



Acute and past subjective stress influence working memory and related neural substrates

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ABSTRACT

Stress has been proposed to affect cognitive control capacities, including working memory (WM) maintenance. This effect may depend on variability in stress reactivity and past subjective stress. However, as most studies employed between-subjects designs, evidence for within-subject stress effects remains scarce. To understand the role of intra-individual stress effects on WM, we adopted a within-subject design to study how acute stress, variability in stress reactivity, and past subjective stress influence behavioral and neural WM mechanisms. Thirty-four healthy males performed a WM task during functional magnetic resonance imaging (fMRI) in a control versus acute stress condition following the Trier Social Stress Test, a validated psychosocial stressor method. We tested for stress effects on WM performance and related neural activation by associating them with individual acute stress responsivity and past subjective stress experience using retrospective self-report questionnaires. We found no evidence of an effect of acute stress or related stress-reactivity on intra-individual WM performance. However, past subjective stress negatively influenced acute stress-induced changes to WM. On the neural level, acute stress reduced WM-related activation in the dorsolateral prefrontal cortex (dlPFC). The observed negative influence of inter-individual variability in past subjective stress experience on changes in WM performance, suggests that past subjective stress might induce vulnerability for impairing effects of acute stress on cognitive functioning. Because acute stress reduced WM-related dlPFC activation while WM performance remained unaffected, acute stress might boost neural processing efficiency in this group of high performing healthy individuals. Our study suggests that measures of past subjective stress should be considered when studying and interpreting the effects of acute stress on cognition.

1. Introduction

When experiencing stress, it is essential to maintain cognitive control to successfully modulate thoughts and actions. For example, when arriving at a noisy crowded train station and the train is due to depart shortly, it is crucial to ascertain the correct platform of departure from the departure boards, despite experiencing stress. Stress is a psychophysiological process elicited by physical or psychosocial strains, leading to subjective evaluation of situations as stressful (Cohen et al., 2016; Rajesh et al., 2014) and triggering reactions via the sympathetic-adrenal-medullary (SAM)-system and hypothalamic-pituitary-adrenal (HPA)-axis (Calvo and Gutiérrez-García, 2016). Although stress responses alert the individual in life threatening situations, these

reactions might be less functional in modern societies, for example due to a lack of natural predators. Stress can severely affect social, cognitive functioning and is crucially involved in the pathogenesis and maintenance of psychiatric disorders (Koob, 2008; Koob et al., 2014; McEwen, 2004). A deepened understanding of the behavioral and neural mechanisms of acute stress on cognitive abilities has major societal and clinical implications.

Studies suggest that acute stress, stress-induced increases of glucocorticoids, and catecholamines alter cognitive functioning such as (working) memory (Arnsten, 2009; Bogdanov and Schwabe, 2016; Cornelisse et al., 2011; Oei et al., 2007, 2006; Otto et al., 2013; Schoofs et al., 2013, 2008) or decision-making (Otto et al., 2013; Radenbach et al., 2015; Schwabe and Wolf, 2009). Working memory (WM)

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comprises the ability to maintain, manipulate, and update information as well as protecting it against distraction (Baddeley, 2003). Additionally, WM represents cognitive control and underlies goal-directed behavior (Otto et al., 2013). Neurally, WM functioning depends on fronto-parietal brain circuits (D'Esposito, 2007; D'Esposito and Postle, 2015; Owen et al., 2005). Within these circuits the dorsolateral prefrontal cortex (dlPFC) is thought to control which information will be maintained, depending on task relevance (D'Esposito, 2007; D'Esposito and Postle, 2015; Riley and Constantinidis, 2016).

Neuroimaging studies in humans have shown that acute stress decreases WM-related neural activation in the right dlPFC (Oei et al., 2012; Qin et al., 2009; Van Ast et al., 2016), emphasizing its stress susceptibility (Bogdanov and Schwabe, 2016). However, the direction of stress effects on behavioral WM performance is less clear. While some studies have shown detrimental effects of acute stress on WM performance (e.g., Luethi et al., 2009; Schoofs et al., 2008), other studies point towards performance increases (e.g., Cornelisse et al., 2011; Schoofs et al., 2013) or no changes (Qin et al., 2009). A meta-analysis found that acute stress impairs WM, even though the overall effect is small and varies across studies (Shields et al., 2016). Moreover, the delay time between stress intervention and task performance seems to be an important moderator (Bendahan et al., 2017; Hermans et al., 2014; Margittai et al., 2015; Shields et al., 2016, 2015).

Importantly, beyond the effects of delay, stress-induced changes in cognitive abilities depend on individual variability of trait anxiety (Goette et al., 2015), catecholamine-related arousal-responses (Arnsten, 2009; Arnsten and Li, 2005; Berridge and Arnsten, 2013; Radenbach et al., 2015), and cortisol levels (Oei et al., 2006; Radenbach et al., 2015; Van Ast et al., 2016). Qin and colleagues found that performance reductions in an *n*-back WM task scaled with increases of cortisol and heart rate (Qin et al., 2009). Consistently, Oei and colleagues observed an association between slowed reaction times in a Sternberg WM task under acute stress and higher levels of cortisol (Oei et al., 2006). Additionally, acute stress-induced impairments of WM performance are associated with self-reported previous stress exposure (Shields et al., 2017). Past stress experiences might render individuals more vulnerable to impairing effects of acute stress on cognitive processing, consistent with psychological stress theories claiming that repeated coping is taxing and depletes individual coping resources (Calvo and Gutiérrez-García, 2016; Lazarus and Folkman, 1984). Indeed, converging evidence from studies in animals and humans shows that decision-making capacities are predicted by levels of past stress (Dias-Ferreira et al., 2009; Radenbach et al., 2015), and past stress is negatively related to spatial WM in children with autism spectrum disorder (Ogawa et al., 2017). These results suggest that the interplay of past and acute stress might have detrimental influences on cognitive functioning.

However, virtually all presented studies employed between-subject designs. The inherent inability to dissociate within- from between-subject effects in those designs precludes any statements about modulation of intra-individual acute stress effects on WM and its neural correlates by stress responsivity or past subjective stress. It remains elusive whether changes in WM performance due to acute stress can truly be attributed to within-subject changes in cortisol levels. This knowledge gap implicates an urgent need of investigation using within-subject designs.

Additionally, the existing literature has focused on cortisol as a marker of stress responsivity, widely ignoring the fact that stress is more than an increase of circulating cortisol (Calvo and Gutiérrez-García, 2016; Shields et al., 2016), as stress changes the subjective stress experience of the individual (Calvo and Gutiérrez-García, 2016). According to psychological stress theories, determination of stressful events should be based on the subjective evaluation of situations as being stressful (Calvo and Gutiérrez-García, 2016; Lazarus, 1966; Lazarus and Folkman, 1984). It is currently unknown how changes to subjective stress response are related to WM performance and its neural correlates under acute stress.

