Acute Psychological Stress Reduces Working Memory-Related Activity in the Dorsolateral Prefrontal Cortex

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Background: Acute psychological stress impairs higher-order cognitive function such as working memory (WM). Similar impairments are seen in various psychiatric disorders that are associated with higher susceptibility to stress and with prefrontal cortical dysfunctions, suggesting that acute stress may play a potential role in such dysfunctions. However, it remains unknown whether acute stress has immediate effects on WM-related prefrontal activity.

Methods: Using functional magnetic resonance imaging (fMRI), we investigated neural activity of 27 healthy female participants during a blocked WM task (numerical N-back) while moderate psychological stress was induced by viewing strongly aversive (vs. neutral) movie material together with a self-referencing instruction. To assess stress manipulation, autonomic and endocrine, as well as subjective, measurements were acquired throughout the experiment.

Results: Successfully induced acute stress resulted in significantly reduced WM-related activity in the dorsolateral prefrontal cortex (DLPFC), and was accompanied by less deactivation in brain regions that are jointly referred to as the default mode network.

Conclusions: This study demonstrates that experimentally induced acute stress in healthy volunteers results in a reduction of WM-related DLPFC activity and reallocation of neural resources away from executive function networks. These effects may be explained by supraoptimal levels of catecholamines potentially in conjunction with elevated levels of cortisol. A similar mechanism involving acute stress as a mediating factor may play an important role in higher-order cognitive deficits and hypofrontality observed in various psychiatric disorders.

Key Words: Dorsolateral prefrontal cortex, fMRI, psychological stress, working memory

Exposure to acute stress impairs higher-order cognitive function as exemplified by impairment of working memory (WM) (1–4). Similar impairments are observed in various psychiatric disorders that are associated with higher susceptibility to stress and prefrontal dysfunction (5–9). This implicates acute stress as a potential mediating factor in symptoms of higher-order cognitive dysfunction. However, little is known about the immediate effects of acute stress on WM-related prefrontal function in humans.

WM refers to a system maintaining relevant information in a temporary buffer that is constantly updated to guide behavior and is well-known to be supported by a frontoparietal network (10). Exposure to acute stress leads to rapid activation of the sympathetic nervous system (SNS), accompanied by the release of norepinephrine (NE) from a widely distributed brain network of synapses including abundant projections to the prefrontal cortex (PFC; 1–4,7). Acute stress also results in rapid activation of the prefrontal dopamine (DA) system (11). Hence, detrimental effects of acute stress on WM are thought to result from supraoptimal levels of catecholamines in the PFC. Empirical evidence from multiple pharmacological studies in nonhuman primates has revealed that catecholamines exert an inverted U-shaped influence on prefrontal cognitive function in which sub- or supraoptimal levels weaken WM processing (7,8), and high doses of catecholamines are indeed associated with decreased neuronal firing in the dorsolateral PFC (DLPFC) (2,12,13). On a slightly longer time scale, acute stress results in activation of the hypothalamic-pituitary-adrenal (HPA) axis, which regulates the release of glucocorticoids (1,14,15). Animal studies have demonstrated detrimental effects of glucocorticoids on WM, but only in the presence of concomitant arousal-related noradrenergic activation (16), which in turn appears to be dependent on the amygdala (17). In humans, similar detrimental effects of glucocorticoids on WM have been shown to be limited to a time window during which the SNS and the HPA axis are synergistically activated and do not persist after SNS recovery while glucocorticoid levels are still elevated (3,4). In sum, the HPA axis appears to exacerbate detrimental effects of supraoptimal levels of catecholamines on PFC functioning. From this neurobiological account, we therefore predicted that acute stress would lead to attenuated WM-related DLPFC activity.

In addition, activation in WM-related frontoparietal executive function networks is consistently accompanied by deactivation in a set of brain regions referred to as the default mode network (DMN) (18,19). Performing a WM task while coping with an acutely stressful situation can be considered a form of continuous dual processing: acute stress may result in more difficulty inhibiting stress-related task-irrelevant internal thoughts (4,20–22) and therefore lead to alterations in, and reallocation of, attentional resources. Because the DMN and the frontoparietal executive network are known to exhibit reciprocal activity (23,24), we conjectured that acute stress induction could lead to redistribution of neural resources away from executive functioning networks and toward the DMN.

