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Insights from a laboratory and naturalistic investigation on stress, rumination and frontal brain functioning in MDD: An fNIRS study

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ABSTRACT

Recent research has emphasized rumination as an important maintaining factor in various mental disorders. However, operationalization and therefore induction of rumination in experimental settings poses a major challenge in terms of ecological validity. As stress seems to play a key role in everyday situations eliciting rumination, we conducted two stress paradigms while assessing behavioral and neurophysiological measures.

Aiming to replicate previous findings on induced rumination by means of the Trier Social Stress Test (TSST) and comparing them to physiological (pain) stress, a clinical sample of patients with Major Depressive Disorder (MDD; n = 22) and healthy controls (HC; n = 23) was recruited. Cortical blood oxygenation was assessed during the stress paradigms using functional near-infrared spectroscopy (fNIRS). Further, we used ecological momentary assessment (EMA) of stress, rumination and mood to be able to correlate ruminative responses during induced stress and everyday rumination.

Our results showed that social stress but not physiological stress induced depressive rumination in MDD but not in HC. Further, rumination reactivity in response to social stress but not to physiological stress was significantly associated with rumination reactivity in everyday life as assessed with EMA. With respect to cortical oxygenation, MDD subjects showed hypoactivity in the Cognitive Control Network during the TSST, which mediated the differences between MDD and HC in post-stress rumination.

Our findings emphasize the role of negative social triggers in depressive rumination and validate the TSST as an induction method for depressive rumination. The results inform future developments in psychotherapeutic treatment for depressive rumination.

1. Introduction

Major Depressive Disorder (MDD) is a mental disorder with high prevalence, high burden of disease and relatively high recurrence (American Psychiatric Association, 2013; Mathers et al., 2008). One of its pathological factors that is associated with the severity, treatment response and recurrence is the cognitive-affective process of rumination (Smith and Alloy, 2009), which is why recent treatment developments try to tackle this process directly (Jacobs et al., 2016; Kuyken et al., 2016; Watkins et al., 2011). Depressive rumination is a perseverative cognitive process characterized by a highly self-referential, pessimistic and abstract style of thinking about problems, with little or no goal- and change-orientation (Teismann, 2012). Although depressive rumination is defined as a cognitive process, it is important to note that rumination

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is grounded on negative emotions of an ongoing internal conflict. The process of rumination is a rather common phenomenon of thinking in humans; however, MDD subjects ruminate more often and for longer periods of time, with lower controllability (Rosenbaum et al., 2020). It is hypothesized that rumination has a maintaining effect on negative emotions, as the mental conflict that causes negative emotions is upheld. Indeed, patients often report that even more memories of negatively loaded past events are activated through rumination. First evidence for the maladaptive role of rumination in response to stress comes from two studies using ecological momentary assessments (EMA) in students (Connolly and Alloy, 2017) and subjects with MDD and generalized anxiety disorder (Ruscio et al., 2015). These studies highlight that rumination after stressful life events predicts elevated levels of negative affect and symptoms at later time points. Previous studies have shown the reciprocity of stress and rumination, in a way that stress induces depressive rumination on the one hand (Gianferante et al., 2014; Hilt et al., 2015; Shull et al., 2016) and that the stress response itself is influenced by depressive rumination on the other hand (Ottaviani et al., 2016). In a previous study, we investigated an adapted version of the Trier Social Stress Test (TSST; Kirschbaum et al., 1993; Rosenbaum et al., 2018a) in high and low habitual ruminators with additional measurements of cortical oxygenation by means of functional near-infrared spectroscopy (fNIRS) (Naseer and Hong, 2015; Satomura et al., 2019; Scholkmann et al., 2014). We replicated the findings of previous studies on the induction of rumination using the TSST and could further show that during the TSST high trait ruminators show reduced cortical activity in the Cognitive Control Network (CCN), a cortical network of mostly fronto-parietal regions involved in the implementation of cognitive control in various contexts (Breukelaar et al., 2016; Cole and Schneider, 2007; Rosenbaum et al., 2016). This decrease mediated the group differences between high and low trait ruminators in post-stress rumination and negative affect (Rosenbaum et al, 2018b, 2018c).

While these results establish the TSST's ability to induce rumination, two points remain unclear. They do not show that the induced rumination, especially in patients with MDD, is specific to social stress, nor do they show that laboratory-induced rumination is comparable to everyday rumination. Evidence that depressive rumination is specific to social stressors, combined with a validated method to induce it in controlled circumstances, could inform the development of new psychotherapeutic treatments.

The current study investigates the following three research questions: Can the previous findings on induced rumination by means of the TSST be replicated in a clinical sample of MDD patients? Are the behavioral and neural effects specific to primary psychosocial stress in comparison to physiological (pain) stress? Are the behavioral parameters as assessed with the TSST related to everyday rumination gathered with EMA? To answer these questions 22 subjects with MDD and 23 healthy controls (HC) completed an evaluation panel consisting of the TSST, an adapted version of the Social Evaluated Cold Pressor Test (SECPT) to induce physiological (pain) stress, and a two-week EMA on stress, rumination and mood. During the TSST and SECPT cortical blood oxygenation was measured by means of fNIRS in areas of the CCN.

We hypothesized that the TSST would induce elevated negative affect and state rumination in general but especially in the MDD group. In contrast, we expected that the SECPT would not influence state rumination but only negative affect. In comparison to the SECPT, the conducted tasks during the TSST include social critical situations such as a job interview and an arithmetic task, which should be more strongly related to conflict-laden cognitive schemata in MDD patients than a physiological stress induction. Further, we expected that the TSST stress and rumination reactivity would be more strongly related to EMA measures of every-day stress and rumination than SECPT measures. Finally, in line with the rich literature on neural correlates of psychological and physiological stress inductions (Kogler et al., 2015), we expected the TSST to increase activity in the CCN and the SECPT to increase activity in the IFG. With respect to differences between the groups, we expected that the MDD group would show reduced activity in prefrontal CCN regions in comparison to the HC group and that this hypoactivation would mediate the relation between group membership and post-stress rumination. Finally, we explored in how far state rumination is associated with prefrontal activity in both groups.

2. Materials and methods

Participants. A total of 55 participants were recruited (see supplementary Fig.9), seven of which withdrew from the study before the first measurement date; two participants were excluded as they either fainted during the SECPT ($n = 1$) or due to excessive stress associated with the study ($n = 1$). The final sample included 22 patients diagnosed with MDD and 23 HC. Both groups did not differ in age or distribution of sex (see Table 1). Diagnoses in the MDD group included recurrent MDD ($n = 15$) and first episode MDD ($n = 7$). Comorbid diagnoses included somatic symptom disorder ($n = 2$), anxiety disorders ($n = 2$) and personality disorders ($n = 2$). 60% of the patients were treated with psychotherapy and 58% were treated with antidepressant medication (see Table 1). All participants completed the TSST and SECPT separately on two different days with random assignments of order and the completion of EMA in the time between the measurements. On average, the stress paradigms were assessed with two weeks between the appointments.

2.1. Procedures

TSST. We used the TSST paradigm as described in our previous publications (Rosenbaum et al, 2018a, 2018b, 2018c). Prior to a 7-min resting-state measurement, questionnaires and an initial stress rating on a Visual Analogue Scale (VAS, 0–100%) were completed. Following the resting-state measurement, state rumination during the measurement was assessed and a first salivary sample was collected. Then, participants completed two control tasks and a stress rating after each task. The first task consisted of six trials reading numbers for 40 s, followed by a 20 s pause. In the second control task with analogue time course, they had to subtract elements in steps of 13 given different starting points without time pressure or social stress. Then, two experimenters wearing white coats and remaining unresponsive to social signals entered the room, taking a seat and instructing the participant to prepare for a 5-min job interview talking about their personal strengths and qualifications. Subjects were instructed that they would be videotaped for later analysis of their behavior. The interview was followed by an arithmetic task as in the previous control task, but with different starting points and the instruction to be as fast and as correct as possible. Further, participants

Table 1
Demographic and basic variables of the depressed patients (MDD) and healthy controls (HC). BDI-II=Beck Depression Inventory II (Kühner et al., 2007), RRS = Rumination Response Scale (Nolen-Hoeksema, 1991; Treynor et al., 2003), LSAS = Liebowitz Social Anxiety Scale (Liebowitz, 1987).

