples of 17 participants were lost. However, the number of participants with available cortisol data was comparable between groups (stress: $n = 13$; control: $n = 16$). To examine whether the experimental groups differed in control variables, differences in depressive mood (BDI scores), state and trait anxiety STAI-S and STAI-T subscale score), and perceived chronic stress (TICS scores) as well as subjective mood immediately before testing (mood, calmness, and wakefulness scores) between stress and control group were tested using *t*-tests for independent samples. All reported *P* values are two-tailed and were Bonferroni-corrected (P_{corr}) if required.

fNIRS recording and analysis

Cortical activation was measured in all 3 experiments with a NIRScout System (NIRx Medical technologies LLC, L.A., USA) with 16 sources and 16 detectors. This system included Avalanche Photooptodes that enabled an optimal signal-to-noise ratio. In addition, we used short-distance detectors that measured extracerebral hemodynamic signals. These signals were regressed out from cerebral signals and thus controlled for task-related blood pressure changes as a potential source of group differences in fNIRS signals. A channel was defined as a source-detector pair resulting in 37 channels for the utilized system. As illustrated in Figure 1, our montage covered the dlPFC, frontal eye fields (FEFs), pre-supplementary motor area (pre-SMA), fusiform face area (FFA), inferior temporal gyrus (IT), temporoparietal junction (TPJ), and dPPC. Hemodynamic fluctuations were recorded with a sampling rate of 3.91 Hz. The wavelengths used for oxyhemoglobin (oxy-Hb) detection were 760 and 850 nm, respectively. Data were preprocessed in nirsLAB (v2016.01, NIRx Medical technologies LLC, Glen Head, NY). We controlled for detector saturation and interpolated consecutive channels if necessary. Channels with a variation criterion of ≥15%, indicating a poor signal-to-noise ratio, were excluded from further analyses. Raw optical density signals were converted to concentration changes of oxygenated hemoglobin using the modified Beer–Lambert law (Cope and Delpy 1988) with the differential path-length factors of $\lambda_{760} = 7.25$ and $\lambda_{850} = 6.38$. To account for serial correlations, we implemented a prewhitening approach with autoregression (Lühr and Goebel 2017).

The preprocessed fNIRS data were further processed using custom scripts implemented in Matlab 2018b (The Mathworks, Natick, MA) that generated a matrix of the oxy-Hb values across all channels. Then, all channels that belonged to one topographical cluster were integrated with each channel being weighed by the specificity of the channel for the respective brain region. Furthermore, fNIRS signal measurements were baseline corrected by subtracting the mean concentration of the 5-min baseline period that we recorded prior to the stress and control manipulation, respectively.

For all experiments, mean cortical activation was first tested during the task (i.e. stress vs. control manipulation) using a mixed-design ANOVA with the within-subject factor region (dlPFC, FEF, pre-SMA, FFA, IT, TPJ, and dPPC) and the between-subjects factor group (stress vs. control). To further examine the temporal dynamics during and in the 40 min after the stress (or control) manipulation, we included, in a second step, the within-subject factor time window (experiment 1: 1 to 5 and 6 to 10 min after task onset; experiment 2: 1 to 5, 6 to 10, 11 to 20, 21 to 30, and 31 to 40 min after task onset, and experiment 3: 1 to 3, 6 to 10, 11 to 20, 21 to 30, and 31 to 40 min after task onset). Significant interaction effects were followed by appropriate post hoc tests. All reported *P* values are 2-tailed and were Bonferroni-corrected if required. Bonferroni correction was also used to correct for tests in multiple cortical areas. In order to link cortical activity to the individual cortisol response (baseline-to-peak difference) and subjective stress ratings (averaged across the 3 subjective stress items), respectively, we performed respective Pearson's correlational analyses for those areas in which we obtained a significant difference between groups. Statistical analyses were calculated using SPSS 25 (IBM SPSS Statistics), and JASP version 0.14.0.0 software (www.jasp-stats.org).

Results

Experiment 1: cortical dynamics during a psychosocial stressor

Experiment 1 aimed to elucidate stress effects on cortical dynamics during a standardized psychosocial stressor. To this end, participants underwent the TSST that represents a gold standard

Table 1. Subjective responses to the stressor or control manipulation for all 3 experiments.

	Control		Stress	
	M	SEM	M	SEM
Experiment 1				
Stressfulness	3.09	0.39	8.35[a]	0.43
Unpleasantness	3.30	0.38	8.22[a]	0.54
Difficulty	3.52	0.46	7.09[a]	0.55
Experiment 2				
Stressfulness	3.00	0.37	7.93[a]	0.41
Unpleasantness	2.75	0.41	8.25[a]	0.40
Difficulty	3.71	0.44	7.79[a]	0.43
Experiment 3				
Stressfulness	1.64	0.21	5.23[a]	0.52
Unpleasantness	1.75	0.18	6.39[a]	0.43
Difficulty	1.82	0.23	4.85[a]	0.48

Subjective assessments were rated on a scale from 0 ("not at all") to 10 ("very much"). [a]$P < 0.001$.

in experimental stress research (Allen et al. 2014), or a nonstressful control manipulation, while we recorded cortical activation using fNIRS.

Successful stress manipulation

Subjective and physiological changes in response to the TSST confirmed the successful stress induction. Compared to participants in the control group, participants exposed to the TSST experienced the task as significantly more stressful, difficult and unpleasant than those in the control condition [all $t(44) > 4.978$, all $P_{corr} < 0.001$, all Cohen's d (d) > 1.468, all 95% Confidence Intervals (CI) = 0.807 to 3.462; Table 1]. Similarly, cortisol reactivity was significantly higher in the stress group than in the control group [task phase × group interaction: $F(3,81) = 7.914$, $P < 0.001$, $\eta_p^2 = 0.227$, 95% CI = 0.044 to 0.157; $t(1,27) = 3.396$, $P = 0.002$, $d = 1.268$, 95% CI = 0.453 to 2.064; Fig. 2A]. As shown in Figure 2A, salivary cortisol increased over time in the stress group [$F(3,36) = 10.215$, $P < 0.001$, $\eta_p^2 = 0.460$, 95% CI = 0.113 to 0.338] but not in the control group [$F(3,45) = 2.634$, $P = 0.061$, $\eta_p^2 = 0.149$, 95% CI = 0.026 to 0.097]. Notably, the stress group had higher cortisol concentrations than the control group at all time points of measurement [all t (27) > 3.230, all $P_{corr} < 0.012$, all $d > 0.430$, all 95% CI = 0.398 to 2.421], including the baseline [t (27) = 3.230, $P_{corr} = 0.003$, $d = 0.430$, 95% CI = 0.398 to 1.996], but the most pronounced difference was obtained 30 min after stressor, when the peak of the stress-induced cortisol response was expected. Similarly, although it is to be noted that cortisol concentrations were already elevated in stressed compared to control participants before the experimental manipulation [$t(27) = 3.230$, $P_{corr} = 0.004$, $d = 1.206$, 95% CI = 0.398 to 1.996], cortisol reactivity was significantly higher in the stress group than in the control group [task phase × group interaction: $F(3,81) = 7.914$, $P < 0.001$, $\eta_p^2 = 0.227$, 95% CI = 0.044 to 0.157; $t(27) = 3.396$, $P = 0.002$, $d = 1.268$, 95% CI = 0.453 to 2.064; Fig. 2A]. For the stress group, we found highest cortisol concentrations after 30 min relative to stressor onset (peak time point: M = 3.154, SEM = 0.104), whereas the control group showed maximum cortisol levels at the second timepoint of measurement, i.e. directly after the control task was finished (peak time point: M = 2.125, SEM = 0.256; peak concentration: 3.468, SEM = 0.525). The time of the maximum cortisol levels differed significantly between groups [t (27) = 3.428, $P = 0.002$, $d = 1.280$, 95 CI = 0.463 to 2.077].