In the present within-subject study, we investigated the effects of acute psychosocial stress, related individual stress reactivity, and past subjective stress experiences on intra-individual changes of WM performance and its neural signatures using functional magnetic resonance imaging (fMRI). We hypothesized that intra-individual WM performance and its neural signatures would be negatively affected by acute stress, that stress effects would be related to individual cortisol reactivity and subjective stress responses, and that past subjective stress would be associated with acute stress-induced changes to WM on both the behavioral and neural level.

2. Methods

2.1. Participants

Thirty-four healthy male participants completed the study (see Power Analysis in the Supplement). Participants were recruited from the database of the Max Planck Institute for Human Cognitive and Brain Sciences in Leipzig, Germany and from the local community through advertising. Only males were included in the study to avoid confounding effects of hormonal cycles that might interact with stress responsivity (Cornelisse et al., 2011; Schoofs et al., 2013).

Exclusion criteria were medical, neurological disorders, and any current or lifetime psychiatric disorder assessed using the German Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders (SCID-IV, Wittchen et al., 1997). Participants reporting chronic intake of any medication known to interact with the central nervous system or endocrine responses were excluded.

The study was approved by the ethics committee of the medical faculty at the University of Leipzig and was conducted in accordance with the Declaration of Helsinki. All participants provided written informed consent before participation and were fully debriefed about the aims of the study after completing the entire protocol.

2.2. Design

The study entailed a within-subjects design, where participants performed an *n*-back WM task (e.g., Deserno et al., 2012) during fMRI in two separate test sessions. One session involved acute stress intervention (stress condition), and the other session involved no stress (control condition). The two sessions took place seven days apart, and the order of sessions was counterbalanced across participants. Each test session started in the afternoon between 1.30 and 4.30 pm to control for natural effects of circadian rhythms on cortisol (Kudielka et al., 2004; Radenbach et al., 2015; Starcke et al., 2013). Each participant's control and stress session were scheduled at the same time (e.g., a participant's stress condition started at 1.30 p.m. on a Monday and his control condition started at 1.30 p.m. on the Monday one week later). Acute stress reactivation in the form of saliva samples (cortisol response) and mood questionnaires (subjective acute stress experience) were assessed at six time-points during each test session (see Fig. 1).

2.3. Acute stress induction

During the stress condition participants were subjected to the standardized Trier Social Stress Test (TSST, Kirschbaum et al., 1993), which is known to increase endocrine, autonomic, and subjective markers of stress (Kirschbaum et al., 1993; Kudielka et al., 2004) more reliably than other stress induction paradigms (Dickerson and Kemeny, 2004; Giles et al., 2014). The test includes an interview and arithmetics in front of an emotionally neutral committee in white laboratory coats (see Supplement for detailed description). During the control condition, participants read a neutral piece of text without the presence of a committee (Radenbach et al., 2015). Importantly, both interventions were performed in different rooms, assuring no crossover effects due to location context. They were located at approximately the same distance