Variable	MDD ($n = 22$)		HC ($n = 23$)		t/χ^2	p
	M	SD	M	SD		
Age in years	27.14	6.15	25.35	5.75	$t_{(43)}<1$	>.1
Percent of female participants	77%		78%		$X^2_{(1)} = .01$	>.1
BDI-II	24.14	11.85	2.13	1.96	$t_{(43)} = 8.59$	<.001
RRS	2.59	0.50	1.73	0.39	$t_{(43)} = 6.41$	<.001
LSAS	2.63	1.09	1.02	0.65	$t_{(43)} = 6.03$	<.001
Psychotherapy	60%		0%		$X^2_{(1)} = 19.10$	<.001
Antidepressant medication	54%		0%		$X^2_{(1)} = 17.11$	<.001

had to hold eye contact with one of the experimenters. In case of an error, participants had to start all over again. After the last pause, the experimenters turned off the camera and left the room without saying a word. Then, participants gave a stress rating and salivary sample and a second 7-min resting-state measurement was performed. Afterwards, state rumination was assessed with qualitative and quantitative measures. Further, participants rated their stress and gave salivary samples every 15 min for four times (see Fig. 1 & Fig. 2).

SECPT. The original paradigm of the SECPT (Schwabe et al., 2008) was adapted as follows: Prior to a 7-min resting-state measurement, several questionnaires and an initial stress rating were assessed. Then, an experimenter wearing a white coat entered the room, remaining unresponsive to social signals of the participants. He instructed the participants to immerse their right hand into either cold (0–2 °C) or warm water (18–20 °C) and informed them that they would be videotaped to later analyze their behavior. During cold trials, participants had to hold eye contact with the experimenter. The order of cold and warm trials was pseudo-randomized so that no more than two trials of the same type followed each other. We used this pseudo randomization to increase pain-related stress, as the feeling of pain decreased after more than two trials due to numbness. At the beginning of each trial, current pain and stress levels were rated, followed by the announcement of the following trial. After the 40-s immersion, participants were asked again to rate their pain and stress level during the trial. In sum, the stress induction consisted of eight cold and eight warm trials. To ensure standardized experimental conditions, we used a special apparatus, with a water pump, in the cold water bucket. After the last trial, the experimenter turned off the camera and left the room without saying a word. Then, the participants rated their subjective stress on the VAS and a second 7-min resting-state measurement followed. Afterwards, participants rated their stress every 15 min for four times.

EMA. To assess rumination on a day-to-day basis, participants completed a questionnaire twice a day for a total of two weeks using the PsyAssesor researcher edition V2, 2019 (Machine Learning Solutions, Luxembourg). First, participants rated their subjective stress regarding the last 5 h and in how far this stress was caused by a specific event on a slider (0% = not at all; 100% = very much), with the opportunity to report events in a free text afterwards. Further, it was assessed whether regulation strategies were used to cope and how effective the coping was (Jerusalem and Schwarzer, 2003). Then, participants rated their agreement concerning three items assessing self-efficacy. To assess rumination-based thinking-styles, we selected items of the Perseverative Cognitions Questionnaire (PCQ) and items of the Ruminative Response Scale (Nolen-Hoeksema, 1991; Ehring et al., 2011; Nolen-Hoeksema and Morrow, 1991; Szkodny and Newman, 2019). Lastly, participants rated their mood and arousal on a circumplex item. Data of one patient of the final sample was excluded as only two data entries were made in the momentary assessment due to technical problems. On average 25 EMA measurements (28 were maximally possible) were recorded per participant.

Cortisol. Saliva was collected using salivettes (Sarsted AG & Co, REF 51.1534.500) and stored at −20 °C. Afterwards, salivettes were centrifuged for 2 min at 1000 g before analysis was performed with enzyme immunoassay (IBL International, Cortisol ELISA, REF RE52611) according to the manufacturer's instructions. Measurements took place during the whole day for reasons of scheduling. As individual cortisol levels are influenced by circadian rhythms, we regressed the effect of daytime out of the cortisol data and used the corrected data.

Heart rate. Heart rate was assessed with a one channel electrocardiogram. For this procedure, two standard Ag/AgCl ring electrodes of 8 mm diameter were attached using a conductive EEG paste to the disinfected skin above the right collarbone and below the left costal arch. Another ring electrode was placed on the neck as reference. The signal was recorded using the BrainAmp ExG amplifier and Brain Vision Recorder software (Brain Products, Munich, Germany). The sampling rate of the signal was 1000 Hz. Data was preprocessed and analyzed using Brain Vision Analyzer 2.1 and MATLAB 2017a. Preprocessing included band-pass filtering (1–45 Hz). The data of one subject was highly contaminated by power line artifacts. Hence, an additional 50 Hz notch filter was applied. Thereafter, we calculated the mean interval between subsequent R-peaks for each recorded condition in beats per minute.

fNIRS. We used the same probeset placement as in Rosenbaum et al. (2018a,b,c) with two frontal and one parietal probeset covering the following regions of interest (ROI): bilateral dorsolateral prefrontal cortex (DLPFC), bilateral inferior frontal gyrus (IFG) and superior parietal lobule (SPL). Optodes (18 emitter, 15 receiver) were inserted into electrode caps (easycap) with 3 cm inter-optode distance and adjusted to electrode positions Fpz and Cz according to the 10-20-system (Jasper, 1958). Optode holders were enforced by sponge rings to gain more

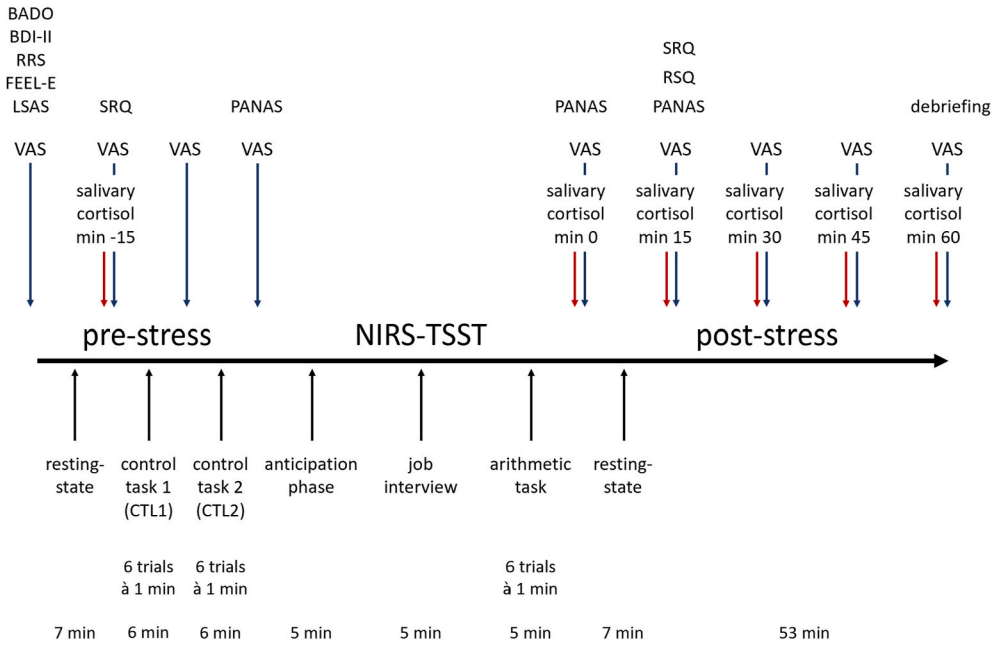

Fig. 1. Time course of the TSST. BADO = Social Demographic Data, BDI = Beck Depression Inventory II, RRS = Rumination Response Scale, FEEL-E = Questionnaire to assess emotion regulation strategies, LSAS = Liebowitz Social Anxiety Scale, PANAS = Positive and Negative Affect Schedule, VAS = Visual Analogue Scale assessing the subjective stress ratings, SRQ = state rumination questionnaire, RSQ = resting-state questionnaire, CTL1 = Control Task 1/ reading numbers, CTL2 = Control Task 2/ calculations without social stress. BADO, BDI and RRS were only assessed at the first measurement date, FEEL-E and LSAS at the second measurement date. Participants got debriefed only after completion of both measurements.