To address these issues, we used blocked-design functional magnetic resonance imaging (fMRI) to investigate how experimentally induced stress modulates neural activity during a numerical N-back task. Moderate psychological stress was induced using strongly aversive (vs. neutral) movie material with a

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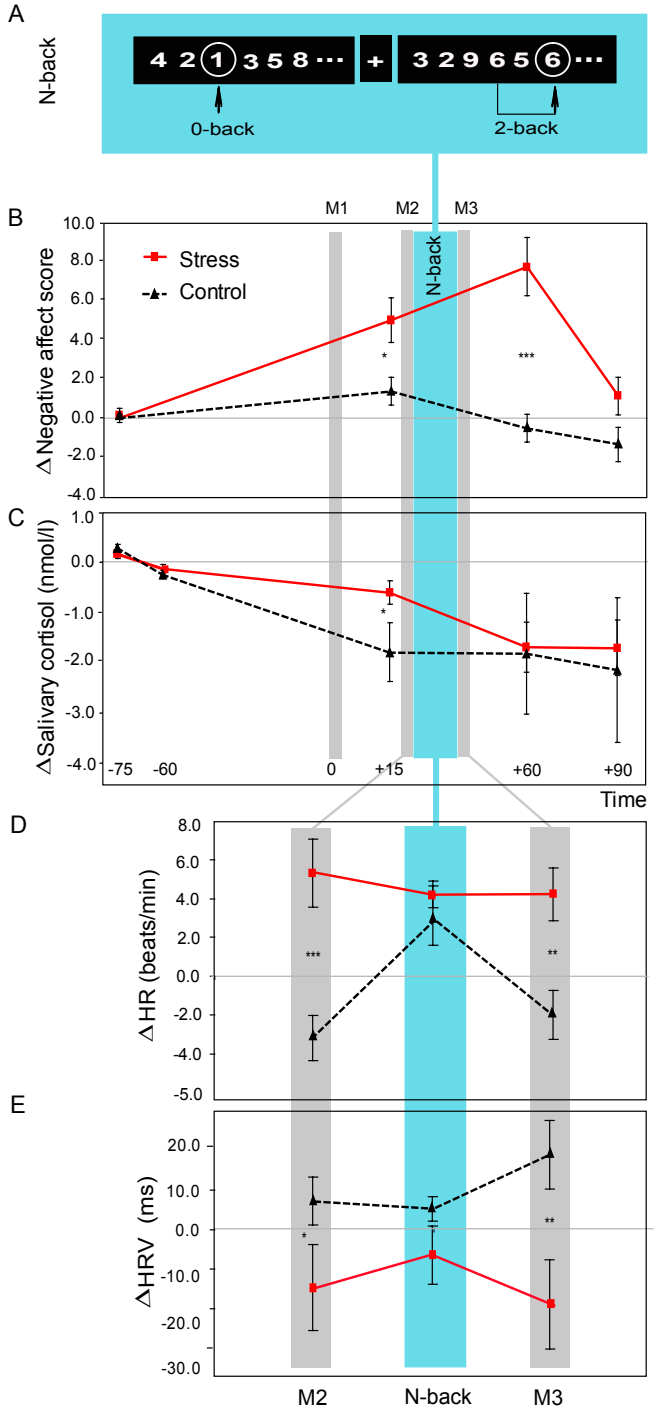
Received November 5, 2008; revised February 27, 2009; accepted March 2, 2009.

0006-3223/09/$36.00
doi:10.1016/j.biopsych.2009.03.006

self-referencing instruction. Participants were trained extensively on the WM task before scanning to minimize interindividual variability and reduce practice effects. To assess the effects of stress induction on the SNS and HPA axis activation, heart rate (HR) was continuously recorded throughout scanning, and salivary cortisol samples were collected at baseline and at various time delays. We predicted that acute stress would reduce WM-related DLPFC activity, potentially in combination with less deactivation of the DMN.



Methods and Materials

Participants

Twenty-nine young, healthy, right-handed female university students (aged 18–25 years) with normal or corrected-to-normal vision participated in this study. Participants reported no history of neurological, psychiatric, or endocrine disease; no current use of any psychoactive drugs or corticosteroids; and no habit of watching violent movies or playing violent video games. None of them had experienced severe physical or emotional trauma. Avoiding confounds related to gender differences and menstrual cycle–dependent variance in stress responsiveness (25,26), only women taking standard single-phase oral contraceptives were included. They were tested in the final 2 weeks of their cycle to ensure stable hormone levels. Data from two participants were excluded because of technical failure and failure to complete the experiment. Written informed consent was obtained before the experiment in accordance with local ethical board requirements.

Participants were tested in a mixed-factorial design with stress induction as between-subject factor and WM-load (0- vs. 2-back) as within-subject factor. They were randomly assigned to either the stress induction (n = 14; aged 21 ± 2.1 years) or the control group (n = 13; aged 20 ± 1.8 years).

General Procedure

The experiment was carried out between 2 and 7 PM to ensure relatively stable and low levels of endogenous cortisol. After arrival, 1.5 hours before scanning, participants trained on the WM task extensively and completed various questionnaires. Baseline measurements of cortisol and subjective affect (positive and negative affect scales [PANAS]; 27) were obtained. After this, participants were told to which of the two experimental groups they were randomly assigned. The actual fMRI experiment consisted of four short movie clips to ensure that tasks of interest were fully embedded in a continuously stressful (or neutral control) context; it ended with a structural scan. Between the second and third movie clips, participants performed the numeric N-back task (Figure 1).