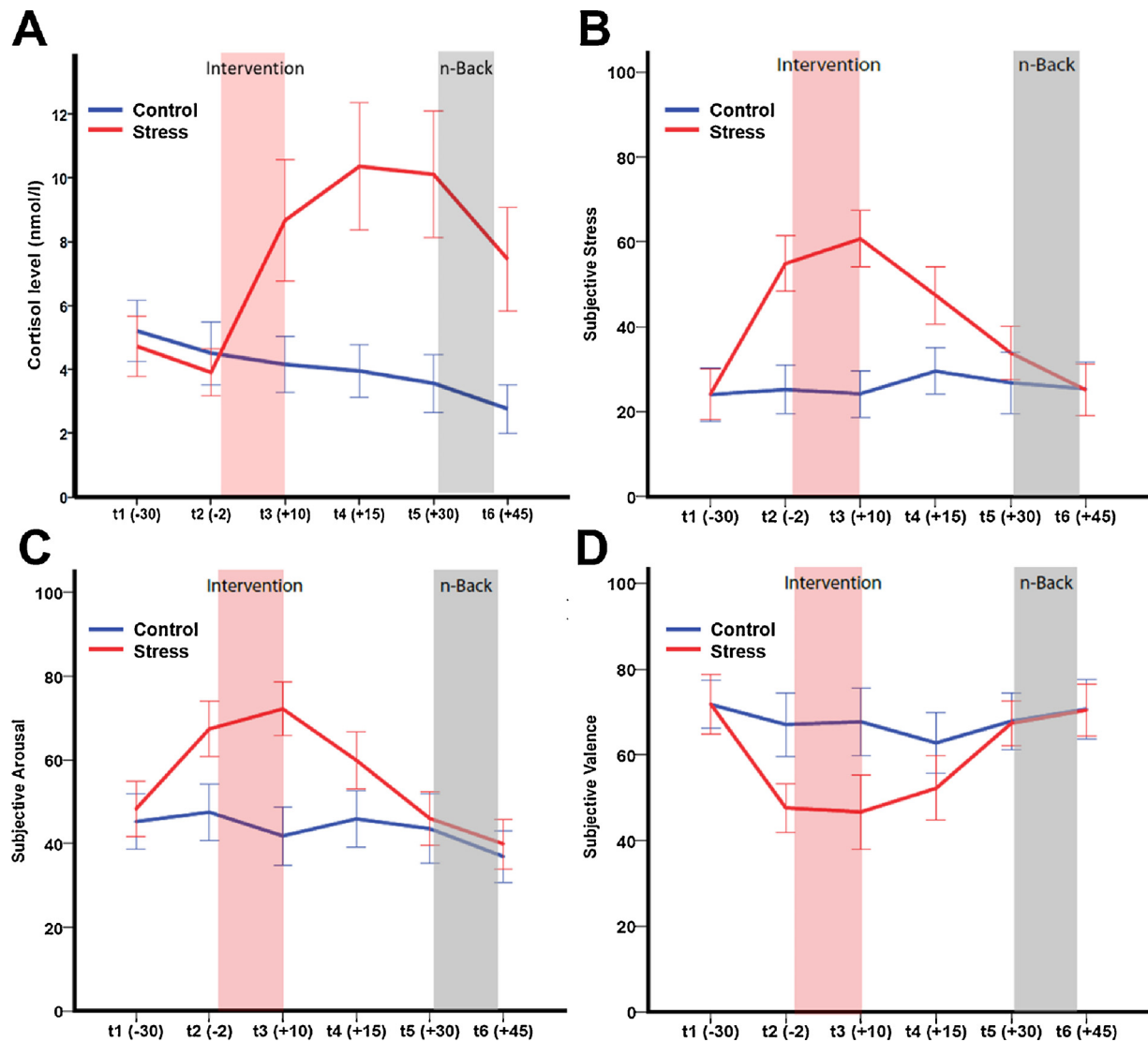


Fig. 1. Cortisol and subjective stress response over the course of the experimental sessions (t1 to t6). X-axis indicates the time relative to the intervention (control or stress) in minutes (in parentheses). Time of the intervention (between t2 and t3) is displayed in light red. The light gray bar indicates the time during which the n-back task was performed (between t5 and t6). A) Cortisol responses (in nmol/l) in $n = 28$ cortisol responders (cortisol response of > 1.5 nmol/l (Miller et al., 2013) from pre- to post-stress during the stress condition), B, C, D) Subjective stress, arousal, and valence ratings on visual analog scales (higher values indicate higher rating) in $n = 33$ participants filling in all visual analog scales. Blue lines = control condition, red lines = stress condition. Error bars represent the 95% confidence interval. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article).

to the MRI scanner, as participants were scanned straight after completion of the interventions.

2.4. Acute stress response assessment

2.4.1. Physiological stress response

Saliva was collected using Salivette saliva sampling tubes (SalivetteCortisol®, Sarstedt, Nuembrecht, Germany) to extract and measure salivary cortisol (see Supplement). Physiologically relevant cortisol increases were defined at a threshold of 1.5 nmol per liter (nmol/l, Miller et al., 2013) increase post-stress (t3 through t6) above the lowest pre-stress level (t1 or t2) during the stress condition as described previously (Radenbach et al., 2015; Schommer et al., 2003). Individual cortisol reactivity was determined by calculating the area under the curve with respect to ground ($AUC_{g-stress}$ and $AUC_{g-control}$, according to Pruessner et al., 2003) separately for both conditions and subtracting $AUC_{g-control}$ from $AUC_{g-stress}$.

2.4.2. Subjective stress response

We assessed subjective arousal (“do you feel active or sleepy”), valence (“do you feel happy or unhappy”), and stress (“do you feel stressed or not stressed”) at all timepoints (t1 to t6) using a visual analog scale (VAS) ranging from 0 (sleepy, unhappy, or not stressed) to 100 (active, happy, or stressed). As a variable of interest representing subjective stress reactivity during the stress condition, stress-induced changes in the VAS measuring subjective stress were calculated by calculating the area under the curve with respect to ground ($AUC_{g-stress}$ and $AUC_{g-control}$, according to Pruessner et al., 2003) separately for both conditions and subtracting $AUC_{g-control}$ from $AUC_{g-stress}$ in the same way as for cortisol reactivity.

2.4.3. Stress response analyses

Cortisol levels and the three subjective VAS scales were analyzed using the Statistical Package for the Social Sciences 22 (SPSS 22, IBM Inc., Chicago, IL, USA). Before assessing individual stress response, we first made the simpler and cruder comparison of the stress versus no stress conditions using a paired-samples *t*-test. Subsequently, changes of

stress levels across time were analyzed using 2×6 repeated-measures analyses of variance (rmANOVA), with condition (stress/control) and time (t1 through t6) as within-subject factors.

2.5. Past subjective stress assessment

Participants filled in trait questionnaires at home via an internet-based survey program (Limesurvey, www.limesurvey.org). This survey included the German version of the Perceived Stress Scale (PSS-10, Cohen et al., 1983), a self-report questionnaire assessing past subjective stress during the last 30 days. Here, past subjective stress is defined in terms of the subjective evaluation of situations in one's life as stressful. The PSS-10 is described in more detail in the Supplement.

2.6. Working memory assessment: *n*-back task

Participants performed a visual numeric *n*-back task, where they had to react to serially displayed numbers. During the 2-back blocks participants had to respond to a displayed number if it was shown two numbers back. In the 0-back blocks participants had to respond when they saw a “0” displayed (see Supplement for detailed description). The task consisted of six alternating blocks of every WM-load (2-back vs 0-back). Behavioral performance in the task was quantified with the sensitivity index d' , the number of hits controlled for the number of false alarms, to ensure a more accurate description of how humans detect and discriminate stimuli than the simple number of hits (Wickens, 2001). We calculated d' separately for 0-back and 2-back conditions in both test sessions by subtracting individual z-scored false alarm probabilities from individual z-scored hit probabilities calculated using an inverse cumulative distribution function (Wickens, 2001). Higher d' indicates more accurate WM performance. Additionally, individual mean reaction times (RT) for hits were calculated for the 0-back and 2-back conditions during both test sessions.

2.7. Analyses

2.7.1. Behavioral data

Behavioral data was analyzed using separate 2×2 repeated-measures ANOVAs with condition (stress/control) and WM load (0-back/2-back) as within-subject factors on the outcome variables d' and RT. Subsequently, to study the additional effects of intra-individual stress responses (cortisol and subjective stress) on task performance we added the covariates cortisol change and subjective stress change, calculated from the difference between $AUC_{g-stress}$ and $AUC_{g-control}$, into 2×2 repeated-measures ANCOVAs. In case of a violation of sphericity (Mauchly's test), degrees of freedom were adjusted using the Greenhouse-Geisser correction. Post-hoc paired-sample *t*-tests were conducted to test the direction of significant main and interaction effects. In the ANCOVAs, post-hoc Pearson's correlations between the covariate and the outcome variable were calculated for stress and control condition separately. To study the influence of past subjective stress on intra-individual stress-induced change in WM performance, we conducted a multivariate regression analysis with the PSS-10 total score as predictor of the difference score d' , $\Delta d'$ ($d'_{2-back\ Stress} - d'_{2-back\ Control}$: Negative values indicated a performance decrease in the stress condition) and the difference score RT for hits, ΔRT ($RT_{2-back\ Stress} - RT_{2-back\ Control}$: Positive values indicated slower performance in the stress condition) as outcomes. For all behavioral analyses two-tailed tests were performed and results were regarded as significant at $p < .05$.

2.7.2. fMRI data

fMRI data was acquired using a 3T high-resolution Siemens PRISMA MR-system (Siemens, Erlangen, Germany), equipped with a 20-channel head coil. Blood oxygenation level dependent (BOLD) signals were acquired using a T2*-weighted echo-planar imaging (EPI)

sequence (TR = 2000 ms, TE = 30 ms, flip angle = 90°, matrix = 192 x 192 mm, voxel size = 3 x 3 x 5 mm). We collected 30 slices covering the whole brain, approximately parallel to the anterior–posterior commissure plane. For details on fMRI data acquisition and preprocessing, please see Supplementary Methods. Statistical fMRI analyses were performed using a two-level general linear model (GLM) approach (Friston et al., 1995). On an individual level (first level), instruction cues and the 0-back and 2-back condition blocks were modeled, and the six realignment parameters were added as additional regressors. Contrast images for 2-back and 0-back were computed for control and stress condition and subsequently submitted to random-effects group statistics (second level). A flexible factorial design was used with condition (stress/control) and WM load (0-back/2-back) as within-subject factors and subject as random effect.