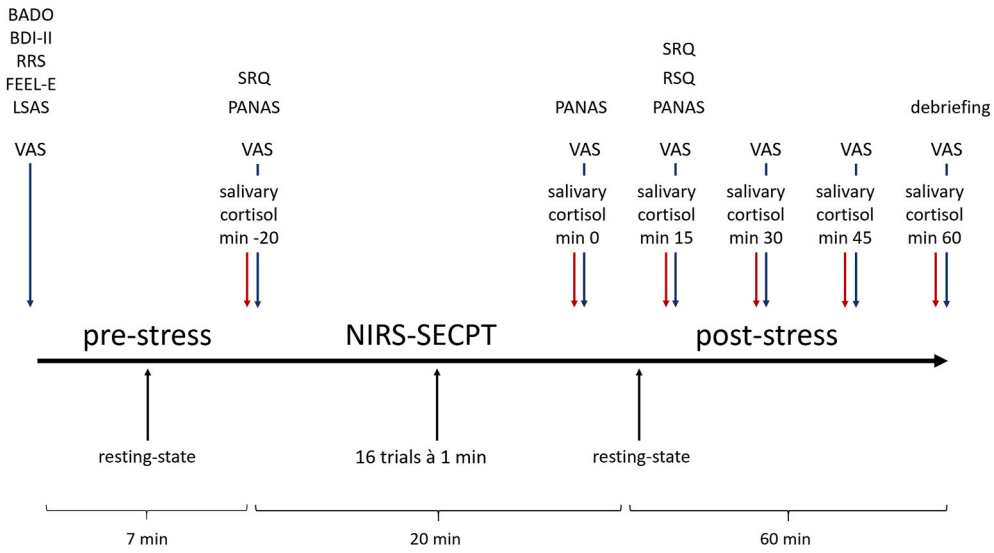

Fig. 2. Time course of the SECPT. BADO = Social Demographic Data, BDI = Beck Depression Inventory II, RRS = Rumination Response Scale, FEEL-E = Questionnaire to assess emotion regulation strategies, LSAS = Liebowitz Social Anxiety Scale, PANAS = Positive and Negative Affect Schedule, VAS = Visual Analogue Scale assessing the subjective stress ratings, SRQ = state rumination questionnaire, RSQ = resting-state questionnaire. BADO, BDI and RRS were only assessed at the first measurement date, FEEL-E and LSAS at the second measurement date. Participants got debriefed only after completion of both measurements.

stability. We used a continuous-wave, multi-channel NIRS system (ETG-4000 Optical Topography System; Hitachi Medical Co., Japan) with a temporal resolution of 10 Hz. The system uses a semiconductor laser and avalanche diodes at two wavelengths (695±20 and 830±20 nm) with 2.0 ± 0.4 mW for each wavelength at each optode. fNIRS data was preprocessed with MATLAB 2017a. Oxygenated (O2Hb) and deoxygenated blood levels (HHb) were computed by means of a modified Beer-Lambert Law. In total, 46 channels were assessed. From these, 3 channels were selected in each case to assess the DLPFC and IFG and to measure the SPL (see supplementary figure 5). Preprocessing of the data included: Correction for high amplitude movement artifacts by the TDDR correction (Fishburn et al., 2019), bandpass filtering (0.01–0.1 Hz), correlation-based signal improvement of O2Hb with HHb data (Cui et al., 2010), interpolation of single artefact-laden channels after visual inspection, reduction of the global signal by a PCA-based gaussian kernel filter (Zhang et al., 2016) and z-standardization of the signal. Note that in the following O2Hb data refers to the correlation-based improved O2Hb signal. Data was then averaged for each condition with a 5 s baseline correction for the 40 s time window of task completion within each ROI. As HHb data often seems to be less sensitive but more robust than O2Hb data, we performed an additional reanalysis of the data with HHb levels (in this case, the correlation-based signal improvement was not performed in the preprocessing). We report the additional information on HHb data in parenthesis but interpret mainly O2Hb. Note that the main results of our analysis were consistent between O2Hb and HHb data; therefore, HHb data is not outlined in the text in detail to reduce redundancy.

2.2. Data analysis

We conducted repeated measurement ANOVAs for the analysis of behavioral data (stress ratings, state rumination, negative affect) during the TSST and SECPT with group (MDD vs. HC) as between-subjects factor, and experimental condition as within-subjects factor. For manipulation checks on whether the stress induction was successful, we additionally analyzed salivary cortisol and heart rate activity during the paradigms. fNIRS data during the paradigms was analyzed with repeated measurement ANOVAs with the between-subjects factor group (MDD vs. HC), and the experimental condition as well as ROI (bilateral IFG, bilateral DLPFC, SPL) as within-subjects factors.

We validated the behavioral effects of the TSST on the induction of state rumination with daily rumination as assessed with ecological momentary assessment. To this end, we correlated mean pre- and post-stress rumination as well as changes in rumination (post-pre) with EMA measurements of rumination via Pearson correlations. With respect to EMA measurements, we investigated mean rumination scores as well as standard deviations of individual EMA rumination measurements. We used standard deviations per subject as measurements of individual reactivity in daily rumination: Subjects with higher daily rumination fluctuation should show higher standard deviations in daily rumination. Further, independent raters assigned the participants' open answer format on the reason of their stress experience to 6 categories: no answer, social interaction (e.g. argument), work (e.g. deadlines), private obligation (e.g. appointments), daily hassles (e.g. organization of the day), personal reasons/internal reasons (e.g. thoughts) and political events/daily events.

Finally, we investigated whether pre- and post-stress rumination during the TSST could be predicted by O2Hb levels during the TSST (control-task 1 and arithmetic task) in a multilevel model. To this end, we conducted multilevel models with pre- and post-stress state rumination as outcomes, group (MDD vs. HC), time (pre- vs. post-stress) and O2Hb levels (pre-stress control task 1, post-stress arithmetic task) in the different ROI and random intercepts. In our basic model, we aimed to replicate the results of the repeated measurement ANOVA, showing the effect of group and time on state rumination. Secondary, we used the O2Hb data as predictors for state rumination. In the models, state rumination (pre vs. post) and O2Hb levels were treated as continuous variables: pre-stress state rumination was predicted by O2Hb levels during TSST control task 1 and post-stress rumination was regressed on O2Hb levels during the TSST arithmetic task. In this way, we checked for baseline associations between state rumination and cortical oxygenation as well as stress-induced associations. Finally, we included group as well O2Hb data in the models. In case of significant effects of O2Hb data, we checked for mediation effects by Sobels z-test. Reported effect sizes represent Cohen's d, *dz*, and partial eta^2. Effect size d for repeated measures was computed as described in Dunlap et al. (1996) as $d = t_c\left[\frac{2(1-r)}{n}\right]^{\frac{1}{2}}$ (Dunlap et al., 1996) and $dz = \frac{t}{\sqrt{n}}$ (Lakens, 2013).

A sensitivity power analysis using G*Power 3.1.9.2 showed that we could detect effects up to f = .13 for state rumination ($\alpha = 0.05$, 1-β = 0.80, N = 45, groups = 2, measurements = 2, r = 0.8, $\varepsilon = 1$), f = 0.12 for a within-between subject interaction in the fNIRS-TSST ($\alpha = 0.05$, 1-β = 0.80, N = 45, groups = 2, measurements = 15, r = 0.5, $\varepsilon = 1$), f = 0.13 for fNIRS-SECPT ($\alpha = 0.05$, 1-β = 0.80, N = 45, groups = 2, measurements = 10, r = 0.5, $\varepsilon = 1$) and correlational associations up to $|\rho|$ = 0.39 ($\alpha = 0.05$, 1-β = 0.80, N = 45).

Statistical analysis was performed using IBM SPSS Statistics version 27 and R (R Core Team, 2013) using the packages *lme4* (Bates et al., 2015), *lmerTest* (Kuznetsova et al., 2017) and *ggplot2* (Wickham, 2009).

