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Stress enhances emotional memory-related theta oscillations in the medial temporal lobe

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ABSTRACT

Stressful events impact memory formation, in particular for emotionally arousing stimuli. Although these stress effects on emotional memory formation have potentially far-reaching implications, the underlying neural mechanisms are not fully understood. Specifically, the temporal processing dimension of the mechanisms involved in emotional memory formation under stress remains elusive. Here, we used magnetoencephalography (MEG) to examine the neural processes underlying stress effects on emotional memory formation with high temporal and spatial resolution and a particular focus on theta oscillations previously implicated in mnemonic binding. Healthy participants (n = 53) underwent a stress or control procedure before encoding emotionally neutral and negative pictures, while MEG was recorded. Memory for the pictures was probed in a recognition test 24 h after encoding. In this recognition test, stress did not modulate the emotional memory enhancement but led to significantly higher confidence in memory for negative compared to neutral stimuli. Our neural data revealed that stress increased memory-related theta oscillations specifically in medial temporal and occipito-parietal regions. Further, this stress-related increase in theta power emerged during memory formation for emotionally negative but not for neutral stimuli. These findings indicate that acute stress can enhance, in the medial temporal lobe, oscillations at a frequency that is ideally suited to bind the elements of an ongoing emotional episode, which may represent a mechanism to facilitate the storage of emotionally salient events that occurred in the context of a stressful encounter.

1. Introduction

Stress has a major impact on our memory. Research over the past decades showed that stress around the time of encoding can enhance memory formation whereas stress before retention testing impairs memory retrieval (Schwabe et al., 2012; Roozendaal and McGaugh, 2011; Joëls et al., 2011; De Quervain et al., 1998). Interestingly, both the enhancing effects of stress on memory formation and the detrimental effects on memory retrieval appear to be most pronounced for emotionally arousing information (Shields et al., 2017; Buchanan et al., 2006; Cahill et al., 2003). In particular, the enhanced (emotional) memory formation under stress may have important implications for our understanding of stress-related mental disorders, such as anxiety disorders or posttraumatic stress disorder (PTSD; De Quervain et al., 2017; Pitman et al., 2012; Hyman, 2005; Dalgleish and Watts, 1990).

Given these important implications, a plethora of studies aimed at elucidating the brain mechanisms involved in the impact of stress on emotional memory formation. It is well known that the hormones and neurotransmitters that are released in response to a stressful event, such as noradrenaline and glucocorticoids, act directly on brain regions critical for memory formation, such as the prefrontal cortex or medial temporal lobe, including the hippocampus (Qin et al., 2012; Lovallo et al., 2010; Arnsten, 2009; Pruessner et al., 2008; Kim and Diamond, 2002). Moreover, noradrenaline has been suggested to initiate a large-scale network reconfiguration, resulting in a bias towards the so-called 'salience network' (Hermans et al., 2011, 2014), which prioritizes emotionally salient information and may thus promote emotional memory formation. Compelling research in rodents further led to a model according to which the enhanced (emotional) memory formation under stress is due to the interactive interplay of

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noradrenaline and glucocorticoids in the basolateral part of the amygdala, which then modulates memory storage processes in other brain areas, such as the hippocampus or the dorsal striatum (Roozendaal et al., 2006, 2009; McGaugh and Roozendall, 2002). Although this model was initially based on studies in rodents, there is also evidence from humans in line with the predictions of this model (Van Stegeren, 2008; De Quervain et al., 2007; Buchanan et al., 2006; Cahill et al., 2003).

Most human research on the processes underlying memory formation under stress used functional magnetic resonance imaging (fMRI), which has an excellent spatial but limited temporal resolution. Accordingly, the temporal processing dimension of the mechanisms through which stress alters memory remains less well understood. Initial evidence from studies using electroencephalography (EEG) shows that stress modulates event-related potentials implicated in memory formation (Wirz et al., 2017; Quaedflieg et al., 2013; Wirkner et al., 2013) and at least some of these effects appeared to be specific for emotionally arousing material (Weymar et al., 2012). Importantly, there is also initial evidence suggesting that stress may modulate activity in the theta band (Gärtner et al., 2014). Theta oscillations may be of particular interest for stress effects on memory given their assumed role in memory formation (Sauseng et al., 2010; Buzsáki and Moser, 2013; Nyhus and Curran, 2010). Interestingly, rodent data suggest that stress may affect theta activity specifically in the medial temporal lobe (Ghosh et al., 2013; Jacinto et al., 2013). EEG studies in humans lack this degree of spatial resolution, accordingly the spatio-temporal correlates through which (emotional) memories are built under stress remain elusive. At this point it is important to note that neuroimaging methods, such as EEG or MEG, are correlative in nature and therefore do not allow causal inferences on the relationship between brain activity and the studied cognitive process. In order to probe the causal role of theta activity in memory, studies utilizing brain stimulation techniques directly modulating theta activity are required. Such evidence comes from a recent study showing that tACS, but not sham stimulation, in the theta range (6 HZ) applied over the right fusiform region increased associative memory performance (Lang et al., 2019). These results indicate that an increase in theta power might indeed be mechanistically related to memory processes.