Increased cortical activity under psychosocial stress

Our fNIRS data showed that the stress exposure, compared to the control manipulation, was associated with an overall increase in cortical activation [$F(1,38) = 10.748$, $P = 0.002$, $\eta_p^2 = 0.220$, 95% CI = 0.118 to 0.350]. In addition, there was also a significant group × region interaction effect [$F(6,228) = 5.166$, $P < 0.001$, $\eta_p^2 = 0.120$, 95% CI = 0.011 to 0.042], suggesting region-specific stress effects on cortical activation. Post-hoc analyses revealed that stressed participants showed particularly increased cortical activity during the task in fronto-lateral regions compared to controls [dlPFC, FEF, and pre-SMA: all $t(44) > 3.475$, all $P_{corr} < 0.007$, all $d > 1.025$, all 95% CI = 0.404 to 2.099]. Moreover, the stress group showed significantly higher activity in the IT, TPJ, and dPPC during the task compared to the control condition [IT: $t(40) = 2.844$, $P_{corr} = 0.049$, $d = 0.879$, 95% CI = 0.239 to 1.509; TPJ: $t(44) = 2.832$, $P_{corr} = 0.049$, $d = 0.835$, 95% CI = 0.227 to 1.434]. We did not obtain group differences during the task in the FFA [$t(42) = 1.843$, $P_{corr} = 0.504$, $d = 0.556$, 95% CI = −0.050 to 1.156]. Thus, most of our regions of interest showed increased activity during the TSST compared to the control manipulation. Crucially, however, the effect size differed between regions (Fig. 3), with the strongest group differences being observed in the dlPFC [$t(44) = 4.928$, $P_{corr} < 0.001$, $d = 1.453$, 95% CI = 0.794 to 2.099].

In order to test whether stress effects on cortical activity during the task depended on the specific part of the psychosocial stressor, we additionally included the factor time window (1 to 5 vs. 6 to 10 min after task onset, during which participants completed the free speech and the mental arithmetic task of the TSST) as within-subject factor. This analysis yielded a significant region × group × task phase interaction [$F(6,228) = 5.155$, $P < 0.001$, $\eta_p^2 = 0.119$, 95% CI = 0.011 to 0.042]. Follow-up ANOVAs showed that activity changes within the dPPC were more related to mathematics-specific demands rather than reflecting general stress components. More specifically, participants showed significantly higher dPPC activation during the mental arithmetic task in the stress compared to the control group [$t(44) = 4.729$, $P_{corr} < 0.001$, $d = 1.395$, 95% CI = 0.741 to 2.035], while groups did not differ in dPPC activation during the free speech part [$t(44) = 1.874$, $P_{corr} = 0.136$, $d = 0.553$, 95% CI = −0.040 to 1.139; $F(1,44) = 12.200$, $P_{corr} = 0.007$, $\eta_p^2 = 0.217$, 95% CI = 0.117 to 0.347]. Beyond the dPPC, there were no significant task phase × group interaction in any of the other regions of interest [all $F(1,44) < 6.327$, all $P_{corr} > 0.112$, all $\eta_p^2 < 0.126$, all 95% CI = 0.064 to 0.216; mean dlPFC activity during free speech vs. mental arithmetic task for both groups is also displayed in Fig. 2D], suggesting that significant stress effects for other regions of interest (see above) were not dependent on the specific phase of the experimental task but rather reflect a general, phase-unspecific impact of acute psychological stress.

Exploratory correlational analyses

In the next step, we assessed whether the cortical regions in which we observed significant group differences during the task were correlated with subjective and physiological stress responses. Therefore, we correlated the brain activity during the task with (i) the cortisol reactivity (baseline-to-peak difference) and (ii) the mean subjective stress ratings after the task. Since we were interested in general stress effects that were not dependent on the specific task phase but rather reflect a general impact of acute psychological stress, we did not include the dPPC in these correlational analyses, as this region did not show stress effects during entire stressor task. After correction for multiple regions,