3. Results

Peripheral physiological measures. Analysis of heart rate measures (see Fig. 3) during the TSST revealed a significant main effect of condition ($F(6, 240) = 65.695$, $p < .001$, $\eta_p^2 = 0.62$). Post-hoc analysis showed a significant variation in condition as indicated by a quadratic ($F(1, 40) = 150.058$, $p < .001$, $\eta_p^2 = 0.79$), cubic ($F(1, 40) = 31.099$, $p < .001$, $\eta_p^2 = 0.43$), 4th order ($F(1, 40) = 107.329$, $p < .001$, $\eta_p^2 = 0.72$), and 6th order contrast ($F(1, 40) = 46.808$, $p < .001$, $\eta_p^2 = 0.54$) (see Fig. 3). To further describe this effect, we performed additional repeated *t*-tests and corrected those by the Benjamini-Hochberg procedure: heart rate increased from rest 1 to CTL1 ($t(43) = 11.858$, $p < .001$, $dz = 1.78$, $d = 0.94$), from CTL1 to CTL2 ($t(43) = 2.360$, $p < .05$, $dz = 0.36$, $d = 0.15$), decreased from CTL2 to anticipation ($t(43) = 2.969$, $p < .01$, $dz = 0.44$, $d = 0.34$), increased from anticipation to the TSST interview ($t(42) = 7.841$, $p < .001$, $dz = 1.2$, $d = 0.68$) and decreased again from TSST arithmetic task to rest 2 ($t(42) = 12.832$, $p < .001$, $dz = 1.97$, $d = 1.39$).

The analysis of heart rate during the SECPT indicated a significant main effect of condition (rest 1 vs. warm water vs. cold water vs. rest 2) ($F(3, 123) = 6.475$, $p < .001$, $\eta_p^2 = 0.14$) and group ($F(1, 41) = 9.028$, $p < .01$, $\eta_p^2 = 0.18$). The main effect of group was characterized by generally increased heart rates in the MDD group in comparison to the HC group. The main effect of condition was characterized by a quadratic relationship ($F(1, 41) = 83.512$, $p < .001$, $\eta_p^2 = 0.67$) displaying an increase in heart rate from rest 1 to the SECPT conditions (cold and warm water) and a decrease at rest 2 (see Fig. 3).

The analysis of salivary cortisol samples revealed significant increases in cortisol due to the TSST ($F(5, 215) = 28.332$, $p < .001$, $\eta_p^2 = 0.40$) as well as the SECPT ($F(5, 215) = 13.335$, $p < .001$, $\eta_p^2 = 0.24$). Cortisol levels in response to both paradigms showed a peak at 15 min post stress and following declines in cortisol concentrations (see Fig. 3 A.1 and A.2). No differences were found between the groups. Following the TSST, cortisol levels increased significantly from baseline to 0 min ($t(44) = 4.292$, $p < .001$, $dz = 0.64$, $d = 0.42$), 15 min ($t(44) = 6.774$, $p < .001$, $dz = 1.01$, $d = 0.73$), 30 min ($t(44) = 5.926$, $p < .001$, $dz = 0.88$, $d = 0.44$), and 45 min ($t(44) = 3.921$, $p < .001$, $dz = 0.58$, $d = 0.18$). With respect to the SECPT, cortisol levels were increased at 0 min ($t(44) = 4.449$, $p < .001$, $dz = 0.66$, $d = 0.56$), 15 min ($t(44) = 4.216$, $p < .001$, $dz = 0.63$, $d = 0.56$), 30 min ($t(44) = 3.643$, $p < .001$, $dz = 0.54$, $d = 0.41$), 45 min ($t(44) = 3.884$, $p < .001$, $dz = 0.58$, $d = 0.32$) and 60 min ($t(44) = 2.825$, $p < .01$, $dz = 0.42$, $d = 0.20$). During the TSST 56% of the subjects had an increase higher than 2.5 nm/l and 66% had an increase higher than 1.25 nm/l. In contrast, during the SECPT 38% of the sample had a cortisol increase higher than 2.5 nm/l and 51% higher than 1.25 nm/l and can thus be considered responders (Miller et al., 2013).

3.1. Behavioral

Subjective stress. Analysis of subjectively rated stress during the TSST showed a main effect of group ($F(1, 43) = 19.562$, $p < .001$, $\eta_p^2 = 0.31$) reflecting higher overall stress in the MDD group as compared to the HC (see Fig. 4). A significant main effect of condition was observed ($F(8, 344) = 58.524$, $p < .001$, $\eta_p^2 = 0.58$) (see Fig. 4). Post-hoc analyses revealed increases in subjective stress from CTL1 to CTL2 ($t(44) = 6.281$, $p < .001$, $dz = 0.94$, $d = 0.70$), from CTL2 to post TSST ($t(44) = 7.358$, $p < .001$, $dz = 1.10$, $d = 1.02$) and decreases for all follow-up measures (all $p < .05$, $dz > 0.42$, $d > 0.17$).

In the same way, we observed a main effect of group ($F(1, 42) = 31.704$, $p < .001$, $\eta_p^2 = 0.42$) and condition ($F(6, 258) = 20.106$, $p < .001$, $\eta_p^2 = 0.32$) during the SECPT. MDD subjects displayed a higher general subjective stress level than HC. Post-hoc analyses revealed increases in subjective stress from post rest 1 to post-SECPT ($t(44) = 5.022$, $p < .001$, $dz = 0.74$, $d = 1.00$), decreases from post SECPT to 15 min ($t(44) = 6.015$, $p < .001$, $dz = 0.89$, $d = 0.70$) and from 15 min post SECPT to 30 min post SECPT ($t(44) = 3.630$, $p < .001$, $dz = 0.54$, $d = 0.56$).

Negative affect. In line with the analysis of subjective stress, we observed a main effect of time ($F(2, 86) = 24.020$, $p < .001$, $\eta_p^2 = 0.36$) and group ($F(1, 43) = 31.323$, $p < .001$, $\eta_p^2 = 0.42$), with MDD patients showing higher negative affect than HC. Disentangling the significant time effect, negative affect increased throughout the TSST ($t(44) = 5.975$, $p < .001$, $dz = 0.89$, $d = 0.60$) and decreased again 60 min after completion of the TSST ($t(44) = 5.750$, $p < .001$, $dz = 0.85$, $d = 0.46$). In contrast, within the SECPT no significant changes in negative affect were observed, but a significant main effect of group emerged ($F(1, 42) = 53.569$, $p < .001$, $\eta_p^2 = 0.56$) displaying higher negative affect in the MDD group in comparison to the HC group (see Fig. 5 A).

State rumination. With respect to state rumination, we observed, as expected, a main effect of group ($F(1, 43) = 68.009$, $p < .001$, $\eta_p^2 = 0.61$), time ($F(1, 43) = 27.08$, $p < .001$, $\eta_p^2 = 0.39$) and an interaction of group by time ($F(1, 43) = 15.529$, $p < .001$, $\eta_p^2 = 0.27$). State rumination

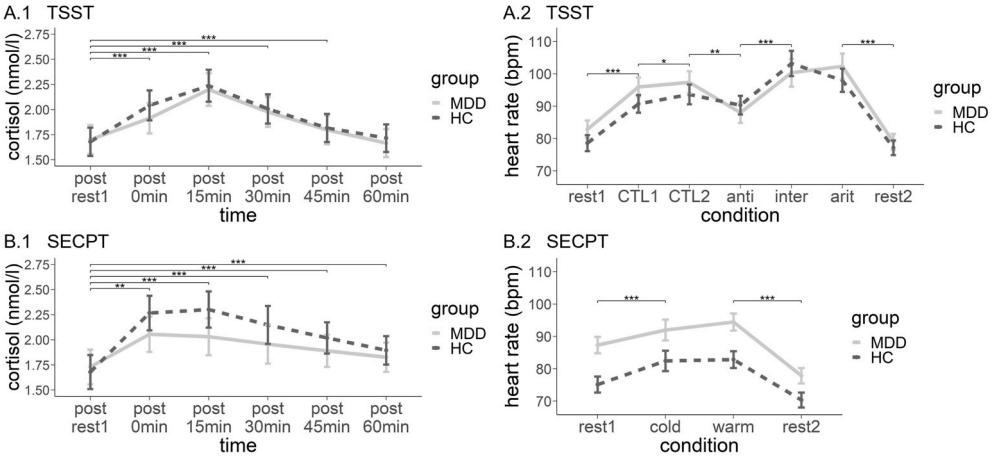

Fig. 3. Cortisol and heart rate in response to the TSST and SECPT. Heart rate in beats per minute (bpm) dependent on condition and group in the TSST (A.1/2) and the SECPT (B.1/2). Error bars indicate standard errors. $^*p < .05$, $^{**}p < .01$, $^{***}p < .001$. CTL = control task, anti = anticipation phase, inter = job interview, arit = arithmetic task, rest = resting state.