In the present experiment, we leveraged magnetoencephalography (MEG) which enables the measurement of neural activity with high temporal and spatial resolution to elucidate the underlying neural signature of emotional memory formation shortly after a stressful event, with a particular focus on potential changes in medial temporal theta activity. To this end, healthy participants underwent a psychosocial stress or control procedure before they encoded a series of neutral and emotionally arousing pictures while MEG was recorded. Memory was tested in a recognition test 24 h later. To probe the neural underpinnings of (emotional) memory formation after stress, we used a subsequent memory analysis contrasting the neural activity during encoding of subsequently remembered and forgotten stimuli. We predicted that acute stress would enhance memory specifically for emotionally arousing events and that emotional memory formation under stress would be linked to increased theta activity in the hippocampus.

2. Materials and methods

2.1. Participants and experimental design

We recruited 67 healthy, right-handed adults with normal or corrected-to-normal vision (35 women, 32 men; age = 19–35 years, mean = 25.05 years, SD = 3.72 years). Exclusion criteria were checked in a standardized interview and comprised a history of any neurological or psychiatric disease, smoking, drug abuse, intake of any prescribed medication, previous participation in the stress protocol. Women were only included if they did not use hormonal contraception and were not tested during their menses because these factors may affect the endocrine stress response (Kudielka and Kirschbaum, 2005). Participants were asked not to drink coffee or other caffeinated beverages and not to do any exercise on the day of the experiment. Additionally, they were requested not to eat or drink anything except water 2 h before the experiment. Participants were pseudo-randomly assigned to the stress or control group, to achieve a comparable number of men and women per group. All participants gave written informed consent and received monetary compensation for participation. The study protocol was approved by the local ethics committee of the Faculty for Psychology and Human Movements Science at the Universität Hamburg.

Fourteen participants were excluded from analyses due to excessive head movement during MEG (mean displacement >20 mm, $n = 3$), not showing up on day 2 ($n = 4$) or technical issues ($n = 7$), thus leaving a final sample of 53 participants (27 men and 26 women, age 19–35, mean = 24.6, SD = 3.74, no age difference between groups, $t_{(52)} = 0.675$, $p = .502$, $d = 0.085$). An a priori power calculation with G*Power (Faul et al., 2007) indicated that a sample size of $N = 46$ is required to detect a *group* × *valence* interaction effect with a size of $f = 0.25$ ($\alpha = 0.05$; $1\text{-}\beta = 0.90$).

2.2. Experimental procedure

Testing was conducted on two consecutive days, with an interval of about 24 h: Day 1 included the experimental stress induction and a picture encoding task in the MEG followed by an unrelated task that is reported elsewhere (Quaedflieg et al., 2020). In brief, this task involved a think/no-think paradigm (Anderson and Green, 2001), in which participants were asked to learn and subsequently recall word-face pairs, which were clearly distinct from the stimulus materials used in the encoding task and did not include an emotional component, thus making interference (Lechner et al., 1999) or behavioural tagging effects (Vishnoi et al., 2016) rather unlikely. Day 2 included the recognition memory test. In addition, a structural MRI image was acquired from all participants in a separate session. In order to control for the diurnal rhythm of the stress hormone cortisol, all testing took place in the afternoon and early evening. To control for potential group differences in depressive mood and anxiety, participants completed the Beck Depression Inventory (BDI; Beck et al., 1961) and the State Trait Anxiety Inventory (STAI; Spielberger, 1983) prior to the experiment.

2.2.1. Experimental Day 1: stress and control manipulation

In order to induce acute psychosocial stress, participants in the stress condition were exposed to the Trier Social Stress Test (TSST; Kirschbaum et al., 1993), a standardized paradigm in experimental stress research. Participants were first asked to indicate a desired job position and after a 3-min preparation period they were requested to give a 5-min free speech about their qualification for the desired job. Thereafter, participants had to perform a 5-min mental arithmetic task (counting backwards from 2043 in steps of 17). Both tasks were performed in front of a panel of two non-reinforcing committee members (1 man, 1 woman), dressed in white lab coats. The panel was introduced as experts in behavioural analysis and supposed to act rather cold, non-reinforcing and non-responding to questions from the participants. In addition, participants were video-taped during the TSST, and the recording was shown on a TV screen placed behind the TSST panel.