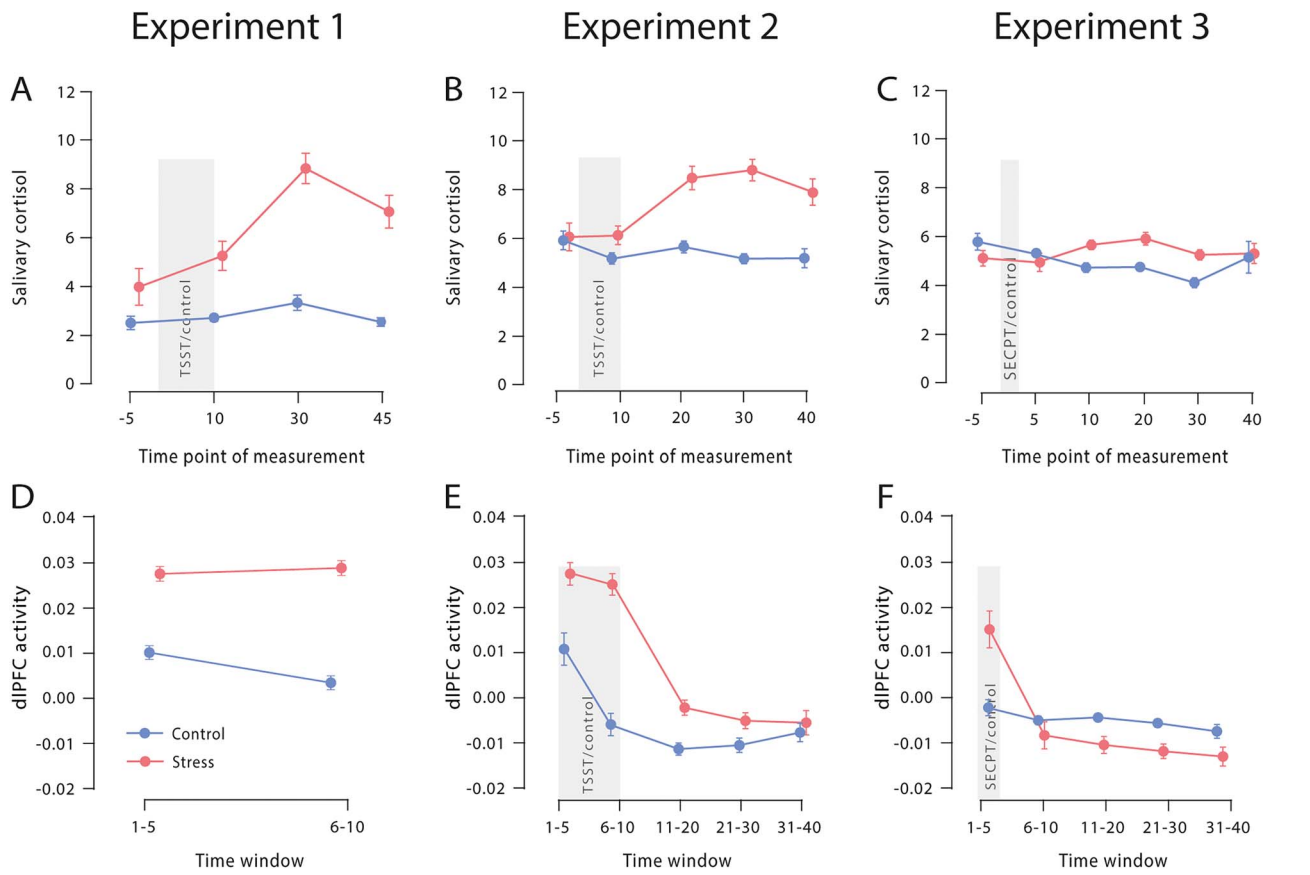

Fig. 2. Salivary cortisol responses and Δ dlPFC activity (relative to baseline) in experiments 1 to 3. A–C) For all experiments, salivary cortisol changes were significantly higher in response to the stressor (experiment 1 A and experiment 2 B, TSST; experiment 3: SECPT) compared to participants of the control group. D) Cortical activity in the dlPFC during both phases of the TSST (i.e. during the free speech phase and the mental arithmetic phase lasting from minute 1 to 5 and from minute 6 to 10, respectively) in experiment 1. Stressed participants showed significantly higher activity changes in the dlPFC compared to the control group. Group differences were not dependent on the specific phase of the experimental task. E) Cortical activity in the dlPFC during the TSST and post-stress-phase in experiment 2. Throughout the task, participants who underwent the stress manipulation had a significantly higher increase in dlPFC activity compared to those who received the control manipulation. F**)** dlPFC activity during and after the SECPT or control condition in experiment 3. Stressed participants responded to the experimental manipulation with significantly higher cortical activity comparted to control participants. Data in line graphs dependent on time and stress phase, respectively, for each group represent means ± SEM.

we found that increased dlPFC and TPJ activity were positively correlated with the cortisol increase [both $r(29) > 0.557$, both $P_{corr} < 0.012$, 95% CI = 0.272 to 0.781; Fig. 4]. Furthermore, cortical activity in all tested regions was positively associated with the subjective stress response [pre-SMA, TPJ and FEF: all $r(46) > 0.470$, all $P_{corr} < 0.012$, all 95% CI = 0.181 to 0.673; FFA: $r(44) > 0.468$, $P_{corr} < 0.006$, 95% CI = 0.098 to 0.611; TP: $r(42) > 0.463$, $P_{corr} < 0.006$, 95% CI = 0.193 to 0.677]. However, the strongest association between the subjective stress responses and cortical activity was found for the dlPFC activity [$r(46) = 0.537$, $P_{corr} < 0.001$, 95% CI = 0.292 to 0.716]. Overall, we obtained positive correlations with both the cortisol increase and the subjective stress assessments only for dlPFC and TPJ activity. Notably, these correlations were observed only across groups but not when groups were analyzed separately (see Supplementary Table S1).

Control variables

At the beginning of the experiment, the stress and control group did not differ in subjective mood [all $t(44) < 1.022$, all $P_{corr} > 0.939$, all $d < 0.301$, all 95% CI = −0.403 to 0.881]. Furthermore, groups did not differ with respect to depressive mood [$t(44) = 1.603$, $P = 0.116$, $d = 0.473$, 95% CI = −0.116 to 1.056], state and trait anxiety [both $t(44) < 1.358$, both $P_{corr} > 0.364$, both $d < 0.400$, both 95% CI = −0.293 to 0.982], and perceived chronic stress [$t(44) = 0.558$, $P = 0.579$, $d = 0.165$, 95% CI = −0.743 to 0.415]. Scores of the MDBF, BDI, STAI and TICS are shown in Table 2.

Experiment 2: cortical dynamics during and after a psychosocial stressor

In experiment 1, we obtained region-specific enhancements of cortical activity during the TSST compared to the control condition, in particular in the dlPFC. Moreover, increased dlPFC activity was, across groups, positively correlated with the cortisol baseline-to-peak difference and subjective stress responses, respectively. Experiment 2 was designed to replicate and extend these findings of experiment 1. Specifically, participants again underwent the TSST or control manipulation while the fNIRS signal was recorded. Critically, in order to additionally assess cortical dynamics in the 30 min after a psychosocial stressor, we implemented a post-stress phase in which the fNIRS signal was recorded while participants were not engaged in any task. Moreover, while the TSST was conducted in the afternoon in experiment 1, we tested in experiment 2 whether the observed effects hold, when participants undergo the stressor in the morning.

Successful stress manipulation

As in experiment 1, participants in the TSST condition experienced the task as significantly more stressful compared to