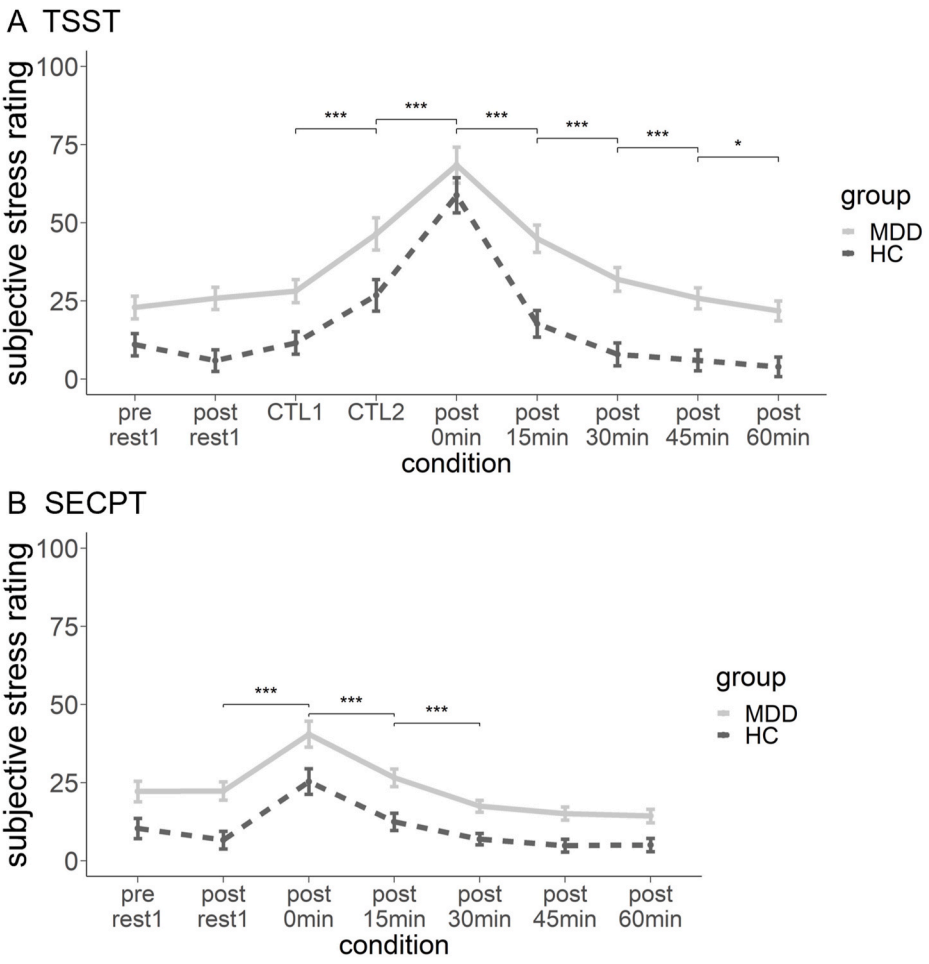

Fig. 4. Subjective stress ratings assessed with the Visual Analogue Scale (VAS) dependent on condition and group in the TSST (A) and SECPT (B). Error bars indicate standard errors. *$p < .05$, **$p < .01$,***$p < .001$, comparisons in both graphs are related to differences between time points.

was higher in the MDD group than in the HC group, and increased from pre-to post-TSST more strongly in the MDD group than in the HC group ($t(30.605) = 3.887$, $p < .001$, $d = 1.17$). When analyzed separately for the groups, stress-induced increases in rumination were only significant in the MDD ($t(21) = 5.023$, $p < .001$, $d = 0.62$) but not the HC group ($t(22) = 1.417$, $p > .1$, $d = 0.31$). In contrast, during the SECPT no effect of state rumination was observed except for a main effect of group ($F(1, 42) = 58.431$, $p < .001$, $\eta_p^2 = 0.57$) (see Fig. 5 B).

3.2. EMA data group differences and validation of TSST-associated rumination with daily reported rumination

Both groups differed significantly in the EMA assessed variables ($F(6, 37) = 17.914$, Wilk's $\lambda = 0.256$, $p < .001$, $\eta_p^2 = 0.74$). Post-hoc analysis indicated that the MDD group showed higher daily reported stress ($F(1,42) = 16.727$, $p < .001$, $\eta_p^2 = 0.29$), lower self-efficacy ($F(1,42) = 51.749$, $p < .001$, $\eta_p^2 = 0.55$), higher rumination ($F(1,42) = 83.519$, $p < .001$, $\eta_p^2 = 0.67$) and higher negative affect ($F(1, 42) = 42.348$, $p < .001$, $\eta_p^2 = 0.52$). High levels of daily rumination were associated with high stress ($r = 0.67$, $p < .001$), reduced self-efficacy with respect to coping with the stressful event ($r = -0.70$, $p < .001$) and increased negative affect ($r = -0.78$, $p < .001$) (see supplementary table 2). With respect to the open answer format for stress eliciting events, the MDD group reported more often stressful events ($U = 390.5$, $Z = -3.123$, $p < .01$), more often social interactions as stress triggers ($U = 125.5$, $Z = -2.907$, $p < .01$) and more often personal/internal triggers ($U = 159.5$, $Z = -2.125$, $p < .05$) (see Fig. 6).

Finally, we validated the induction of rumination during the experimental designs with daily rumination reactions as assessed with EMA. We correlated mean rumination before and after as well as increases in state rumination through the experimental designs with mean reported ruminations in EMA as well as standard deviations in daily rumination as a measure of rumination reactivity. Our results showed that state rumination during the TSST and SECPT were highly correlated with the average daily ruminations. However, most importantly, TSST-induced rumination correlated strongly ($r(44) = 0.55$, $p < .001$) with the within-subject standard deviation of daily ruminations, showing that the reactivity in rumination during the TSST is strongly associated with daily reactivity in rumination. Note that this correlation remained significant when the data was separated according to group in the MDD group ($r(21) = 0.48$, $p < .05$) but not in the HC group ($r(22) = -0.07$, $p > .1$), and both correlation coefficients differed marginally significantly ($z = 1.851$, $p < .1$) (Eid et al., 2017), indicating that the correlation of TSST-related rumination increase and everyday rumination reactivity in the whole sample was driven by the MDD group. No such correlation was found for rumination increases through the SECPT and daily rumination emphasizing the discriminative validity (see Table 2/Fig. 7).

fNIRS. fNIRS data of the TSST was analyzed with a mixed repeated-measurements ANOVA with the within-subject factors condition (control task 1, control task 2, arithmetic task) and ROI (left IFG, right IFG, left DLPFC, right DLPFC, SPL) and the between-subject factor group (MDD vs. HC). Results revealed a significant main effect of group (O2Hb: $F(1, 43) = 4.878$, $p < .05$, $\eta_p^2 = 0.10$; HHb: $F(1, 43) = 4.407$, $p < .05$, η_p^2

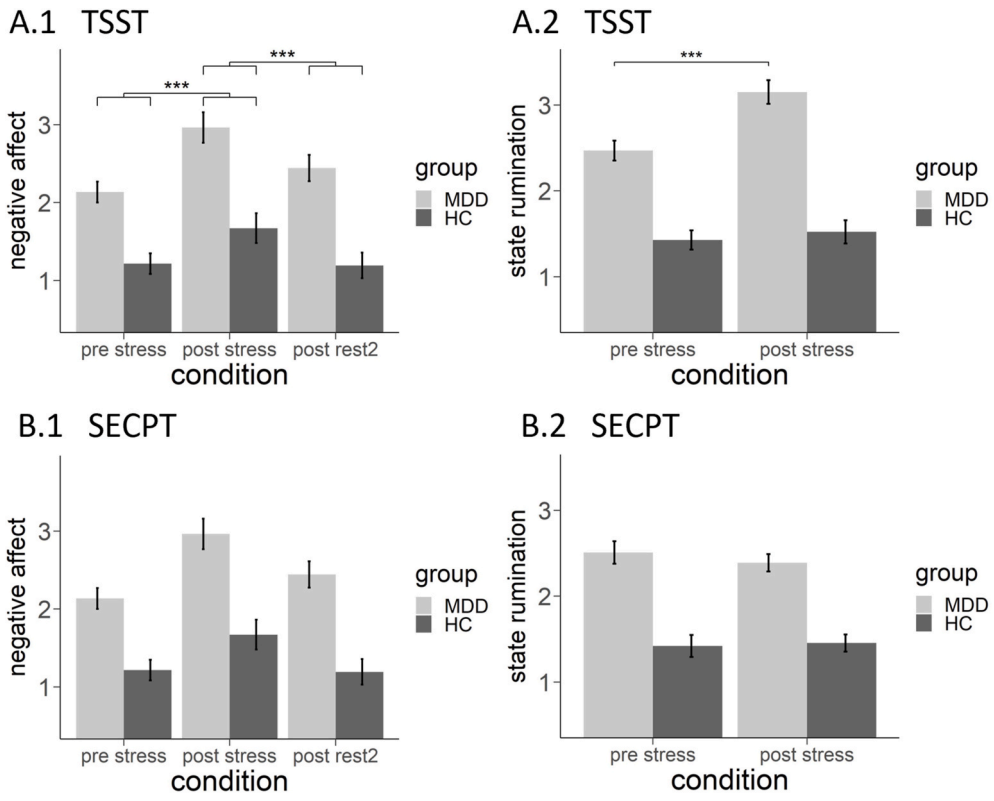

Fig. 5. Negative affect assessed by the PANAS dependent on condition and group in the TSST (A.1) and SECPT (B.1). State rumination dependent on condition and group in the TSST (A.2) and SECPT (B.2). Error bars indicate standard errors. *$p < .05$, **$p < .01$,***$p < .001$.