To control for multiple comparisons, family-wise error correction (p_{FWE}) was applied at the whole-brain level, using small volume correction for the right dorsolateral prefrontal cortex (dlPFC). The right dlPFC was a priori chosen based on its importance for mediating WM (Owen et al., 2005) and specifically due to previous findings of acute stress effects in this region (Qin et al., 2009; Van Ast et al., 2016). This region was defined by the middle frontal gyrus (MFG) mask taken from the Wake Forest University (WfU) Pick Atlas (Maldjian et al., 2003), implemented as a toolbox in SPM (IBASPM 116 Atlas).

The association of WM BOLD signals with physiological and subjective stress response was tested using extracted parameter estimates from the cluster of the interaction effect of condition by WM load in the right dlPFC. Specifically, difference scores for the mean cluster values (extracted at a threshold of $p_{uncorrected} < .005$), namely the stress-induced change in neural activation from control to stress condition during high WM load (2-back stress – 2-back control) were calculated.

Separate Pearson's product-moment correlations were performed between stress-induced activation changes in the right dlPFC and the individual cortisol changes as well as the subjective stress changes, calculated from the difference between $AUC_{g-stress}$ and $AUC_{g-control}$. To elucidate the influence of past subjective stress on stress-induced changes in dlPFC WM BOLD signals, a Pearson's product-moment correlation with PSS-10 scores and the stress-related activation changes in the right dlPFC was performed.

3. Results

3.1. Sample characteristics

Sample descriptions for the complete sample and the fMRI subsample are depicted in Table 1.

3.2. Physiological and subjective stress response

Average time points of saliva sampling and visual analog scale assessments are depicted in Table S1.

Of the 34 participants, 28 (82%) showed a cortisol increase above the set threshold of 1.5 nmol/l and were therefore considered responders. These cortisol responders showed significantly elevated levels of cortisol during the stress condition. With a more conservative criterion of 2.5 nmol/l cortisol increase, we classified 22 of 34 (65%) of the participants as responders. However, because we used the whole sample for our main behavioral analyses (WM), the choice of cortisol responder criterion did not influence the behavioral results. The stress intervention strongly affected the reported subjective experiences (arousal, valence, and subjective stress) in the whole sample. For a detailed description and statistics of the cortisol reactivity and subjective stress responses, see Supplement (Tables S1 and S2) and Fig. 1.

3.3. WM performance

Because two participants showed deviant behavior on the WM task

Table 1
Sample characteristics.

	Complete Sample (<i>n</i> = 34)	fMRI Subsample (<i>n</i> = 29)
Age (years)	26.62 (5.16)	26.48 (5.20)
BMI	24.24 (3.02)	24.01 (2.98)
Education years	12.12 (1.19) ^a	12.12 (1.05)
Handedness	31 / 1 / 1	28 / 1 / 0
(right/bilateral/left: <i>n</i> , %)	94% / 3% / 3% ^a	97% / 3% / 0%
Past subjective stress (PSS-10)	17.53 (4.63) ^b	17.31 (4.77)
Verbal Intelligence (IQ, WST)	102.79 (11.02) ^a	102.59 (11.46)

Note. Means and standard deviations are shown (in parentheses) and frequencies/percentage (handedness) for the complete sample and the fMRI subsample. Abbreviations: BMI = Body-Mass-Index (weight/height²), IQ = Intelligence quotient, PSS-10 = Perceived Stress Scale (Cohen et al., 1983), WST = Wortschatztest (Schmidt and Metzler, 1992).

^a based on 33 participants who filled in the sociodemographic questionnaire and completed the verbal intelligence assessment.

^b based on 32 participants who filled in the PSS-10.

and were thus outliers in the range of > 2 SD, we excluded them from further behavioral analyses. In the remaining sample ($n = 32$), we show significant main effects of WM load for both d' ($F_{1, 31} = 147.70$, $p < .001$, $\eta_p^2 = .83$) and RT for hits ($F_{1, 31} = 148.84$, $p < .001$, $\eta_p^2 = .83$), regardless of the stress conditions. Post-hoc paired-sample t -tests comparing the two levels of WM load showed that this effect was driven by lower average d' in the 2-back condition compared with the 0-back condition ($t_{31} = 12.15$, $p < .001$) and by slower average reaction times in the 2-back condition compared with the 0-back condition ($t_{31} = 12.20$, $p < .001$). This effect was well in line with previous studies employing n -back paradigms (Deserno et al., 2012; Kaminski et al., 2011; Qin et al., 2009; Schoofs et al., 2013, 2008; Van Ast et al., 2016).

3.4. Effect of acute stress on WM performance

RMANOVAs on d' and RT for hits (see Fig. 2) revealed no significant main effects of condition (d' : $F_{1, 31} = .01$, $p = .93$, $\eta_p^2 < .001$, RT: $F_{1, 31} = .52$, $p = .48$, $\eta_p^2 = .02$), indicating that accuracy and reaction times, regardless of WM load, were comparable in the stress and control conditions. Opposing our predictions, we did not find significant interactions of condition and WM load (d' : $F_{1, 31} = .07$, $p = .80$, $\eta_p^2 = .002$; RT: $F_{1, 31} = 2.08$, $p = .16$, $\eta_p^2 = .06$), indicating that d' and RT differences on WM load were not further modulated by a specific condition. Neither a repetition of both analyses, including two behavioral outliers in which WM performance was below or above 2 SD of the mean, nor within the fMRI subsample changed the reported results.

We conducted control analyses to address important potential caveats of repeated-measures designs. First, we included order of the experimental session (order: stress-control or control-stress) as a between-subjects factor in our rMANOVAs. This did not influence the above-mentioned results: Neither the main effects of order on d' and RT nor any two-way interaction with order were significant (all F s < 1.03 , p s $> .25$, η_p^2 s $< .042$). However, there was a marginal, but non-significant three-way interaction of condition, working memory load, and order on RT ($F_{1, 30} = 3.53$, $p = .07$, $\eta_p^2 = .11$), driven by a slight reduction of 2-back RTs from control to stress condition in participants receiving control condition first and stress condition second. It should be noted that this marginal effect was no longer present when including the two behavioral outliers in the analysis ($F_{1, 32} = 1.71$, $p = .20$, $\eta_p^2 = .05$).