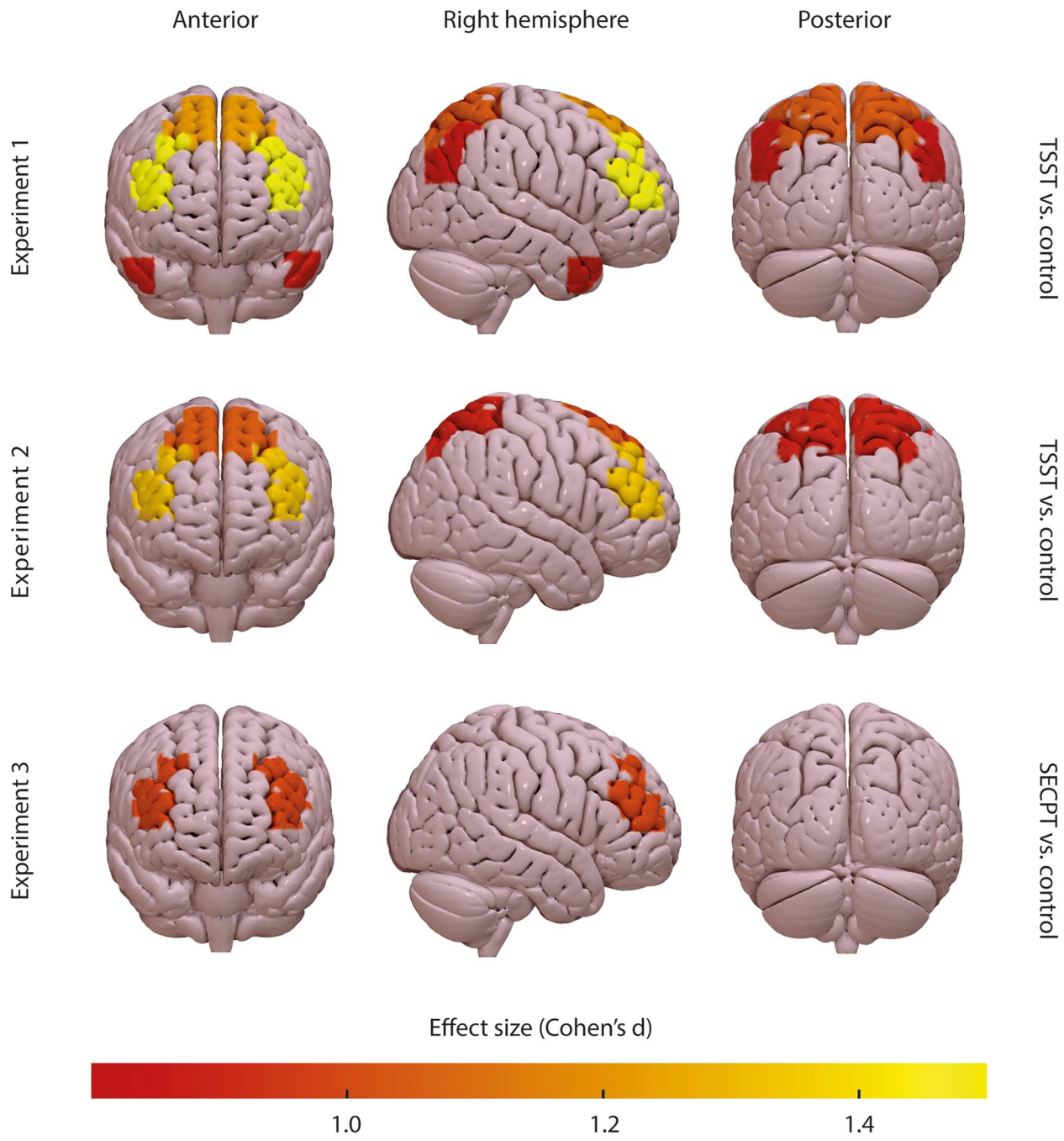

Fig. 3. Group differences in cortical activity during the stress or control condition for all 3 experiments. Across all experiments, we obtained significantly higher dlPFC activity during the stressful event compared to the control condition suggesting that this effect did not depend on the specific stress protocols. Instead, higher dlPFC activity rather reflects a general cortical correlate of acute stress.

those in the control condition [i.e. stressfulness, painfulness, and unpleasantness; all $t(54) > 6.661$, all $P_{corr} < 0.001$, all $d > 1.780$, all 95% CI = 1.153 to 3.269, Table 1]. Cortisol responses to the TSST in experiment 2 are displayed in Figure 2B. As expected, the cortisol response to the experimental manipulation was significantly higher in the stress than in the control group [baseline-to-peak-difference: $t(54) = 3.591$, $P < 0.001$, $d = 0.960$, 95% CI = 0.402 to 1.510; task phase × group interaction ($F(4,216) = 6.641$, $P < 0.001$, $\eta_p^2 = 0.110$, 95% CI = 0.015 to 0.570]. As shown in Figure 2B, salivary cortisol increased over time in the stress group [$F(4,108) = 7.418$, $P < 0.001$, $\eta_p^2 = 0.216$, 95% CI = 0.032 to 0.116] but not in the control group [$F(4,108) = 1.318$, $P = 0.268$, $\eta_p^2 = 0.047$, 95% CI = 0.006 to 0.023]. Notably, while groups had comparable cortisol concentrations at baseline [$t(54) = 0.176$, $P_{corr} = 1$,. $d = 0.047$, 95% CI = 0.477 to 0.571] and immediately and 5 min after the task was completed [both $t(54) = 2.548$, both $P_{corr} = 1$, both $d > 0.340$, both 95% CI = 0,190 to 1.217], the stress group had higher cortisol concentrations than the control group 30 and 40 min after the task [both all $t(54) > 2.905$, both $P_{corr} < 0.025$, both $d > 0.776$, both 98% CI = 0.229 to 1.529]. The stress group also showed on average a cortisol peak after 30 min (peak time point: M = 2.679, SEM = 0.200; peak concentration: 9.685, SEM = 0. 923), while the control group, same as in experiment 1, showed maximal cortisol values relative to baseline after 15 min after control task onset (M = 1.964, SEM = 0.221; peak concentration: 6.810, SEM = 0.676). The time of the maximum cortisol levels differed significantly