Stress Induction

In the stress-induction group, acute psychological stress was induced by showing short movie clips in the MRI scanner containing scenes with extremely aversive content (extreme male to male and female violence), selected from a commercial movie (*Irreversible,* 2002, by Gaspar Noé). In the control group,

Figure 1. Experimental design and subjective, endocrine, and autonomic measurements of stress. Experimental design: the experiment started with the first movie clip (M1: 2.20 min) at time point 0 in the magnetic resonance imaging (MRI) scanner and was followed by a passive viewing task involving facial expressions (12 min), a second movie clip (M2: 1.30 min), the N-back task (13.60 min), a third movie clip (M3: 1.30 min), and other tasks (30 min); subjective (positive and negative affective scale [PANAS]), endocrine (cortisol), and autonomic (heart rate [HR], HR variability [HRV]) measurements of stress were acquired throughout the experiment. **(A)** The digit sequence in the rectangular box is an example of the 0- and 2-back conditions in the N-back task (see Methods and Materials for more details). **(B and C)** Averaged and baseline-corrected negative affect ratings and free salivary cortisol at different time points for the two groups: four PANAS measurements coinciding with five salivary samples were acquired (i.e., two baseline salivary samples at −75 min and −60 min, three additional ones at + 15, + 60, and + 90 min relative to the start of MRI scanning). **(D and E)** Averaged and baseline-corrected HR and HRV during the N-back task and its surrounding movie clips (M2 and M3) for the stress and the control groups. Control, control group; Stress, stress group. *$p < .05$; **$p < .01$; ***$p < 0.001$.

participants watched equally long movie clips from another movie (*Comment j'ai tué mon père,* 2001, by Anne Fontaine), which was equalized in luminance and similar in language and human presence to the stress-induction film but contained only nonarousing scenes. After short introductory texts, participants were asked to watch the movies attentively and imagine themselves in the scene from an eyewitness perspective, thereby attempting to involve them maximally in the movie.

The present stress induction method closely corresponds with the determinants of human stress response described by Mason (28)—that is, unpredictability, novelty, and uncontrollability. It also meets the criteria for stress impaired WM to occur—that is, close proximity of stressor and task to ensure concurrent (nor) adrenergic activity (3).

N-Back Task

Using a blocked-design, participants completed 10 cycles of alternating 0- and 2-back conditions interleaved by a jittered resting-fixation baseline ranging from 8 to 12 sec (average 10 sec). Within each block, a random digit sequence consisting of 15 single digits was shown to participants (see Figure 1A). Each digit was presented for 400 msec, followed by an inter-stimulus-interval of 1400 msec. Each block lasted 27 sec, and started with a 2-sec cue presentation indicating the 0- or 2-back condition. During the 0-back condition, participants were asked to detect whether the current item on the screen was a "1" or not. During the 2-back condition, participants were asked to detect whether the current item had appeared two positions back in the sequence. Participants were instructed to make a button press with their index finger when detecting a target. Before fMRI scanning, they were extensively trained in performing the task (i.e., 10 cycles of alternating 0- and 2-back conditions) to minimize interindividual variability and reduce practice effects. Data from the last four training cycles served as prestress induction baseline performance measure.

Subjective and Physiological Measurements of Stress

Subjective mood was assessed using the PANAS at baseline and three additional time points coinciding with collection of salivary samples (see Figure 1B and 1C). To monitor the HPA axis response, saliva samples were collected using salivette collection devices (Sarstedt, Rommelsdorf, Germany). Participants were requested to abstain from eating, drinking, or smoking for 1 hour before arrival. Salivary sampling consisted of two baseline measurements (before MRI scanning) and three additional ones (right before the N-back task, right after the last movie clip, and 20 min after leaving scanner). All samples were stored at −20°C until analysis. Samples were prepared for biochemical analysis by centrifuging at 3000 rpm for 5 min, which resulted in a clear supernatant of low viscosity. Salivary-free cortisol concentrations were determined employing a chemiluminescence assay (CLIA) with high sensitivity of .16 ng/mL (IBL, Hamburg, Germany).

To assess the autonomic nervous system response, HR was recorded continuously throughout MRI scanning using an MR-compatible pulse oximeter attached to the left index finger. Offline analysis included calculation of both HR frequency and HR variability (HRV; calculated as the root mean square of successive differences [rMSSD], an index of respiratory sinus arrhythmia) (29). Data from two participants were excluded from this analysis because of excessive artifacts (one in the stress group). Additionally, eye tracking was performed using an MR-compatible eye-tracking device (MEye Track-LR camera unit, SensoMotoric Instruments, Teltow, Germany) to confirm attentive viewing of the movie clips.