Second, we investigated practice effects by adding the experimental session (day 1/day 2) to the rMANOVAs on d' and RT, ignoring the respective condition (stress/control). There was a significant main

effect of WM load (d' : $F_{1, 31} = 147.70$, $p < .001$, $\eta_p^2 = .83$; RT: $F_{1, 31} = 148.84$, $p < .001$, $\eta_p^2 = .83$). Importantly, we did not observe a significant main effect of session (d' : $F_{1, 31} = 1.11$, $p = .30$, $\eta_p^2 = .04$; RT: $F_{1, 31} = 2.32$, $p = .14$, $\eta_p^2 = .07$), ruling out general practice effects from session 1 to session 2. There was a non-significant interaction effect between session and WM load (d' : $F_{1, 31} = .003$, $p = .96$, $\eta_p^2 < .001$; RT: $F_{1, 31} = 4.13$, $p = .051$, $\eta_p^2 = .12$). The direction of this marginal effect on RTs was again driven by a reduction of 2-back RTs from session 1 to session 2, which was not present in 0-back. These control analyses rule out potential confounds of our repeated-measures design.

3.5. Association of subjective and physiological stress responses with WM performance

The rMANCOVAs including our two measurements of stress response delivered similar results to the rMANOVA without the covariates (see Supplement). Critically, the three-way interaction of cortisol, condition and WM load (d' : $F_{1, 28} = .34$, $p = .56$, $\eta_p^2 = .012$; RT: $F_{1, 28} = .04$, $p = .85$, $\eta_p^2 = .001$) was not significant. Also, the three-way interaction of subjective stress, condition and WM load (d' : $F_{1, 28} = .72$, $p = .40$, $\eta_p^2 = .03$; RT: $F_{1, 28} = .09$, $p = .77$, $\eta_p^2 = .003$), did not show a significant effect. In conclusion, there was no evidence for effects of acute stress responsivity (cortisol and subjective stress) on WM performance.

3.6. Influence of past subjective stress on acute stress-induced WM performance

The analysis showed a multivariate effect of PSS-10 total scores on acute stress-induced WM changes using Pillai's trace ($V = .40$, $F_{2, 27} = 9.13$, $p = .001$, $\eta_p^2 = .40$). Specifically, PSS-10 total scores were negatively associated with $\Delta d'$ ($R^2 = .17$, $b = -.11$, $t = 2.4$, $p = .023$), but not with ΔRT ($R^2 = .07$, $b = -.01$, $t = 1.48$, $p = .15$). Importantly, the specific negative association with $\Delta d'$ survived a Bonferroni correction for multiple comparisons (alpha-level adjustment for two performed tests, $p = .05/2 = .025$). Thus, higher PSS-10 total scores were specifically related to less accurate WM performance under acute stress (see Fig. 3).

3.7. fMRI: acute stress effects on WM-related brain activation

The main effect of WM load showed widespread fronto-parietal activation (see Table S1 and Fig. S2) due to higher activation during 2-back compared to 0-back in the dlPFC, posterior parietal cortex (PPC), anterior insula, cerebellum, and brain stem (see Fig. S1 and Table S3).

The main effect of condition yielded a small but whole-brain correctable cluster in the right putamen (see Supplementary Table 3), driven by higher activation during the control condition compared to the stress condition.

The interaction of condition and WM load yielded no whole-brain correctable results. However, the right dlPFC showed a significant effect of acute stress on WM related activation using small-volume correction for our a priori ROI ($x = 27$, $y = 59$, $z = 26$; $F_{1, 83} = 19.65$, $p_{FWE-SVC} = .026$) (see Fig. 4 and Supplementary Table 3). Post-hoc paired samples t -tests showed that this effect was due to significantly reduced 2-back related activation during the stress compared to the control condition ($x = 27$, $y = 59$, $z = 26$; $t_{83} = 4.43$, $p_{FWE-SVC} = .013$), while 0-back activation did not differ between the control and stress conditions ($t_{83} = 3.05$, $p_{FWE-SVC} = .51$).

Association of acute stress responses and past subjective stress with stress induced dlPFC WM BOLD signal change

Following the acute stress effects on brain activity during WM performance in the dlPFC (see 3.7), we further studied the possibility of an influence of past subjective stress on stress responses in the brain, mirroring our behavioral results. To this end, we extracted the