Fig. 6. Boxplots indicating the percentage of triggers of rumination over the two weeks of EMA assessment dependent on group (MDD = depressed patients, HC = healthy controls). Note that only the three triggers significantly differing in their occurrence between the groups were depicted. No events = average number of reporting no stressful event per subject, interactions = average number of social interactions that led to stress per subject, internal = average number of internal events (e.g. thoughts, emotions) that led to the experience of stress per subject.

= 0.09) displaying overall reduced O2Hb-levels in the CCN in the MDD group (see Fig. 8). Further, we found main effects of ROI (O2Hb: $F(4, 172) = 4.406$, $p < .01$, $\eta_p^2 = 0.09$; HHb: $F(4, 172) = 1.86$, $p > .1$, $\eta_p^2 = 0.04$) and condition (O2Hb: $F(2, 86) = 6.350$, $p < .01$, $\eta_p^2 = 0.13$; HHb: $F(2, 86) = 8.227$, $p < .001$, $\eta_p^2 = 0.16$). As expected, the main effect of condition was characterized by a linear increase from control task 1 to control task 2 and the TSST arithmetic challenge (O2Hb: $F(1, 43) = 10.324$, $p < .01$, $\eta_p^2 = 0.19$; HHb: $F(1, 43) = 13.993$, $p < .001$, $\eta_p^2 = 0.25$) (see supplementary figure 1). Note that post-hoc tests between different ROIs were not performed because of potential confounds of absolute differences due to different optical path lengths.

Cortical oxygenation during the SECPT was analyzed with a mixed

Table 2
Correlations between mean rumination and rumination increase (post-stress – pre-stress) during the TSST and SECPT and individual average and standard deviations of daily reported rumination (EMA data). *$p < .05$, **$p < .01$,***$p < .001$.

	TSST pre	TSST post	TSST increase	SECPT pre	SECPT post	SECPT increase	EMA *Mean*	EMA *SD*
TSST pre	1							
TSST post	.84***	1						
TSST increase	.22	.71***	1					
SECPT pre	.60***	.70***	.49***	1				
SECPT post	.60***	.76***	.58***	.65***	1			
SECPT increase	-.13	-.11	-.03	-.61***	.21	1		
EMA *Mean*	.81***	.80***	**.38***	.73***	.74***	**-.16**	1	
EMA *SD*	.52**	.69***	**.55****	.59***	.64***	**-.10**	.77***	1

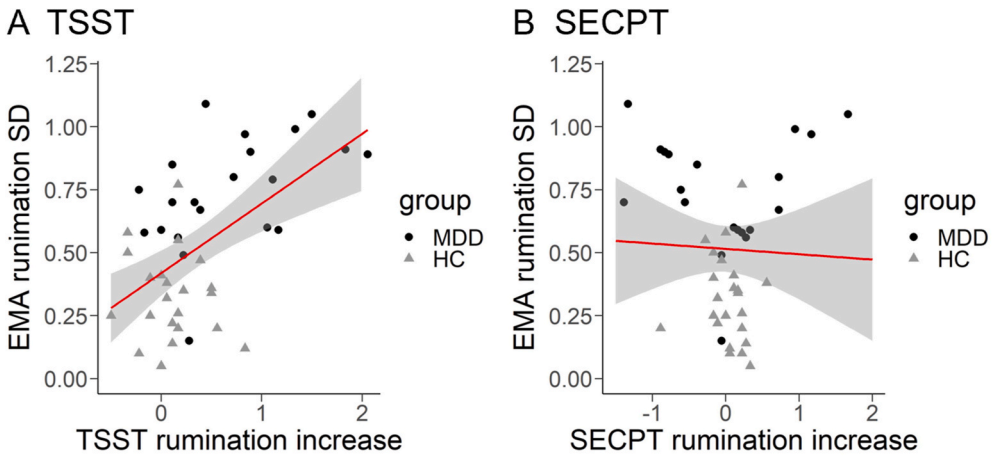

Fig. 7. Correlation of the TSST- (A) and SECPT- (B) related increases in state rumination and daily rumination reactivity. Confidence bands indicate standard errors.

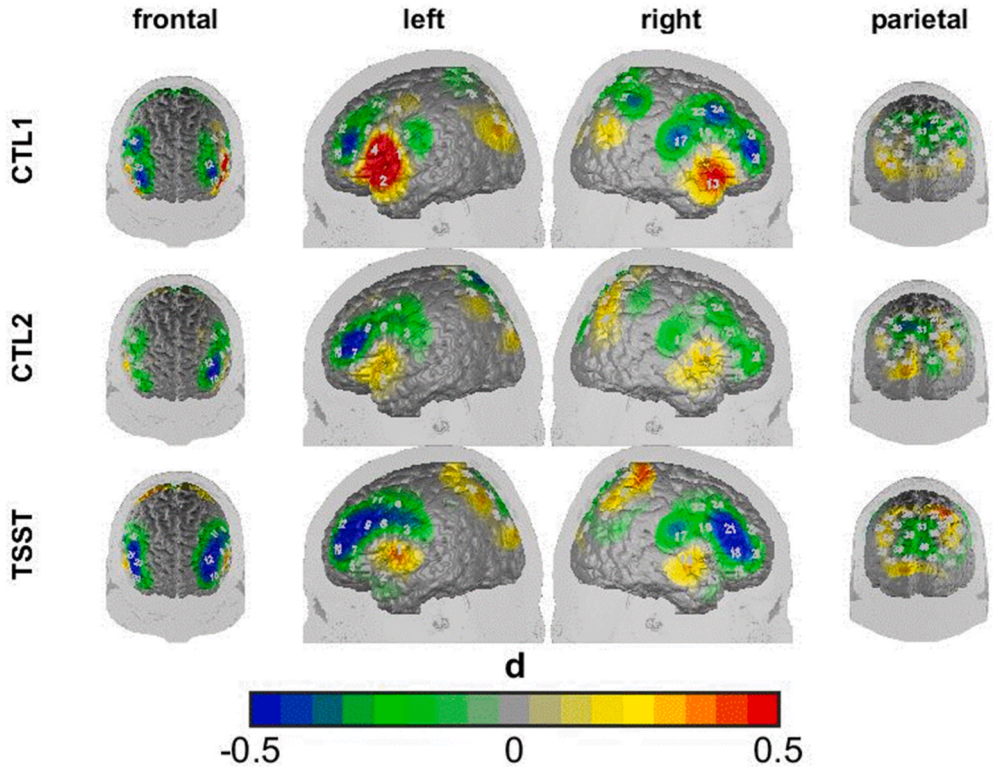

Fig. 8. Differences between MDD and HC during control task 1 (CTL1 = reading numbers), control task 2 (CTL2 = performing calculations without social stress) and TSST (arithmetic challenge). Cool colors indicate reduced O2Hb-levels in the MDD group as compared to the HC group; warm colors vice versa. Differences are depicted in Cohen's *d*. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