fMRI Data Acquisition

During MRI scanning, whole brain T2*-weighted echo planar imaging based on blood oxygenation level-dependent contrast (EPI-BOLD) fMRI data were acquired with a Siemens Trio 3.0-T MR-scanner (Erlangen, Germany) using an ascending slice acquisition sequence (37 axial slices, volume repetition time [TR] = 2.18 sec, echo time [TE] = 25 msec, 80° flip angle, slice matrix size = 64 × 64, slice-thickness = 3.0 mm, slice gap = .3 mm, field of view [FOV] 212 × 212 mm). Three hundred seventy-six volumes were acquired during the N-back task. High-resolution structural images (1 × 1 × 1 mm) were acquired using a T1-weighted three dimensional magnetization-prepared rapid gradient-echo (MP-RAGE) sequence (TR 2.3 sec, TE 2.96 msec, 8° flip-angle, 192 contiguous sagittal slices, slice matrix size 256 × 256, FOV 256 × 256 mm), and Siemens' integrated parallel acquisition technique (iPAT) in conjunction with generalized autocalibrating partially parallel acquisitions (GRAPPA) reconstruction (factor two accelerated) (30).

fMRI Data Analysis

Image preprocessing and statistical analysis was performed using SPM5 (http://www.fil.ion.ucl.ac.uk/spm). The first five EPI volumes were discarded to allow for T1 equilibration. Remaining functional images were rigid-body motion corrected and the mean image was coregistered to each participant's T1-weighted MR-image. Subsequently, images were transformed into a common stereotactic space (MNI152 T1-template), and resampled into 2 mm isotropic voxels. Finally, images were spatially smoothed by convolving with an isotropic 3D-Gaussian kernel (8-mm full width at half maximum). The data were statistically analyzed using general linear models and statistical parametric mapping (31).

To assess neural activity associated with 0- and 2-back conditions, the two conditions were modeled separately as boxcar regressors and convolved with the canonical hemodynamic response function in SPM5. Additionally, realignment parameters were included to account for movement-related variability. The analysis furthermore included high-pass filtering using a cutoff of 1/128 Hz, global intensity normalization, and serial correlations correction using a first-order autoregressive (or AR[1]) model.

The contrast parameter images for both conditions relative to baseline, which were generated at the single-subject level, were submitted to a second-level analysis within a 2 (group) by 2 (WM-load) mixed factorial analysis of variance (ANOVA). We used an alpha of .05 corrected for multiple comparisons based suprathreshold cluster size statistics (32). The initial threshold for this analysis was set at $p < .001$, uncorrected, which was also used for visualization of activations. Given our clear hypotheses regarding the DLPFC, this region was additionally investigated with a reduced search region consisting of a sphere (radius 20 mm) at coordinates reported in previous studies with similar N-back tasks (33,34), using a small volume correction procedure (SVC). The SVC procedure was also employed for brain regions within the DMN at coordinates reported by Greicius and colleagues (35). Parameter estimates were extracted from those regions to characterize the response patterns of 0- and 2-back conditions of the two groups using MarsBar (36).

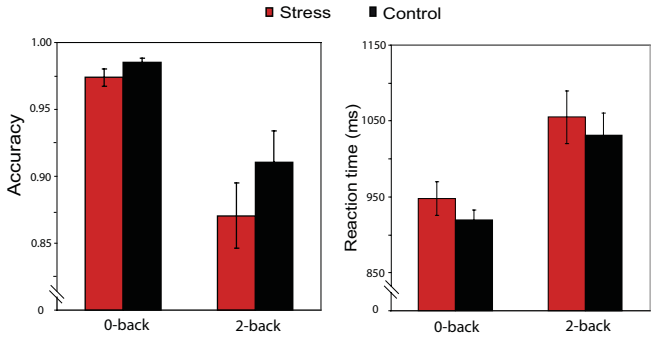


Figure 2. Behavioral performance in the N-back task. Mean accuracy (± SEM) and mean RTs (± SEM) of 0- and 2-back conditions for the stress induction and the control groups. Stress, stress group; Control, control group.

Results

Subjective and Physiological Measurements of Stress

Subjective negative affect scores at different time points are shown in Figure 1B for the two groups. A 2-by-3 ANOVA with group as the between-subjects factor and time as the within-subjects factor (three post-baseline time points) revealed significant main effects of group [$F(1,25) = 18.56$, $p < .001$] and time [$F(2,24) = 12.31$, $p < .001$], and a significant interaction effect [$F(2,24) = 7.56$, $p < .003$], indicating that stress induction resulted in significantly increased negative affect.

Baseline-corrected salivary cortisol measures are shown in Figure 1C. A 2 (group) by 3 (time: three post-baseline time points) ANOVA revealed a significant downward pattern in cortisol for both groups over time [$F(1,25) = 9.59$, $p = .005$], most likely due to diurnal rhythm and stress anticipation, and a significant interaction effect of group and time [$F(2,24) = 3.43$, $p = .049$]. Further testing revealed significantly higher cortisol levels for the stress group than the control group at the time point directly preceding the N-back task and surrounding movie clips [$t(15.8) = 1.91$, $p = .037$ one-tailed].