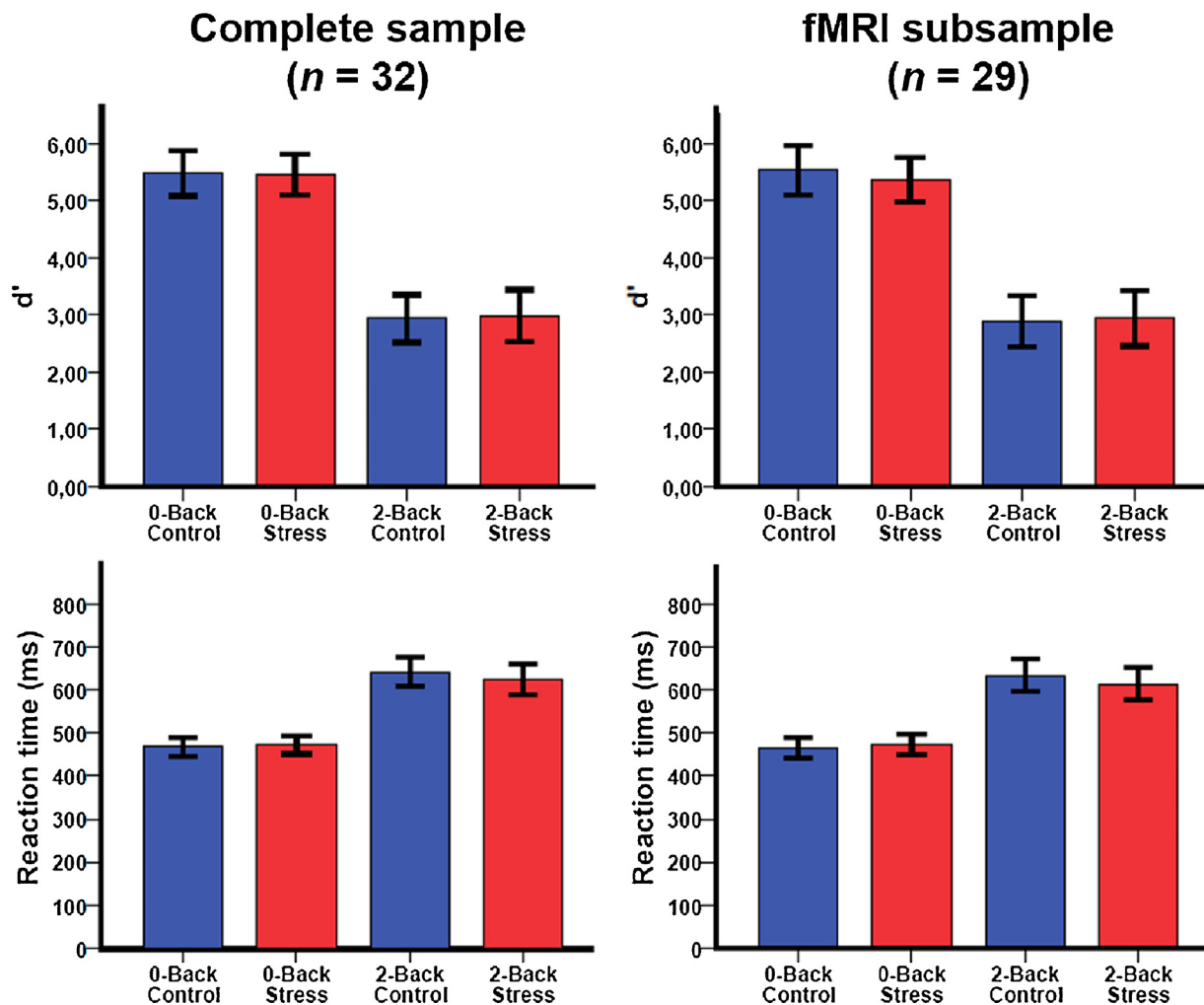


Fig. 2. Behavioral results. Depicted are the two experimental conditions stress (red) and control (blue), and the two working memory loads (0-back and 2-back) of the n-back task. Left: group mean plots of d' (z-transformed correct responses minus z-transformed false alarms, higher d' indicates higher task performance) and reaction times for hits (lower reaction times for hits indicate faster performance) in the complete sample without outliers. Right: group mean plots of d' and reaction times for hits in the fMRI subsample. No significant effects of stress are seen on either WM load or performance parameter. Error bars depict the 95% confidence interval. Abbreviations: d' = d-prime; fMRI = functional magnetic resonance imaging; ms = milliseconds (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article).

parameter values in the pre-defined dlPFC ROI during the condition-by-WM load contrast and correlated this stress-related change in WM activation with stress reactivity measures and past subjective stress scores. One outlier (> 2 SD) on activation change in the dlPFC was removed from the sample, leaving $n = 28$ participants for correlational analyses. Stress-related changes in BOLD activation in the right dlPFC derived from ROI analyses showed no significant association with individual cortisol changes ($r_{26} = .029$, $p = .88$), nor with subjective stress changes ($r_{26} = .186$, $p = .34$). There was also no evidence of a linear relationship between past subjective stress and acute stress-induced changes in right dlPFC WM BOLD ($r_{26} = -.024$, $p = .90$).

4. Discussion

The present study employed a within-subject design in a sample of healthy male participants to investigate the effects of acute psychosocial stress, related individual stress reactivity (cortisol and subjective stress), and past subjective stress experiences on intra-individual changes of WM performance and its neural signatures. Acute stress and related individual stress reactivity did not directly impact WM performance, but WM-related neural activation was significantly reduced in the dorsolateral prefrontal cortex (dlPFC) under stress. Furthermore, we

found that past subjective stress influenced the effects of acute stress on WM performance with participants who reported higher levels of past subjective stress, showing reduced WM performance under acute stress.

Our results do not replicate previously (between-subject) reported acute stress-induced changes in WM performance (Luethi et al., 2009; Oei et al., 2006; Schoofs et al., 2008; Shields et al., 2016) or WM performance speed shown in male subjects (Cornelisse et al., 2011; Schoofs et al., 2013). As a recent meta-analysis also found that acute stress impairs working memory in men more strongly than in women (Shields et al., 2016), our non-significant effect of acute stress on WM in our male sample was unexpected. A likely explanation for the observed non-significant results is that timing between stress intervention and task performance determines directionality of acute stress effects on WM, as has been shown for social/economic decision-making (Bendahan et al., 2017; Margittai et al., 2015). While theoretical accounts assume that short-term effects of cortisol release impair WM and that long-term effects improve WM (Hermans et al., 2014; Shields et al., 2015), more recent meta-analytic evidence conversely shows that longer delays between stress intervention and working memory task result in more impaired working memory task performance (Shields et al., 2016). In the present study, the WM task started on average 45 min after the start of the stress intervention (~ 35 min after the end