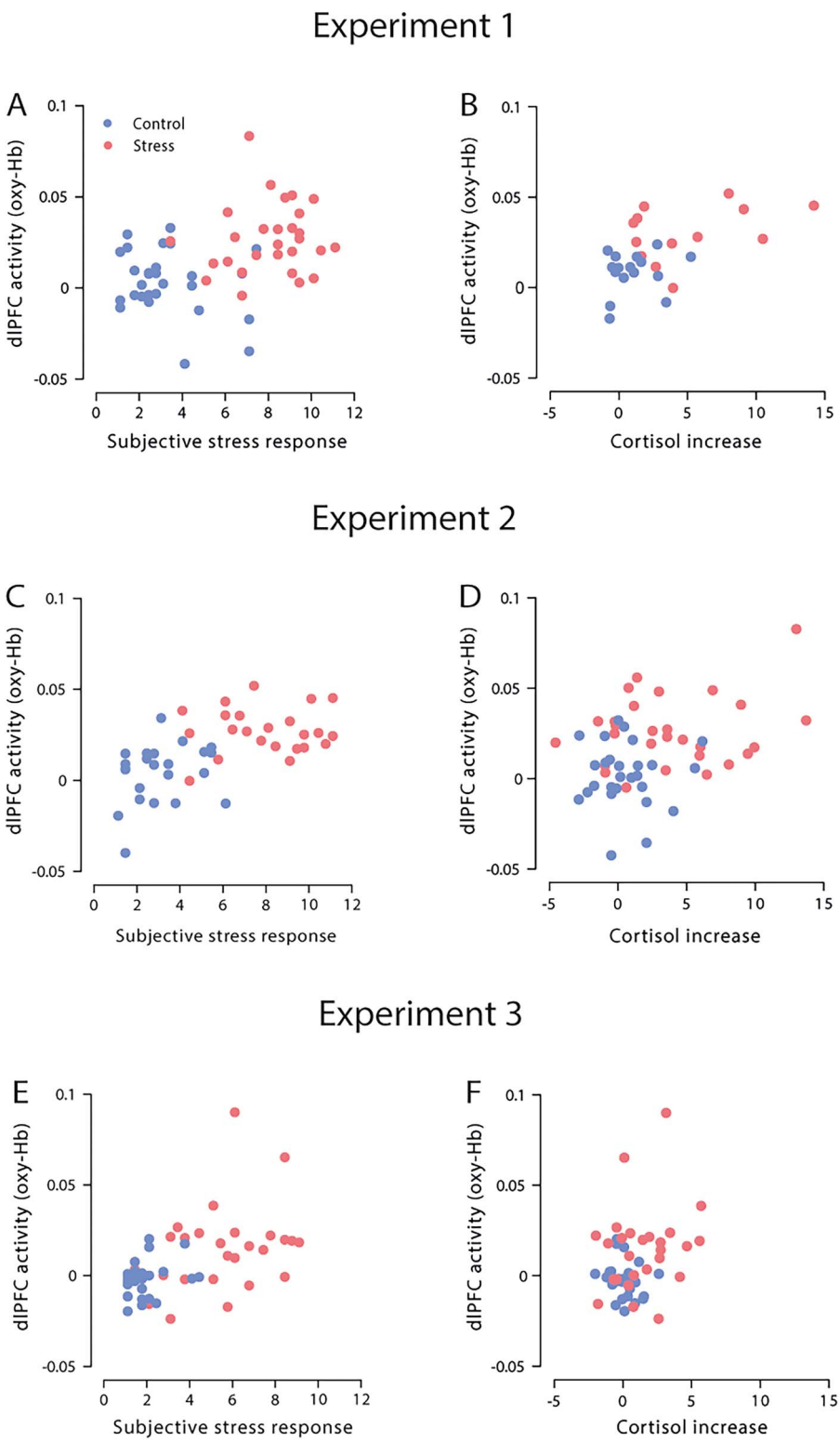

Fig. 4. Associations between dlPFC activity, cortisol and subjective stress responses. Correlations between dlPFC activity and subjective stress responses A) and cortisol increases B) in experiment 1. Correlations between dlPFC activity and subjective stress responses C) and cortisol increases D) in experiment 2. Correlations between dlPFC activity with subjective stress responses E) and cortisol increases F) in experiment 3.

between groups [t (54) = 2.398, P = 0.020, d = 0.641, 95% CI = 0.101 to 1.176].

Increased dlPFC activity under psychosocial stress

As in experiment 1, our fNIRS data showed an overall increase in cortical activity during the stress exposure compared to the control condition [$F(1,51) = 13.306$, $P < 0.001$, $\eta_p^2 = 0.207$, 95% CI = 0.112 to 0.334]. Importantly, there was also a significant region × group interaction [$F(6,306) = 4.949$, $P < 0.001$, $\eta_p^2 = 0.088$, 95% CI = 0.008 to 0.031]. In line with the results of experiment 1, follow-up tests revealed significantly higher activity in the DPPC, dlPFC, FEF, and pre-SMA during the TSST compared to

Table 2. Control variables for all 3 experiments.

	Control		Stress	
	M	**SEM**	**M**	**SEM**
Experiment 1				
MDBF scales				
Elevated vs. depressed mood	35.13	0.62	33.91	1.02
Sleepiness vs. wakefulness	29.96	1.24	28.13	1.39
Calmness vs. restlessness	33.48	0.89	32.52	1.32
BDI	5.17	0.70	7.26	1.09
STAI scales				
State anxiety	35.61	1.24	37.74	1.78
Trait anxiety	35.65	1.52	39.13	2.06
TICS	26.91	1.69	28.17	1.50
Experiment 2				
MDBF scales				
Elevated vs. depressed mood	33.43	1.05	33.75	0.85
Sleepiness vs. wakefulness	29.79	1.15	29.96	1.04
Calmness vs. restlessness	31.14	1.01	31.86	0.93
BDI	6.39	1.25	7.29	1.45
STAI scales				
State anxiety	34.64	1.83	38.61	1.71
Trait anxiety	34.61	1.81	38.21	1.78
TICS	25.39	1.70	28.07	2.80
Experiment 3				
MDBF scales				
Elevated vs. depressed mood	32.50	1.14	32.04	1.04
Sleepiness vs. wakefulness	26.72	1.25	27.50	1.16
Calmness vs. restlessness	31.14	0.96	31.23	1.07
BDI	4.21	1.04	4.80	0.86
STAI scales				
State anxiety	34.40	1.58	34.29	1.31
Trait anxiety	22.12	1.58	25.83	1.45
TICS	32.50	1.14	32.04	1.04

MDBF, Multidimensional Mood Questionnaire; BDI, Beck Depression Inventory; STAI, State–Trait Anxiety Inventory; TICS, Trier Inventory of Chronic Stress.

the control manipulation [all $t(54) > 3.820$, all $P_{corr} < 0.001$, all $d > 1.021$, all 95% CI = 0.466 to 1.857]. All other regions of interest did not differ between groups [FFA and TPJ: both $t(54) < 2.152$, both $P_{corr} > 0.113$, both $d < 0.648$, both 95% CI = 0.028 to 1.183; IT: $t(51) = 2.426$, $P_{corr} = 0.252$, $d = 0.592$, 95% CI = 0.038 to 1.141]. Thus, similar to experiment 1, we obtained region-specific stress effects on cortical activation during the experimental task. Importantly, to further elucidate the temporal dynamics during and after the stress or control procedure, we additionally included the within-subject factor time window (1 to 5, 6 to 10, 11 to 20, 21 to 30, and 31 to 40 min after task onset). This analysis yielded a significant region × group × time interaction [$F(18,918) = 3.181$, $P < 0.001$, $\eta_p^2 = 0.088$, 95% CI = 0.008 to 0.003]. Follow-up ANOVAs revealed stress effects depending on the time window for the dlPFC, FEF, and pre-SMA [all $F(4,216) > 3.428$, all $P_{corr} < 0.001$, all $\eta_p^2 > 0.098$, all 95% CI = 0.008 to 0.030].

For the dlPFC, stressed participants had higher cortical activation throughout the experimental task [1 to 5 and 6 to 10 min after stress onset: both $t(54) > 2.897$, both $P_{corr} < 0.025$, both $d > 0.774$, both 95% CI = 0.227 to 2.228]. Thus, same as in experiment 1, we obtained group differences for the dlPFC activity irrespective of the specific TSST phase. However, after stressor offset, groups did not differ in dlPFC activity anymore [all $t(54) > 2.079$, all $P_{corr} > 0.186$, all $d < 0.666$, all 95% CI = −0.398 to 0.860, Fig. 2E]. In contrast, cortical activity within the FEF and pre-SMA, respectively, depended on the specific phase of the TSST. More specifically, stressed participants showed higher FEF and pre-SMA activity during the mental arithmetic task (i.e. 6 to 10 min after stressor onset) compared to control participants [both $t(54) > 4.383$, both $P_{corr} < 0.001$, both $d > 1.171$, both 95% CI = 0.598 to 1.817], while groups did not differ in the FEF and pre-SMA activity for the free speech part [i.e. 6 to 10 min after stress onset; both $t(54) < 2.645$, both $P_{corr} > 0.055$, both $d < 0.707$, both 95% CI = 0.152 to 1.244], nor during any time window after the task [11 to 20, 21 to 30, and 31 to 50 min after stress onset: all $t(54) < 2.049$, all $P_{corr} > 0.225$, all $d < 0.548$, all 95% CI = −0.410 to 1.079]. Collectively, these results suggest that effects of the TSST on the FEF and pre-SMA activity, respectively, reflect a phase-specific (i.e. for the mental arithmetic component) impact on brain activation rather than a general stress effect. In contrast, phase-unspecific changes of the dlPFC activity point to a more general stress effect. However, there were no effects of stress on dlPFC activity once the stressor was over.