repeated-measurement ANOVA with the between-subject factor group (MDD vs. HC) and the within-subject factors phase (anticipation vs. hand immersion), condition (cold vs. warm water) and ROI. We observed a significant main effect of phase (O2Hb: $F(1, 41) = 7.618$, $p < .01$, $\eta_p^2 = 0.16$; HHb: $F(1, 41) = 4.414$, $p < .05$, $\eta_p^2 = 0.10$) and ROI (O2Hb: $F(4, 164) = 16.170$, $p < .001$, $\eta_p^2 = 0.28$; HHb: $F(4, 164) = 3.824$, $p < .01$, $\eta_p^2 = 0.09$), as well as an interaction of ROI by condition (O2Hb: $F(4, 164) = 3.848$, $p < .01$, $\eta_p^2 = 0.09$; HHb: $F(4, 164) = 3.197$, $p < .05$, $\eta_p^2 = 0.07$), an interaction of phase by condition (O2Hb: $F(1, 41) = 5.598$, $p < .05$, $\eta_p^2 = 0.12$; HHb: $F(1, 41)<1$, $p>.1$, $\eta_p^2 = 0.00$) and an interaction of phase by condition by ROI (O2Hb: $F(4, 164) = 4.710$, $p < .01$, $\eta_p^2 = 0.10$; HHb: $F(4, 164) = 4.947$, $p < .001$, $\eta_p^2 = 0.11$). Post-hoc analysis of the three-way interaction revealed significantly reduced O2Hb levels during hand immersion but not during anticipation in cold water trials in the right IFG (O2Hb: $t(42) = 2.871$, $p < .01$, $dz = 0.44$, $d = 0.50$; HHb: $t(42) = 1.698$, $p < .1$, $dz = 0.26$, $d = 0.27$) and right DLPFC (O2Hb: $t(42) = 2.481$, $p < .05$, $dz = 0.38$, $d = 0.40$; HHb: $t(42) < 1$, $p > 1$, $dz = 0$, $d = 0$).

3.3. Exploratory analysis

Lastly, we explored the association between brain activity during the TSST and post-stress rumination by fitting multilevel models. The basic model showed, as expected, a main effect of time - reflecting increases from pre-to post-stress rumination - a main effect of group - indicating higher state rumination in the MDD group - and an interaction of group by time, showing higher reactivity (in terms of stronger increases in state rumination from pre-to post-stress) in the MDD group than in the HC group (see Table 3).

In our second model, we observed an interaction of O2Hb values and time for all prefrontal regions of interest, except for the SPL. The interaction indicated a negative association between O2Hb values during the arithmetic task and post-stress rumination. In contrast, pre-stress rumination was not associated with O2Hb values during control task 1 (non-stressful number reading) (see Table 3 and supplementary figure 2). This pattern was replicated using the HHb data (see supplementary table 4), although the time by HHb-level interaction was only significant for the left DLPFC and right IFG and marginally significant in the right DLPFC and left IFG.

In our final model, we included the group factor in the analysis, as hypoactivation in the prefrontal cortex and higher state rumination could both be explained by differences in the diagnostic groups. The interaction between time and O2Hb values remained significant in the left DLPFC and marginally significant in the left IFG, when group was introduced as a predictor, indicating that the association between prefrontal hypoactivity during the TSST and subsequent rumination was independent of group membership (see Table 3). Using HHb data, again the interaction of time and left DLPFC remained significant. Further, the right IFG showed a significant interaction with time (see supplementary table 4).

Finally, we checked for potential mediations of the group differences in post-stress rumination (MDD vs. HC) by fNIRS hypoactivation during the TSST in the left DLPFC. As expected from the previous multilevel model, our results showed that the influence of group membership on post-stress rumination scores (c: $B = 1.630$ (0.193), $p < .001$, $R^2 = 0.62$) was partly mediated by the reduced O2Hb levels during the TSST arithmetic task in the left DLPFC (a: $B = -1.630$ (0.193), $p < .001$, $R^2 = 0.62$; b: $B = -1.105$ (0.292), $p < .001$, $R^2 = 0.25$; $Z = 1.969$ (0.173), $p < .05$). With respect to HHb levels, this mediation proved to be only marginally significant in the left DLPFC (a: $B = -0.24$ (0.121), $p < .1$, $R^2 = 0.08$; b: $B = 1.01$ (0.348), $p < .01$, $R^2 = 0.16$; $Z = 1.63$, $p < .1$). However, for HHb data the mediation was observed in the right IFG (a: $B = -0.46$ (0.158), $p < .01$, $R^2 = 0.16$; b: $B = 0.717$ (0.255), $p < .01$, $R^2 = 0.16$; $Z = 2.02$, $p < .05$).

4. Discussion

The aim of the current study was to replicate and extend our previous findings on stress-related induction of rumination. To this end, we investigated behavioral and neural reactions to psychosocial and physiological stress as well as daily rumination in patients with MDD and healthy controls.

As expected, we observed increases in subjectively rated stress and physiological stress during the TSST and SECPT. However, increases in state rumination and negative affect following the stress induction procedures were only observed following the TSST, despite strong subjective stress, and high cortisol reactions as well as pain in the SECPT (see supplementary table 1). Rumination reactivity during the TSST but not SECPT was highly correlated with daily measured rumination. We observed an expected pattern of linear O2Hb increases in the CCN during the TSST (Rosenbaum et al., 2018a; Schaal et al., 2019) and hypoactivity in MDD patients as compared to HC. Finally, we were able to show that hypoactivity during the TSST arithmetic task in the bilateral DLPFC and IFG were significant negatively associated with post-stress rumination, but not activity during control task 1 with pre-stress rumination. In the left DLPFC this association was even stable when controlling for differences between the diagnostic groups. In a final mediation test, we showed that the group differences between MDD and HC in post-stress rumination were partly mediated by hypoactivity

Table 3
Results of the Multilevel Model exploring the associations between cortical oxygenation in the different ROI, clinical group membership and state rumination (DV = dependent variable). #$p < .1$, *$p < .05$, **$p < .01$,***$p < .001$.

	DV: State rumination	Basic Model	lIFG	lDLPFC	rIFG	rDLPFC	SPL
Basic Model Group	Intercept	1.94*** (0.087)					
	Group	**−0.52***** (0.088)					
	Time	**0.38***** (0.072)					
	Group*Time	**−0.30***** (0.073)					
Basic Model O2Hb	Intercept		1.93*** (0.130)	1.91*** (0.127)	1.93*** (0.130)	1.89*** (0.140)	1.90*** (0.140)
	O2Hb		0.065 (0.130)	0.14 (.122)	0.06 (0.111)	0.20 (0.134)	0.15 (0.141)
	Time		**0.50***** (0.089)	**0.68***** (0.111)	**0.50***** (0.090)	**0.52***** (0.105)	**0.47***** (0.119)
	O2Hb*Time		**−0.43*** (0.170)	**−0.71***** (0.195)	**−0.41*** (0.156)	**−0.40*** (0.176)	−0.23 (0.189)
Full Model	Intercept		1.94*** (0.087)	1.92*** (0.084)	1.93*** (0.087)	1.91*** (0.091)	1.90*** (0.091)
	Time		**0.45***** (0.080)	**0.58***** (0.108)	**0.43***** (0.081)	**0.43***** (0.095)	**0.48***** (0.101)
	Group		**−0.52***** (0.087)	**−0.54***** (0.085)	**−0.53***** (0.087)	**−0.54***** (0.092)	**−0.57***** (0.089)
	Time*Group		**−0.27***** (0.076)	**−0.24**** (0.084)	**−0.27**** (0.078)	**−0.28**** (0.082)	**−0.33***** (0.077)
	O2Hb		0.05 (0.105)	0.12 (0.110)	0.04 (0.095)	0.09 (0.121)	0.09 (0.117)
	O2Hb*Time		**−0.27#** (0.148)	**−0.50**** (0.185)	−0.21 (0.141)	−0.15 (0.162)	−0.21 (0.158)
	O2Hb*Group		0.02 (0.08)	−0.03 (0.090)	0.05 (0.08)	−0.03 (0.082)	0.14 (0.088)

in the left DLPFC during the TSST arithmetic task.

Previous investigations already showed that the TSST is able to induce rumination (Hilt et al., 2015; Shull et al., 2016). The results of increased state rumination in the depressed subjects but not healthy controls following the TSST are very well in line with our previous investigation in high and low trait ruminators (Rosenbaum et al., 2018b, 2018c). Moreover, in the current study, we showed that this elevated reactivity in state rumination is specific to the TSST, as we did not observe such changes following the SECPT. In both tasks, the interviewers were emotionally non-responsive and subjects were videotaped during the task. We assume that the rumination-elevating nature of the TSST in depressed subjects is due to specific features of the task. During the TSST subjects perform tasks that encourage internal attributional styles. Mistakes and failures might most probably be attributed to the lack of competence during the TSST. Such attributions may trigger strong emotional reactions that – combined with relevant pathological schemata in subject with MDD – lead to the secondary emotional drive (e.g. feelings of failure, worthlessness, shame, guilt) that foster depressive rumination. This assumption is further fostered by the behavioral data on affective changes during the paradigms. Following the TSST but not the SECPT negative affect increased, despite the high pain ratings during the SECPT.