Baseline-corrected HR and HRV were averaged separately for the N-back task and surrounding movie clips (see Figure 1D and 1E). A 2 (group) by 3 (time: pre-, during-, and post-N-back task) ANOVA was conducted separately for HR and HRV data. A significant main effect of group was found for HR [$F(1,23) = 10.77$, $p < .003$] as well as HRV [$F(1,23) = 6.69$, $p = .016$], with significantly increased HR, and decreased HRV, in the stress group compared with the control group. The two groups did not differ in either HR [$t(24) = .85$, ns] or HRV [$t(24) = -1.15$, ns] at baseline.

Taken together, the results from subjective and physiological measurements of stress consistently confirm that the N-back task was indeed embedded in a stressful context for the stress group.

N-Back Performance

Two separate ANOVAs for accuracy and reaction times (RTs) were conducted with session (prestress baseline vs. scanning) and WM-load as within-subject factors and group as between-subject factor. There were robust main effects of WM-load for both accuracy and RTs [$F(1,25) = 25.197$ and $F(1,25) = 36.672$, respectively, both p values $< .001$]. We found no interaction between WM-load and session (both F values < 1), indicating no significant change in the WM-load effect from prestress baseline to scanning. Also, we found no three-way interaction effect involving group, indicating no significant stress effect on WM performance change. Additionally, two separate 2 (group) by 2 (WM-load) ANOVAs were conducted for accuracy and RTs specifically on the data acquired during scanning. Again, robust main effects of WM-load on accuracy and RTs were found [$F(1,25) = 31.572$ and $F(1,25) = 40.097$, respectively, both p values $< .001$]. Neither a main effect of group nor an interaction effect was found (all F values < 1; see Figure 2). Thus, performance data show robust WM-load effects but no changes in WM-load effects from prestress baseline to scanning and no effects of stress induction on WM-load effects.

To investigate further whether stress-induced performance decreases may have occurred in participants with a stronger physiological stress response exclusively, we calculated correlations between physiological stress measurements and changes in performance from prestress baseline to scanning within the stress group. Cortisol levels just before the N-back task ($r = .546$, $p = .043$) and HR during the N-back task ($r = .649$, $p = .016$) correlated positively with RT change (see Figure 1 in Supplement 1), showing that participants with the strongest stress response slowed down most.

Neuroimaging Results

First, by contrasting 2- with 0-back conditions (collapsing across groups), we replicated robust activations of a WM-related network including the bilateral DLPFC (local maxima at [36,48,18] and [−34,52,14], $p < .05$, whole-brain family-wise error [FWE] corrected), bilateral intraparietal cortex (local maxima at [−44,−42,50] and [40,−44,46], $p < .05$, whole-brain FWE corrected), cerebellum (local maxima at [30,−58,−32] and [−30,−58,−34], $p < .05$, whole-brain FWE corrected), and other related regions (see Table 1).

Table 1. Brain Activations Related to WM Load and Modulations of Stress Induction

Brain Regions	BA	*T* Value	MNI 152 Coordinates x y z
Main Effect of WM Load (2- vs. 0-Back, Collapsing Across Two Groups)			
Superior/middle PFC	R 6	15.15[a]	28 4 58
	L 6	12.90[a]	−30 2 58
Inferior PFC	R 47	12.94[a]	32 24 0
	L 47	11.30[a]	−28 24 4
DLPFC	R 46	10.67[a]	36 48 18
	L 46	9.59[a]	−34 52 14
Lentiform nucleus	R −	8.21[a]	18 −4 0
	L −	10.35[a]	−16 −4 0
Inferior parietal cortex	R 40	12.18[a]	40 –44 46
	L 40	13.24[a]	−44 −42 50
Superior parietal cortex	R 7	11.83[a]	18 −66 60
	L 7	11.76[a]	−14 −68 58
Cerebellum	R −	12.12[a]	30 −58 −32
	L −	11.48[a]	−30 −58 −34
Interaction Effect Between WM Load and Group (2- vs. 0-Back × Control vs. Stress)			
DLPFC	R 46	3.97[b]	30 46 20
	L 46	3.79[b]	−36 48 8

Only clusters significant at $p < .05$, corrected at cluster level, are reported.

BA, Brodmann area; control, control group; DLPFC, dorsolateral prefrontal cortex; L, left; MNI, Montreal Neurological Institute in SPM5; PFC, prefrontal cortex; R, right; stress, stress group; WM, working memory.

[a] $p < .05$, whole-brain corrected.

[b] $p < .05$, small volume correction procedure.