Exploratory correlational analyses

As in experiment 1, we further aimed to investigate potential correlations between cortical activity during the task with subjective stress and cortisol responses. Our analysis showed that dlPFC activity during the task was positively correlated with the cortisol increase [$r(56) = 0.325$, $P = 0.015$, 95% CI = 0.068 to 0.542]. In addition, we assessed the association between the dlPFC activity in the 30 min after the stressor and the cortisol baseline-to-peak difference. This analysis revealed that the dlPFC activity directly after stressor offset was still positively linked to the cortisol increase [11 to 20 min after stress onset: $r(56) = 0.283$, $P = 0.035$, 95% CI = 0.021 to 0.508], while there were no significant associations between cortisol responses and cortical activity during later time windows [21 to 30 and 31 to 40 min after stress onset: both $r(56) < |0.106|$, both $P > 0.439$, both 95% CI = |0.162|to |0.358|]. In addition to the cortisol increase, dlPFC activity during the task was positively correlated with subjective stress assessments [$r(56) = 0.400$, $P = 0.002$, 95% CI = 0.153 to 0.600] However, there were no associations between dlPFC activity after the task and subjective stress responses [11 to 20, 21 to 30, and 31 to 40 min after stress onset: all $r(56) < |0.173|$, all $P > 0.202$, all 95% CI = |0.094| to |0.417|]. Thus, the pattern of results was largely identical to the findings of experiment 1, showing significantly increased dlPFC activity during the TSST that was linked to subjective and endocrine stress responses. Again, correlations were observed exclusively across groups, while no significant correlations were obtained if these were analyzed in the experimental groups separately (see Supplementary Material).

Control variables

At the beginning of experiment 2, the stress and control group did not differ in subjective mood [all $t(54) < 0.520$, all $P > 0.605$, all $d < 0.139$, all 95% CI = −0.461 to 0.663]. Moreover, there were no group differences in depressive mood [$t(54) = 0.467$, $P = 0.642$, $d = 0.125$, 95% CI = −0.400 to 0.649], state or trait anxiety [both $t(54) < 1.582$, both $P > 0.120$, both $d < 0.423$, both 95% CI = −0.151 to 0.951] or subjective chronic stress [$t(54) = 0.997$, $P = 0.323$, $d = 0.266$, 95% CI = −0.791 to 0.261; Table 2].

Experiment 3: cortical dynamics during and after a combined physical–psychosocial stressor

Experiments 1 and 2 revealed consistent region-specific stress effects on cortical activation during psychosocial stressor (i.e. the

TSST), with a particularly pronounced stress-induced increase in dlPFC activity, which was linked, across groups, to the subsequent increase in salivary cortisol. Experiment 3 aimed to determine whether the previous findings were specific to the TSST or whether these findings hold across different types of stressors. Specifically, we aimed to assess the cortical dynamics during and after the SECPT, another standardized protocol for the efficient experimental stress induction, which combines a physical stress component (hand immersion into ice water) with socio-evaluative elements.

Successful stress manipulation

The exposure to the SECPT elicited marked subjective and physiological changes (Table 1). Participants of the stress group rated the task as being significantly more stressful, painful and unpleasant than controls [all $t(52) > 5.88$, all $P_{corr} < 0.001$, all $d > 1.601$, all 95% CI = −1.995 to 3.496]. Likewise, the increase of salivary cortisol in response to the experimental manipulation was significantly higher in the stress group than in the control group [baseline-to-peak difference: $t(52) = 3.362$, $P = 0.001$, $d = 0.916$, 95% CI = 0.350 to 1.474; task phase × group interaction: $F(5,250) = 8.607$, $P = 0.009$, $\eta_p^2 = 0.06$, 95% CI = 0.017 to 0.063]. As shown in Fig. 2C, there was a time-dependent decrease in salivary cortisol in the control group [$F(4,108) = 3.001$, $P = 0.014$, $\eta_p^2 = 0.107$, 95% CI = 0.044 to 0.157], presumably due to the diurnal rhythm of cortisol, which was absent in the stress group [$F(4,108) = 1.398$, $P = 0.230$, $\eta_p^2 = 0.053$, 95% CI = 0.006 to 0.0.24]. While groups had comparable cortisol concentrations at baseline [$t(52) = 0.327$, $P = 0.745$, $d = 0.089$, 95% CI = 0.089 to 0.273] as well as immediately after the test (approximately 5 min after task onset) and after 15 min [both $t(51) > 1.108$, both $P > 0.273$, both $d < 0.304$, both 95% CI = 0.061 to 0.304], the stress group tended to have higher cortisol levels than the control group 20 and 30 min after the task (both $t > 1.521$, both $P > 0.134$, both $d > 0.304$, both 95% CI = 0.278 to 0.414), which did however not survive the conservative Bonferroni correction. After 40 min, cortisol levels returned to a similar level between the groups [$t(52) = 0.373$, $P = 0.711$, $d = 0.102$, 95% CI = 0.102 to 0.273]. In experiment 3, the stress group showed cortisol peak level 25 min after task onset (peak time point: M = 2.433, SEM = 0.196; peak concentration: 8.324, SEM = 1.161, while the control group had maximal cortisol concentrations after 15 min (peak time point: M = 2.067, SEM = 0.225; peak concentration: 6.124, SEM = 0.679).