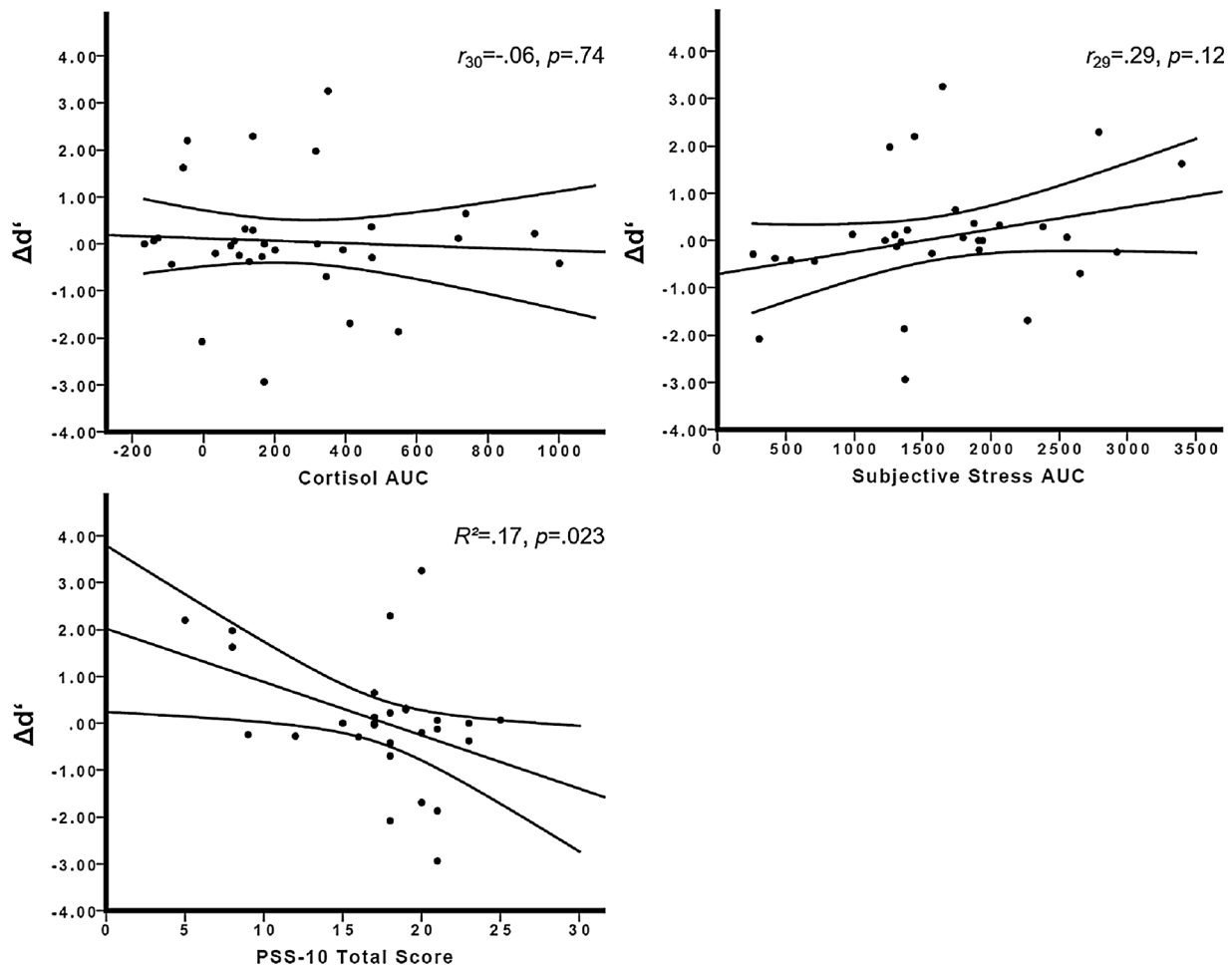


Fig. 3. No significant relationship between acute stress responses (cortisol AUC_g ($n = 32$) and subjective stress AUC_g ($n = 31$), top row) and stress-induced change on d' ($\Delta d'$, 2-back Stress – 2-back Control, negative values indicate decrease in task performance under stress). Stress-induced change on d' is negatively associated with past subjective stress ($n = 30$, PSS-10 total scores, bottom). Curved lines indicate the 95% confidence interval of the regression slope.

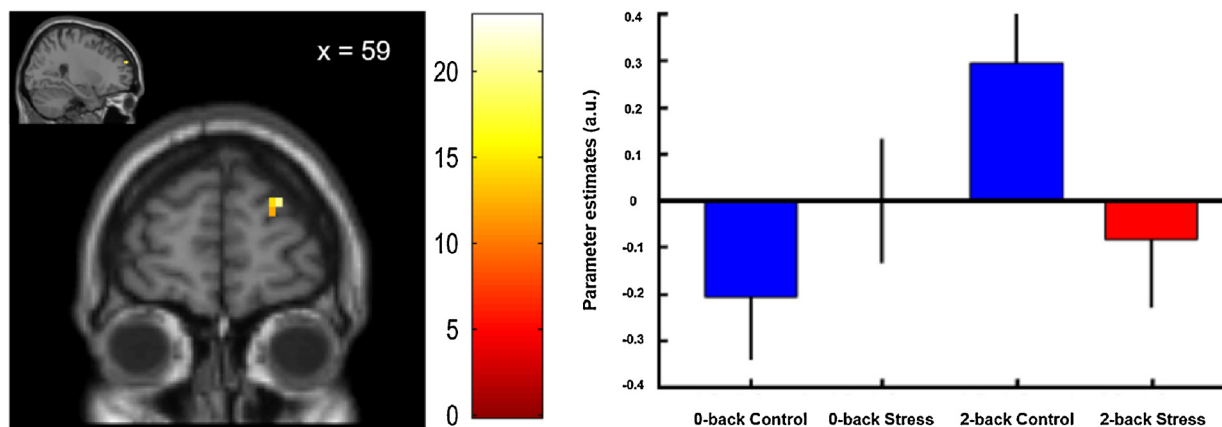


Fig. 4. Effect of acute stress on right dlPFC activation. Left: interaction effect of condition (stress vs. control) and working memory load (2-back vs. 0-back) in the right dlPFC (small-volume corrected $p_{FWE-SVC} < .05$ for an anatomical mask of the right MFG and displayed at $p_{uncorrected} < 0.001$, cluster-size > 5 for display purposes).

Right: plot of the parameter estimates across the two conditions (blue = control condition, red = stress condition) and the two working memory loads for the right dlPFC peak voxel (MNI-coordinates: $x = 27, y = 59, z = 26$). Activation patterns show BOLD signal differences in the 2-back working memory load in the control condition compared to the stress condition (control $>$ stress), but not in the 0-back working memory load in $n = 29$ participants.

Color bar represents F-values, error bars in the plot depict the 90%-confidence interval.

of the stress intervention). Presumably, performance of the task might have fallen into a timeframe where impairing effects of stress on WM had not yet fully settled. However, it should be noted that cortisol levels peaked just before performance of the WM task, and a recent study showed an effect of acute stress on verbal WM performance in a between group design, in which the experiment started approximately 35 min after the start of the stress intervention (Van Ast et al., 2016). Nonetheless, our results are consistent with an fMRI study reporting no significant behavioral stress effects on pre-post measurements of numerical WM (Qin et al., 2009).

Contrasting with our predictions, but consistent with one study (Van Ast et al., 2016), we did not show that intra-individual increases of cortisol and subjective stress influence WM task performance accuracy or reaction times. The dependency of stress effects on changes of individual cortisol levels, as previously reported for decision-making strategies (Radenbach et al., 2015) and WM (Oei et al., 2006), remains unsupported by the present study. As many previous studies that reported stress effects on WM (Cornelisse et al., 2011; Luethi et al., 2009; Schoofs et al., 2013, 2008) employed small-sample between-subject designs, it could be speculated that the previously found stress effects on WM might indeed not represent intra-individual change, but instead reflect inter-individual differences in experienced past subjective stress.