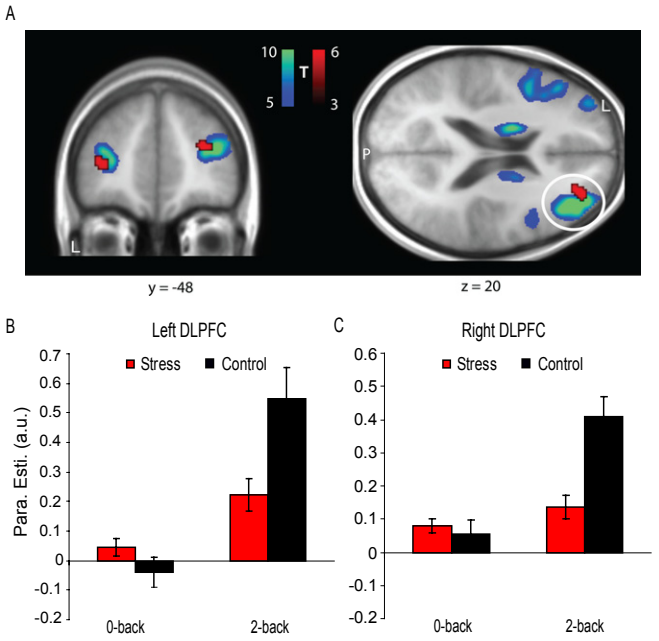


Figure 3. Brain regions involved in working memory in general (shown in blue, thresholded at $p < .05$, whole-brain family-wise error corrected) and reduced activation in the dorsolateral prefrontal cortex (DLPFC) in the stress (vs. control) group (coded in red, thresholded at $p < .001$, uncorrected, for visualization purposes). Statistical parametric maps are superimposed onto spatially normalized and averaged ($n = 27$) high-resolution T1-weighted images. **(A)** Coronal view of activation in the bilateral DLPFC (left panel) and transversal view of activation in the right DLPFC (right panel; marked by white circle). **(B and C)** Bar graphs representing parameter estimates of 0- and 2-back conditions for the stress induction and the control groups in the left and right DLPFC. Parameter estimates were extracted from brain regions coded in red. Control, control group; L, left; p, posterior; R, right; stress, stress group; T, corresponding *t* values.

More important for the question at issue, we found significant clusters in the bilateral DLPFC (local maxima at [30,46,20] and [−36,48,8], cluster $p < .05$, SVC) when contrasting neural activity related to 2- versus 0-back in the control group with that of the stress group (Figure 3). In other words, there was an interaction between WM-load (2- vs. 0-back) and group (control vs. stress), indicating that WM-related DLPFC activation was significantly reduced in participants exposed to stress induction compared with participants in the control group. Subsequent whole-brain regression analyses within the stress group, with physiological measurements of stress as separate covariates, revealed no significant clusters in WM-related structures. However, a more specific region of interest analysis on averaged parameter estimates from the cluster of voxels exhibiting a stress-induced reduction effect in the left DLPFC did reveal a significant positive correlation between HRV and left DLPFC activation (see Figure 2 in Supplement 1).

In addition, by contrasting the active task-demanding conditions with fixation baseline (collapsing across groups), we replicated earlier findings showing deactivation in the DMN including the posterior cingulate cortex (local maxima at [6,−52,16] and [−6,−54,16], $p < .05$, whole-brain FWE corrected), the ventral medial PFC extending into the orbitofrontal cortex (local maxima at [0,58,2] and [10,52,−6], $p < .05$, whole-brain FWE corrected; see Table 2). Moreover, we found that stress induction led to significantly less deactivation in regions within the DMN, more specifically in the posterior cingulate cortex and the medial aspect of orbitofrontal cortex (local maxima at [−4,−40,28] and [12,46,−12] respectively; cluster $p < .05$, SVC; see Figure 4). Within the stress group, whole-brain regression analysis revealed that cortisol levels correlated with activity in the medial PFC extending into the anterior cingulate cortex (ACC; local maxima at [−8,48,−2], cluster $p < .05$, SVC; see Figure 3 in Supplement 1), indicating that participants with larger cortisol responses exhibited less deactivation of this DMN subregion.

Discussion

We aimed to investigate stress-induced modulations in WM-related prefrontal activity. Results confirmed our hypothesis of reduced WM-related activation in the DLPFC. This reduction was accompanied by less deactivation of brain structures within the DMN. As indicated by increased HR and decreased HRV, our stress induction procedure resulted in a shift toward more sympathetic, and less parasympathetic, autonomic nervous system activity. Moreover, stress induction increased HPA axis activity as measured from salivary cortisol. We therefore discuss elevations of stress-sensitive catecholamines, which are associated with increased sympathetic tonus, and cortisol as potential, but not mutually exclusive, factors that may account for our observed alterations in neural activity.