Increased dlPFC activity during a combined physical–psychosocial stressor

Our neural data revealed an overall increase in cortical activation during the SECPT compared to the control manipulation [$F(1,48) = 5.762$, $P = 0.020$, $\eta_p^2 = 0.107$, 95% CI = 0.054 to 0.187]. In line with the findings of experiments 1 and 2, these stress-induced increases in cortical activity differed between regions [group × region: $F(6,288) = 5.933$, $P < 0.001$, $\eta_p^2 = 0.110$, 95% CI = 0.010 to 0.039]. Follow-up analyses revealed that the stress group, compared to the control group, showed significantly higher activity of the dlPFC during the task [$t(52) = 3.570$, $P_{corr} < 0.001$, $d = 0.972$, 95% CI = 0.403 to 1.533, Fig. 3]. In other regions of interest, there were no significant differences between the stress and control groups [pre-SMA: $t(49) = 0.483$, $P_{corr} = 1$, $d = 0.132$, 95% CI = −0.403 to 0.665; dPPC: $t(51) = 1.568$, $P_{corr} = 0.861$, $d = 0.427$, 95% CI = −0.115 to 0.965; FEF, IT, FFA and TPJ: all $t(52) < 2.316$, $P_{corr} > 0.084$, $d < 0.735$, 95% CI = −0.435 to 1.301]. In order to test whether the stress-induced changes in cortical activity are specific to the exposure to the stressor or whether there are lingering stress effects after the stressor, we ran an additional analysis that included the within-subject factor time window (1 to 3, 6 to 10, 11 to 20, 21 to 30 and 31 to 40 min after task onset). This analysis yielded a significant region × group × time interaction [$F(24,1152) = 4.374$, $P < 0.001$, $\eta_p^2 = 0.084$, 95% CI = 0.002 to 0.007]. Follow-up analyses revealed time-dependent stress effects on activity of the dlPFC, IT, TPJ, and FFA [time × group interaction: all $F(4,208) > 3.681$, all $P_{corr} < 0.042$, all $\eta_p^2 > 0.067$, all 95% CI = 0.009 to 0.033; Fig. 3]. For the dlPFC, we observed significantly higher activity during the SECPT compared to the control manipulation [$t(52) = 3.570$, $P_{corr} < 0.001$, $d = 0.972$, 95% $CI = 0.403$ to 1.533], while we did not find any group differences in dlPFC activity after the task (all $t(52) < 2.212$, all $P_{corr} > 0.155$, all $d < 0.602$, all 95% $CI = -1.146$ to 0.053, Fig. 2F]. For the IT, TPJ, and FFA activity, there was no reliable stress effect during the task, nor after the task [IT: all $t(49) < 2.610$, all $P_{corr} > 0.084$, all $d < 0.735$, all 95% $CI = 0.161$ to 1.1301; TPJ: $t(52) < 2.316$, $P_{corr} = 0.175$, $d = 0.631$, 95% $CI = 0.081$ to 1.175; FFA: all $t(51) < 2.490$, all $P_{corr} > 0.112$, all d 0.685, all 95% $CI = -0.406$ to 1.237] after correction for multiple comparisons.

Exploratory correlational analyses

To further elucidate the potential relevance of the stress-induced increase in dlPFC activity for the subjective and cortisol response to stress, we assessed in the next step the association of increased dlPFC activity during task-related responses with subjective and cortisol responses, respectively. To this end, we correlated dlPFC activity during the experimental task with (i) the cortisol baseline-to-peak difference and (ii) the mean subjective stress rating. This analysis showed that dlPFC activity during the task were positively correlated with the cortisol increase [$r(54) = 0.283$, $P = 0.038$, 95% CI = 0.017 to 0.512]. In addition, we also tested the relationship between dlPFC activity after the task and the cortisol baseline-to-peak difference. Interestingly, the dlPFC activity shortly after stressor offset (i.e. within 6 to 10 and 11 to 20 min after stressor onset) correlated negatively with the cortisol increase [6 to 10 min after stress onset: $r(54) = -0.311$, $P = 0.022$, 95% CI = −0.534 to −0.047; 11 to 20 min after stress onset: ($r(54) = -0.366$, $P_{corr} = 0.024$, 95% CI = −0.577 to −0.109]. However, the correlation between increased dlPFC activity directly after stressor offset and cortisol increase was only at trend-level after correction for multiple testing (6 to 10 min after stress onset: $P_{corr} = 0.088$). dlPFC activity at later time windows was not correlated with cortisol increase anymore [21 to 30 and 31 to 40 min after stress onset: both $r(54) < 0.238$, both $P_{corr} = 0.332$, both 95% CI = |0.476| to |0.100|]. For subjective stress responses, we obtained a positive correlation with dlPFC activity during the task [$r(54) = 0.521$, $P < 0.001$, 95% CI = 0.294 to 0.692]. There were no correlations between subjective stress responses and dlPFC activity at later time windows [all $r(54) = |0.136|$, all $P_{corr} = 1$, all 95% CI = |0.137| to |0.389|]. Same as in experiments 1 and 2, these correlations were observed exclusively across both groups but not if correlations were analyzed in the 2 groups separately (see Supplementary Material).

Control variables

As shown in Table 1, the stress and control groups did not differ in subjective mood [all $t(52) < 0.298$, all $P_{corr} = 1$, all $d < 0.125$, all 95% CI = −0.453 to 0.615] at the beginning of experiment 3. Additionally, there were no group differences in depressive mood [$t(47) = 0.041$, $P = 0.967$, $d = 0.012$, 95% CI = −0.548 to 0.572], state or trait anxiety [both $t(47) < 0.594$, both $P_{corr} = 1$, both $d < 0.170$, both 95% CI = −0.392 to 0.730], or subjective chronic stress [$t(47) = 1.730$, $P = 0.090$, $d = 0.494$, 95% CI = −0.077 to 1.061].

Discussion

Insights into how the human brain responds to acute stress may be crucial for a better understanding of stress-related psychopathologies. Here, we combined fNIRS with well-established psychosocial stress protocols to investigate the neural dynamics during the acute exposure to ecologically valid stressors. Across a series of 3 experiments, we obtained a consistent increase of cortical activity during the exposure to these stressors, which was most pronounced in the dlPFC.

In all 3 experiments, participants of the stress group showed significant increases, compared top controls, in both subjective stress levels and salivary cortisol concentrations in response to the stressor exposure. At the neural level, we observed a stress-related increase in cortical activity that appeared to be unaffected by the time of testing (morning vs. afternoon) and was remarkably consistent across stress protocols. Although the neural response to the TSST appeared to be more pronounced than the neural response to the SECPT, in line with the more pronounced cortisol response to the TSST, we obtained both during the TSST and during the SECPT a significant activation of the dlPFC. This dlPFC activation was found during the different stages of the TSST (free speech and mental arithmetic) but returned quickly to baseline as soon as the TSST or SECPT were over. This transient nature of the dlPFC activation suggests that this activation was associated with the specific demands of the stressor. The TSST requires working memory and planning activities, which both rely on the dlPFC (Curtis and D'Esposito 2003; Koechlin et al. 2003; Blumenfeld and Ranganath 2006; Badre 2008; Kouneiher et al. 2009; Barbey et al. 2013). Although the SECPT is less cognitive in nature, it requires, same as the TSST, inhibitory processes as well as effort expenditure that both involve the dlPFC (Duncan and Owen 2000; Miller and Cohen 2001; Blasi et al. 2006; Dosenbach et al. 2007; Badre 2008; Menon and D'Esposito 2022). In addition, social evaluative processes are a common source of stress in both the TSST and the SECPT. As the dlPFC is known to be involved in the processing of social evaluation and in the selection and implementation of coping behavior (Crone et al. 2020; Minervini et al. 2023), the dlPFC activation during both stressors might also be owing to social evaluative threat processing. It is, however, important to note that the consistent activation of the dlPFC during the TSST and SECPT may also be owing to stressor-specific processes that all involved the dlPFC. For instance, the cognitive components of the TSST might involve more focused attention and working memory processes, whereas the SECPT might involve more inhibitory control or novelty processing. All of these processes may have resulted in increased dlPFC activation. Together, the observed dlPFC activation may reflect the adaptation to the stressor. Notably, while we obtained stress-related increases in activity also in other cortical regions than the dlPFC during the TSST, the increases were specific to the dlPFC during the SECPT, suggesting that in particular, dlPFC activation is consistent across different stress protocols.