Consistent with this claim, we observed that past subjective stress influenced the acute stress-induced reductions on WM task performance, reflecting an inverse relationship. Our result replicates a previous study showing that recent stress exposure predicts acute stress-induced impairments of WM (Shields et al., 2017). The observed effect is well in line with studies on both animals and humans reporting detrimental effects of chronic stress on WM performance (Evans and Schamberg, 2009; Klein and Boals, 2001; Lupien et al., 2009; Mizoguchi et al., 2000) and early life stress on cognitive functioning (Pechtel and Pizzagalli, 2011). In addition, our result closely matches studies on the influence of chronic stress on decision-making shown in animals (Dias-Ferreira et al., 2009) and humans (Radenbach et al., 2015), a process known to heavily rely on working memory (Otto et al., 2013). Here, we show that beyond exposure to recent stressful events or stressful events across one's lifespan (Radenbach et al., 2015; Shields et al., 2017), the subjective evaluation of stressful events makes individuals susceptible to hampering effects of acute stress on WM. Arguably, the subjective evaluations of earlier life events as being stressful over a prolonged state, leaves individuals more prone to the impairing effects of acute stressors on cognitive abilities (Calvo and Gutiérrez-García, 2016; Lazarus and Folkman, 1984). Although our finding was not paralleled by a significant effect in brain activation, our behavioral finding shows that levels of past subjective stress are also related to the influence of acute stress on cognitive control mechanisms, such as WM. However, the direction of the effect might be reversed: It is equally likely that vulnerability to stress-induced WM impairments is caused by the degree to which one interprets adverse life events as being stressful. Because it has been shown that trait anxiety relates to differential effects of acute stress on social/economic decision-making (Goette et al., 2015), the observed relationship between past subjective stress and acute stress-induced WM impairments might be explained by trait anxiety levels in our participants. Heightened trait anxiety might render individuals more prone to interpret life events as being stressful and allocate processing resources on threat-related mental representation after stressful situations (Calvo and Gutiérrez-García, 2016), speculatively resulting in a cognitive coping style that interferes with cognitive functioning. Taken together, our result suggests taking past subjective stress experiences into account when studying the effects of acute stress on cognitive functioning. It should be noted that our correlational approach cannot dissociate cause and effect, indicating an urgent need for further investigation and replications of longitudinal designs, specifically addressing moderating conditions of the observed effect (e.g., trait anxiety levels).

The existing literature on past stress effects has employed hair

cortisol as a biological marker of chronic stress levels. Hair cortisol is a physiological measure of allostatic load, which cannot be addressed using subjective reports of past experienced stress (Stalder et al., 2017). However, in our view, past subjective stress poses a valid way to operationalize past stress in terms of psychological stress theory (Lazarus and Folkman, 1984). Additionally, hair cortisol in humans is likely influenced by a myriad of factors other than purely stress experiences (Hayes et al., 2015; Lovallo et al., 2006), which might not have been adequately controlled for. Moreover, hair cortisol is only present in individuals with hair of a certain length (Stalder et al., 2017), rendering it an invalid approach in short-haired or bald individuals. Therefore, it was unfeasible to assess hair cortisol in our study, where we only included men.

As predicted, we saw lower brain activation in high WM load under stress in the right dlPFC. This finding replicates between-subject fMRI studies showing reduced WM activation in the right dlPFC during acute stress compared to a control condition (Oei et al., 2012; Qin et al., 2009; Van Ast et al., 2016). Our results further substantiate the critical involvement of the right dlPFC in the neural mediation of WM processes and confirm that acute stress alters neural WM processing on an intra-individual level, crucially extending the existing, mainly between-subjects, literature. The reduction of dlPFC activation under acute stress could be interpreted in the context of neural processing efficiency: Individuals might have just needed to recruit fewer neural resources to maintain the same level of task performance. Possibly in line with this, cortisol has been suggested to be a neuromodulator (Milani et al., 2016; Popoli et al., 2012), inducing changes in glutamate neurotransmission that lead to increased neural excitability in the prefrontal cortex (Hermans et al., 2014; Popoli et al., 2012). Consequently, cortisol-induced increased neural excitability might lead to lowered physiological thresholds for action potentials under stress.

The discrepancy between neural and behavioral level could be due to task difficulty. Because acute stress impairs WM performance more strongly in high WM loads (Shields et al., 2016), task demands during the 2-back WM load might have been too low to show performance impairments under acute stress. Nevertheless, it should be noted that in our study, variability of performance accuracy (d') in 2-back, both in control and stress condition, was high (Control: mean = 2.94, range = .58–6.81, standard deviation = 1.16; Stress: mean = 2.99, range = .58–5.47, standard deviation = 1.25). This variability suggests that task difficulty was adequate to avoid confounding ceiling (as observed in 0-back) or floor effects (that might have occurred during higher loads). Thus, expected changes to performance of the task during stress compared to the control condition could have been faithfully attributed to the stressor and would have reflected stress-induced changes.

The current study, like most studies on stress effects, only tested male participants to explicitly rule out the confounding effects of the menstrual cycle on stress responsivity and gender-specific stress effects (Cornelisse et al., 2011; Schoofs et al., 2013; Shields et al., 2016). However, a purely male sample renders generalization of the results to the general population impossible. Additionally, the sample was relatively young and highly educated due to the inclusion sources and criteria, making it further difficult to generalize our results to an older and educationally heterogeneous population, or even patient populations associated with reduced cognitive capacities. Future studies are needed to confirm our finding of non-significant intra-individual stress effects on WM in male and female samples with more heterogeneous educational backgrounds. Moreover, the effects of stress on cognitive control could be augmented in patient samples, rendering them more vulnerable to stressful or demanding environments. Additionally, future studies should aim to confirm the relationship of past subjective stress levels on acute stress-induced changes to WM performance and further show these effects using a longitudinal approach. Specifically, testing samples that exhibit high vs. low levels of past subjective stress could establish the longitudinal interplay of past and acute stress on WM

capacities.

5. Conclusion

In conclusion, the present study shows that past subjective stress levels increase the effects of acute stress on WM task performance, while acute stress reduces WM-related neural activation in the dlPFC. However, we did not find evidence for intra-individual effects of acute stress on WM task performance. Further, WM task performance did not scale with individual stress-induced changes of cortisol or subjective stress. Taken together, these results suggest that rather than an intra-individual effect of acute stress, higher levels of past subjective stress make individuals more susceptible to the impairing effects of acute stress on WM. Crucially, our study might be the first to provide evidence at an intra-individual level that acute stress reduces WM-related neural activation in the dlPFC. The presented results further underline the importance of the dlPFC in the neural mediation of WM (Owen et al., 2005) and the neural effects of stress on WM (Bogdanov and Schwabe, 2016; Oei et al., 2012; Qin et al., 2009; Van Ast et al., 2016). Our results suggest that measures of past subjective stress should be considered when studying acute stress effects on cognitive functioning, which could have implications for the explanation of cognitive deficits seen in stress-related psychiatric disorders, such as major depression (McEwen, 2004) and substance dependence (Koob, 2008; Koob et al., 2014).

Author contributions

ZS and FS designed the study. LL and ZS prepared the study. LL recruited and screened participants. LL and ZS performed data collection. LL, FS and ZS performed data analyses. LL, FS and ZS interpreted the results. LL drafted the paper. LL, FS and ZS read and corrected versions of the manuscript.

Conflict of interest

None.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:<https://doi.org/10.1016/j.psyneuen.2018.05.036>.

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