The PFC is sensitive to its neurochemical environment, and small changes in catecholamine modulation of this region can have substantial impact on higher-order cognitive function such as WM (2,7,8). Exposure to acute stress is thought to result in activation of the locus coeruleus (LC), which rapidly increases NE projections to a widely distributed brain network (1,14). In this way, the LC plays a critical role in promoting behavioral adaptation to stressful situations (37–39). According to an integrative theory of the LC-NE system in neuromodulation of cognitive function (40,41), LC-NE activity exhibits an inverted

Table 2. Brain (De)Activations Related to the Default Mode Network and Modulations of Stress Induction

Brain Regions	BA	*T* Value	MNI 152 Coordinates x y z
Deactivations During Active Conditions (0- and 2-Back vs. Fixation Baseline, Collapsing Across Groups)			
Posterior cingulate cortex	R 30/23	11.05[a]	6 −52 16
	L 30/23	12.22[a]	−6 −54 16
Ventral medial PFC	R 10	7.53[a]	10 52 −6
	L/R 10	7.03[a]	0 58 2
Hippocampus	R −	6.66[a]	26 −18 −18
	L −	8.87[a]	−26 −26 −14
Parahippocampal cortex	R 36	7.99[a]	26 −42 −10
	L 36	8.47[a]	−28 −40 −10
Insula	R 13	8.29[a]	42 −16 0
	L 13	6.57[a]	−44 −6 −4
Main Effect of Group (Stress vs. Control, Collapsing Across 0- and 2-Back Conditions)			
Posterior cingulate cortex	L 31/23	4.80[b]	−4 −40 28
Orbital PFC	R 10/32	4.21[b]	12 46 −12

Only clusters significant at $p < .05$, corrected at cluster level, are reported.

BA, Brodmann area; control, control group; DLPFC, dorsolateral prefrontal cortex; L, left; MNI, Montreal Neurological Institute in SPM5; PFC, prefrontal cortex; R, right; stress, stress group.

[a] $p < .05$, whole-brain corrected.

[b] $p < .05$, small volume correction procedure.

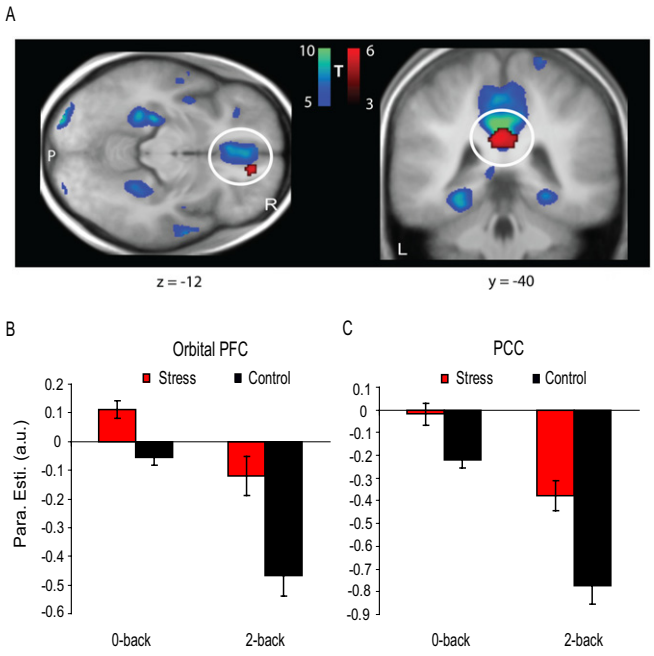


Figure 4. Brain regions showing deactivation during general active task conditions (coded in blue; thresholded at $p < .05$, whole-brain family-wise error corrected) and reduced deactivation in the stress (vs. control) group (coded in red, thresholded at $p < .001$, uncorrected, for visualization purposes). Statistical parametric maps are superimposed onto spatially normalized and averaged ($n = 27$) high-resolution T1-weighted images. **(A)** Coronal view of deactivation in the ventral medial/orbital prefrontal cortex (PFC; left panel; marked by white circle) and coronal view of deactivation in the posterior cingulate cortex (right panel; marked by white circle). **(B and C)** Bar graphs representing parameter estimates of 0- and 2-back conditions for the stress induction and the control groups in orbital PFC and posterior cingulate cortex (PCC). The parameter estimates were extracted from those brain regions coded in red. Control, control group; L, left; p, posterior; R, right; stress, stress group; T, corresponding *t* values.

U-shaped relationship with outcome performance of goal-directed behavior. Optimal performance is associated with an intermediate level of LC activity and a strong phasic LC firing pattern in response to a focused task. In contrast, both LC hypoactivity and tonic hyperactivity lead to an impairment of performance and a reduced phasic LC firing pattern. Moreover, high tonic LC activity has been associated with a state of hypervigilance and increased exploration of adaptive options. In this study, stress induction may thus have led to high tonic LC activity resulting in a right-sided shift on the inverted U-shaped curve. Therefore, the reduction in WM-related DLPFC activity may be explained by a shift from phasic to tonic activation of ascending noradrenergic projections to the PFC.