The increased activation of the dlPFC under stress might appear to be in conflict with the view that catecholamines interfere with PFC function (Arnsten 2009) and bias large-scale networks at the expense of networks including the dlPFC (Hermans et al. 2011; Hermans et al. 2014). Some of the evidence in support of these ideas, however, comes from studies that used pharmacological interventions that are clearly distinct from the current behavioral manipulation or from neuroimaging studies that required the adaptation of the standard protocols for experimental stress induction due to methodological restrictions such as isolation in the scanner room (Pruessner et al. 2008). In particular, it was more difficult to implement socio-evaluative elements in the neuroimaging environment, which are essential for successful stress induction (Dickerson and Kemeny 2004; Schwabe, Haddad & Schächinger 2008). The use of fNIRS in this series of experiments allowed us to implement social evaluation according to standardized and well-established stress procedures without restrictions. Accordingly, participants had to face and cope with a greater social evaluative threat compared to fMRI studies. This distinction between the present study and previous fMRI studies may have contributed to the different findings regarding the activation of the dlPFC under stress, which is known to play a relevant role in social information processing (Crone et al. 2020; Minervini et al. 2023). Interestingly, our finding of increased dlPFC activation under stress is well in line with two other recent fNIRS studies (Rosenbaum et al. 2018; Henze et al. 2023). Our findings, however, extend these studies in several important ways. First and foremost, these previous studies were lacking a proper control condition and analyzed brain activity only during the mental arithmetic phase of the TSST, which made it difficult to dissociate effects of mental arithmetic per se from actual stress effects. Here, we analyzed both the free speech and mental arithmetic parts of the TSST, compared to a nonstressful control condition and show that the dlPFC activation is not only observed across all parts of the TSST but even in another standardized stress protocol (i.e. the SECPT). Moreover, we analyzed the cortical dynamics also up to 40 min after the stressor and show that the increase in dlPFC activity is transient and limited to the period of the ongoing stressor.

The fact that we observed increased dlPFC activity only during the stressful event itself, but not thereafter, suggests that this was mainly driven by rapidly acting catecholamines. Given the potential relevance of catecholamines for the cortical changes during the stressor, the lack of measures of catecholaminergic or autonomic activity is a limitation of the present study and future studies are required to include such measures. At later time points, when cortisol concentrations were significantly elevated, we did not see any significant changes in brain activity. It is, however, important to note that we observed brain activity at rest in the 30 to 40 min after the stressor. Numerous previous studies showed that stress-induced increases in cortisol may affect task-related prefrontal activity and functioning (Jameison and Dinan 2001; Arnsten 2009; Qin et al. 2009; Yuen et al. 2009; Butts et al. 2011; Godoy et al. 2018; Quaedflieg et al. 2020; Schulreich and Schwabe 2021). Thus, it may well be that post-stress reductions in dlPFC activity become only apparent when the dlPFC is recruited during cognitive tasks.

Moreover, it is important to note that while fNIRS allows the measurement of cortical activity in ecologically more valid situations, fNIRS is limited to selected lateral cortical areas. Medial cortical and subcortical activity cannot be measured with fNIRS and there is a plethora of studies demonstrating that stress and stress-induced cortisol influence the activity of, for instance, medial temporal brain areas (Lupien and Lepage 2001; de Quervain et al. 2003; Qin et al. 2012; Vogel et al. 2018). Although we did not observe altered cortical activity at the time when cortisol was significantly elevated, dlPFC activation during the stressor seemed to be correlated with the subsequent elevation in cortisol. This correlation between dlPFC activity and (delayed) cortisol responses could be due to, for instance, dlPFC processing (e.g. stressor appraisal) driving the HPA axis activation or to a common stress-related factor (e.g. emotional processing, effort mobilization) underlying both dlPFC activation and cortisol secretion. These correlations are, however, explorative in nature

and do not allow any conclusions about a potential causal relationship between the increases dlPFC activation during the stressor and the subsequent cortisol increase. Even more importantly, across all 3 experiments, the correlation between dlPFC activation and cortisol increase was only observed across groups and not within the stress group only. This pattern and the distribution of the data (see Fig. 4) strongly suggests that the observed correlations reflect primarily the group differences in the respective variables (i.e. dlPFC activity, subjective stress, and salivary cortisol) and thus do not allow any conclusions regarding associations between stress-induced dlPFC activation and subsequent cortisol increase. Moreover, while we measured brain activity during ecologically more valid stressors than previous imaging studies, it is still important to translate our results to real-world settings, for example, by using mobile electroencephalographic (EEG) systems.

While we observed a functional recruitment of the dlPFC under stress in both stress paradigms and irrespective of the task-specific demands, changes within the dPPC, FEF, and pre-SMA were restricted to the second half of the TSST, i.e. the mental arithmetic task. Although this pattern might be taken as evidence that these regions are, other than the dlPFC, not directly involved in stressor-processing, this conclusion might be premature. For instance, the recruitment of these brain areas could be related to the stress level. Because the stress intensity may have increased during the TSST and appeared to be somewhat higher in the TSST compared to the SECPT, we cannot exclude that the activation of dPPC, FEF, and pre-SMA in the second task part of the TSST is driven by the stress level or part of a general adaptive stress response to a psychosocial stressor. Characterizing the role of the dPPC, FEF, and pre-SMA in the dynamic stress response remains a challenge for future research.

Participants were informed about the stressor (or control manipulation) only after the baseline measurements. Accordingly, groups should not differ at baseline. Nonetheless, in experiment 1, we observed a baseline difference in salivary cortisol between the stress and control groups, with higher baseline cortisol in the stress group. The reasons for this baseline difference remain obscure. Notably, we still observed a significant increase in cortisol after the experimental manipulation in the stress group, which was not observed in controls. Moreover, all fNIRS data were baseline-corrected and we could replicate the results of experiment 1 in experiment 2, in which groups did not differ at baseline. Thus, we consider it very unlikely that the cortisol baseline difference in experiment 1 had a major influence on our main findings.

In sum, across 3 experiments and 2 well-established stress protocols, we observed here an increase of dlPFC activity under acute stress. This increase in dlPFC activity was transient and most likely linked to the specific demands that were associated with the stressful events, presumably aiding the coping with the stressor. Future research is required to determine to what extent this transient stress-induced activation of the dlPFC is altered in stress-related psychopathologies.

Acknowledgments

We gratefully acknowledge the assistance of Annika Lutz, Stina Bange, Vincent Marinelli, Hyunbin Stella Jeong, and Keyvan Khatiri during data collection.

Supplementary material

Supplementary material is available at *Cerebral Cortex* online.

Author contributions

Jacqueline Katharina Meier (Formal analysis, Investigation, Methodology, Visualization, Writing—original draft, Writing—review & editing) and Lars Schwabe (Conceptualization, Funding acquisition, Resources, Supervision, Writing—original draft, Writing—review & editing).

Funding

This work was supported by funding from Universität Hamburg.

Conflict of interest statement: None declared.

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