In the same way, the TSST but not SECPT induced rumination that was highly correlated with everyday fluctuations in daily rumination. This result is highly encouraging in terms of using the TSST as a new standard approach to investigate depressive rumination. From naturalistic studies using EMA it is already known that stress-related rumination predicts and even mediates increases in depressive symptoms and negative affect (Connolly and Alloy, 2017; Ruscio et al., 2015). Despite the highly artificial situation during the TSST – which is obviously very different from everyday situations – the triggered ruminative responses seem to be comparable to those in daily life. It may be expected that high trait ruminators and depressed subjects often encounter situations in everyday life that elicit similar emotional and cognitive processes as in the TSST. Such emotional content (shame, self-doubt, anger) is often reported by depressed patients. Interestingly, although 60% of the study sample was receiving psychotherapy or pharmacotherapy at the time of testing, the TSST-related state rumination response was highly significant. In future investigations and treatment protocols for depressive rumination, TSST-like situations might be used as exposure-like psychotherapeutic elements to overcome depressive rumination. Support for social reasons as triggers of daily rumination comes from the EMA reported triggers of daily stress. Depressed subjects reported social interactions as triggers for daily stress significantly more often than healthy controls.

On a neural level, we observed a well-known pattern of hypoactivation in the bilateral DLPFC and IFG in the MDD group. Previous investigations already showed that MDD is characterized by hypoactivity in the prefrontal areas during cognitive tasks (Zhang et al., 2015; Zhong et al., 2016). Normally, stress induction paradigms are characterized by increased activity in the CCN in fNIRS and fMRI studies (Henze et al., 2020; Kogler et al., 2015; Rosenbaum et al., 2018a; Schaal et al., 2019). In our previous investigation we observed reduced brain activity in the right IFG and DLPFC in high vs. low trait ruminators during the TSST arithmetic challenge but not during the first control task. Note that trends towards hypoactivation in this previous study were also observed in the left DLPFC and IFG. However, the current investigation yielded a main effect of group reflecting reduced O2Hb levels over the CCN regardless of the TSST condition. Notably, descriptive increases in group differences were observed with increasing stress and the multilevel modelling indicated an association of post-stress rumination with O2Hb levels during the TSST arithmetic challenge, but not between pre-stress rumination and O2Hb levels during the non-stressful number reading task. One explanation for the absence of a group by condition effect in O2Hb levels could be the already high stress and rumination levels of the MDD group at the beginning of the experiment. In the previous investigation (Rosenbaum et al., 2018c) the high stress condition of the TSST might have been needed to elicit prefrontal dysfunctioning, while the MDD group investigated in the current study already showed these deficits before stress induction. Interestingly, following this interpretation of the cross-sectional data, one could hypothesize that the subjects might have developed this frontal dysfunctioning over time and were once in their developmental history comparable to the high trait ruminators of our previous investigation. Of course, longitudinal studies are needed to provide more robust evidence for this suggestion. Interestingly, our multilevel models suggest that activity in the left DLPFC during the TSST predicts post-stress rumination regardless of the differences between the MDD and HC group. A following test for mediation further showed evidence of a partial mediation of the group differences in post-stress rumination by left DLPFC activity during the TSST arithmetic task. Interestingly, our results are supported by a pilot study of De Witte et al. (2019) who used iTBS over the left DLPFC in 38 healthy volunteers following the TSST (De Witte et al., 2019). Although this study is limited in its sample size and investigated participant group (healthy controls), the authors observed a marginally significant interaction of trait-rumination and stimulation: While high trait ruminators showed a tendency towards higher state rumination after stress when they were treated with a sham iTBS intervention, high trait ruminators that were treated with an (excitatory) iTBS protocol showed no stress-induced increase in state rumination. In the same way, inhibition and excitation of the DLPFC has been shown to influence impulsive behavior and forgiveness (Maier et al., 2018, 2019). These results further emphasize the potential for neurointerventional methods in the CCN (Cao et al., 2018; Teng et al., 2017). Prefrontal dysfunction in depression and anxiety has been observed in various investigations (Bishop, 2009; Meyer-Lindenberg and Tost, 2012). The potential overlapping feature in both kinds of diseases might be the prolonged exposure to stress which – mediated by rumination (Ottaviani et al., 2016) – leads to allostatic changes in prefrontal functioning (Arnsten, 2015). These allostatic changes in prefrontal functioning might then be seen as a risk factor that mediates the cognitive-emotional response to future stress situations. In line with this suggestion, previous investigations have shown that stress is associated with decreased executive control and diminished emotion regulation in MDD (Garnefski and Kraaij, 2006; Joormann and Gotlib, 2010; Quinn and Joormann, 2020).

Despite the mostly conclusive findings of this study, some important limitations must be addressed. In the current investigation we used the method of functional near-infrared spectroscopy. The method has some important advantages such as the usability in ecologically valid environments. It allowed the investigation of cortical oxygenation during the TSST, which is the gold standard in the investigation of the neurobiology of stress induction (Allen et al., 2017). However, this comes at the cost of a limited spatial- and depth-resolution as fNIRS only allows to measure the upper layer of the cortex (Haeussinger et al, 2011, 2014). Our fNIRS system did not include short distance channels, which would allow further separation of physiological noise. Further, the investigated sample is limited in terms of power for a fine-grained investigation of brain-areas affected in MDD during the TSST or more complex multi-level modelling. Additionally, the cross-sectional design only allows for hypothetical statements about developmental factors of hypoactivity in MDD as well as potential effects of psychotherapeutic treatment and medication. We did not investigate the role of treatment factors in greater detail as the sample size was limited and the patients were at different stages of therapy. Finally, we did not use a randomization of the control and stress conditions during the TSST to prevent carry-over effects when measuring the control conditions after the TSST. However, we assume that the reported effects of this study are not influenced by effects of ordering in a substantial way (e.g. that the TSST would not be stressful, if the control condition was not carried out first). Potential designs controlling for potential sequential effects during the TSST would be very cost effective and would not add much to the

understanding of the research questions raised in this paper.

To our knowledge, this is the first study that validated a laboratory rumination induction paradigm with respect to external everyday rumination. Given the high importance of rumination in the development and maintenance of depression, other rumination paradigms should be validated in the same way. The study at hand gives clear evidence that the TSST induces state rumination increases in MDD subjects that are associated with daily life rumination reactivity. The neural correlates of the stress-induced increases in state rumination involve prefrontal hypoactivity in areas of the CCN.

Future investigations should focus on the role of prefrontal dysfunctioning in triggered depressive rumination. First interventional studies provide good evidence for being optimistic. Further, it is important to investigate in how far this stress-related prefrontal hypoactivity in MDD is reversible through psychotherapeutic intervention.

Significance statement

The results of our study are in line with our hypotheses that the effects were specific to the psychosocial component in the TSST, as the effects were absent in the SECPT. Thereby, hypoactivity in the cognitive control network during the TSST mediated the increases in rumination in the MDD subjects. While the TSST is a highly artificial situation, it seems to induce rumination similar to daily stressors. Prefrontal hypoactivity in response to stress seems to mediate the development of affect-driven rumination in MDD subjects. These effects are specific to social interactions and can be differentiated from physiological stress. These results inform the practitioner on the nature of depressive rumination as well as potential targets of psychotherapeutic treatment and neurostimulation.

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CRediT authorship contribution statement

D.R.,I.I., H.L. and A.-C.E. contributed to the analysis and interpretation of the data for the work and did the primary drafting. D.R.,I.I., H.L. ,A.-C.E., F.T., A.K., J.R., G.L., Z.B., I.B., H.S., K.V.-S., T.D.,R.T.,B.S., H-C.N., B.D., V.N. & A.J.F. contributed to the design and acquisition of the work and revised it critically for important intellectual content.All authors approved the final version to be published and agree to be accountable for all aspects of the work.

Declaration of competing interest

No author reported conflict of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ynstr.2021.100344.

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