Evidence from numerous pharmacological studies supports the notion that NE, but also other stress-sensitive catecholamines such as DA, exhibit inverted U-shaped dose–response relationships with cognitive performance (7,8). On the cellular level, a recent pharmacological study implementing intracellular recordings suggests that catecholamines indeed have such dose–response relationships with neural firing patterns of the DLPFC underlying WM (42). The existence of such an inverted U-shaped pattern is further substantiated by dissociations of detrimental and beneficial effects through distinct cellular mechanisms. At optimal levels of NE, prefrontal function is strengthened through actions of α-2A-adrenoceptors and increasing neural firing via inhibition of cAMP-HCN (cyclic adenosine monophosphate–hyperpolarization-activated cyclic nucleotide-gated cation channel) signaling, whereas optimal levels of DA D1 receptor decrease task-irrelevant neural firing by increasing cAMP-HCN signaling (8,13,42). In contrast, stress-induced excessive levels of catecholamines impair WM-related prefrontal function by high levels of cAMP-HCN signaling and high levels of NE engaging the low-affinity α-1-adrenoceptor, which suppresses the neural firing pattern (7,8,12). In this study, the stress-induced shift in autonomic nervous activity toward more sympathetic tonus implicates strong engagement of the LC-NE system and therefore has likely resulted in the observed reduction of WM-related DLPFC activity.

In addition to this catecholaminergic mechanism, stress-induced glucocorticoids are also known to target the PFC, where corticosteroid receptors are abundantly expressed. On the behavioral level, studies in humans have shown that cortisol and NE activation have additive effects in WM impairment and that NE activation is a necessary condition for glucocorticoid effects to occur (3,4). In contrast to the control group, which only showed elevated SNS activity during the N-back task (see Figure 1D), most likely because of arousal related to performing the task, our physiological stress measurements show that stress induction indeed resulted in significant elevations of both HPA axis and SNS activity. Moreover, some measures of stress correlated with brain activation and WM performance changes within the stress group. Therefore, it is plausible that elevated levels of cortisol, in conjunction with high levels of catecholamines, play a role in stress-related DLPFC hypoactivation. In animal studies, such interactions between corticosteroids and NE have been found in the basolateral amygdala, where glucocorticoids potentiate noradrenergic actions (16,43). It is likely that similar interactions also occur in the PFC, because cortisol blocks extraneuronal catecholamine transporters that remove catecholamines from the synaptic cleft (44). Future studies are required to address such potential interactions in the PFC.

It is well known that the DMN and the frontal-parietal executive network activate reciprocally: frontoparietal activation has often been found to be accompanied by DMN suppression (18,19,23,24). Our data robustly replicate earlier findings of DMN deactivation during WM processing but also show stress-induced reduction of DLPFC activation accompanied by less deactivation in the DMN. Interestingly, recent studies suggest that the DMN is involved in processing information unrelated to a current goal-directed task, or "mind wandering" (45,46). Performance of a WM task in the context of acute stress, which can be taken as a form of dual processing, may result in difficulties inhibiting task-irrelevant internal thoughts (4,20–22) such as intrusive recollection of aversive content of the movie. These notions are supported by our findings of reduced DMN suppression positively correlating with cortisol response in the stress group. Our data converge with other findings showing stress-induced increases in cerebral blood flow in a similar region (47). Thus, stress-related psychological factors may lead to a reallocation of neural resources away from a WM-related network and toward the DMN.

On a broad functional level, such a stress-induced reallocation of resources away from executive function networks may represent a mechanism that is essential for survival. Alongside rapid activation of autonomic and endocrine systems, excessive catecholamines released during acute stress may take prefrontal function "offline" to facilitate more adaptive and habitual responses like the "fight-or-flight" response (2,48), trading the accuracy of slow, higher-order cognitive processing for speed.

Despite its utility in life-threatening situations, such a mechanism may exacerbate symptoms of prefrontal dysfunction in various psychiatric disorders characterized by higher susceptibility to stress, such as depression or schizophrenia. By showing similar prefrontal cortical dysfunctions in healthy individuals under acute stress, our data support the notion that there may be a direct association between symptoms of hypofrontality and heightened stress in these disorders (5,7–9). Future studies in patients with these psychiatric disorders should take this factor into account.

In conclusion, the stress-induced reduction of WM-related activity in the DLPFC and the concomitant reduction of DMN deactivation are most likely caused by supraoptimal elevations of catecholamines (such as NE and DA), potentially in concert with elevated levels of cortisol. Such a reallocation of neural resources away from executive function networks may play an important role in higher-order cognitive dysfunctions observed in many psychiatric disorders, which lead to far-reaching problems for patients and their social environment.

This work was supported by Grant No. 918.66.613 from the Netherlands Organization for Scientific Research (NWO). We thank the anonymous reviewers for insightful suggestions.

The authors reported no biomedical financial interests or potential conflicts of interest.

Supplementary material cited in this article is available online.

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