In the control condition, participants engaged in two tasks of the same duration. The first task included a free speech about the last book they read, a movie they saw or holiday destination they went to. In the second task, participants counted forward in steps of 15. Importantly, there was no panel present, and no video recordings were taken.

In order to assess the successful stress induction, we took subjective ratings, blood pressure, heartrate, and saliva samples at several time points before and after the experimental manipulation. We measured mood changes using the negative affect subscale of the state positive and negative affect schedule (PANAS; Watson et al., 1988). In addition, participants' rating of the stressfulness, unpleasantness and difficulty of the experimental manipulation was measured on a visual analogue

(VAS) scale from 0 (not at all) to 100 (extremely) directly after the experimental manipulation. Blood pressure and heartrate (arm cuff: Omron Healthcare Europe BV) were measured at baseline, before, during, and immediately after the experimental manipulation, and when participants left the MEG (i.e., −25, −1, +10, +15, +90 min relative to TSST onset). Saliva samples were obtained, before and immediately after the experimental manipulation, before the encoding task, after the encoding task as well as well at the end of day 1 (i.e., −1, +15, +30, +70, +105 min relative to the onset of the experimental manipulation). At the end of data collection, cortisol was analysed from saliva samples with a luminescence assay (IBL International, Hamburg, Germany).

2.2.2. Experimental Day 1: picture encoding task

Stimulus materials for the memory tasks consisted of 300 emotionally negative and 300 emotionally neutral pictures taken from the International Affective Picture System (IAPS; Lang and Bradley, 2007). One hundred and fifty pictures of each valence were used as stimuli during encoding on day 1, the remaining 300 pictures (150 negative, 150 neutral) were used for the Recognition Test on day 2, representing *new* Items.

About 20 min after the experimental manipulation, participants performed the picture encoding task in the MEG. In this task, 150 neutral and 150 negative pictures were presented in pseudorandomized order (not more than three emotional or neutral pictures in a row) on a computer screen using MatLab (version R2017b; The MathWorks). Each picture was presented for 2 s in the middle of the screen. Afterwards a scale appeared at the lower part of the screen asking participants to rate the intensity (1–4; anchors: 1 = not intense at all, 4 = very intense) of the presented picture. Between stimuli, a fixation cross was presented for a random interval between 2 and 3 s. Participants were instructed to memorize all presented pictures. This encoding session took about 30 min.

2.2.3. Experimental Day 2: recognition test

In order to control for potential group differences in stress levels before the memory test, blood pressure and heart rate were measured, and another saliva sample was collected at the beginning of day 2. To assess memory performance of the pictures encoded on day 1, a recognition test programmed in MatLab (version R2017b; The MathWorks) was presented on a computer screen. This recognition test included the 300 pictures that were encoded on day 1 as well as 300 new pictures. Old and new pictures were again presented in pseudorandomized order (not more than three new or old pictures in a row). Each item was presented for 4 s, and participants were instructed to indicate whether the picture was presented on day 1 ('old') or not ('new') via button press. If a picture was classifieded as 'old', participants were further asked to rate the confidence of their decision (1–4; anchors: 1 = very unconfident, 4 = very confident; Yonelinas et al., 2005). Each trial was followed by a fixation cross of 2 s.

2.3. Statistical analyses

To test the successful stress induction, data on subjective ratings, vital signs, and salivary cortisol were analysed using 2 × 2 repeated-measures ANOVAs (Type III) with the between-subjects factor *group* (stress/control) and the within-subject factor *time*. During the encoding task on day 1, participants rated the intensity of the presented pictures. We tested potential differences in the expressed intensity using a 2 × 2 repeated-measures ANOVA (Type III) with the between-subjects factor *group* (stress/control) and the within-subject factor *valence* (negative/neutral). In order to analyse the performance in the recognition task, we calculated hits and false alarms as well as the sensitivity index *dprime,* based on signal detection theory (Wickens, 2002), separately for stimuli of neutral and negative valence. Each of these measures was analysed using 2 × 2 repeated-measures ANOVAs (Type III) with the between-subjects factor *group* (stress/control) and the within-subject factor *valence* (negative/neutral). Furthermore, we tested potential differences in recognition confidence with a 2 × 2 repeated-measures ANOVA (Type III) including the between-subjects factor group (stress/control) and the within-subject factor valence (negative/neutral). In an additional, explorative analysis of potential sex differences, we added the factor sex (male vs. female) to this model. In order to relate memory performance, memory confidence and theta power to subjective and objective stress-parameters, pearson correlations were used utilizing changes in *cortisol*, *systolic blood pressure* and *scores of the negative PANAS scale* (pre-to post-stress). Cortisol values were log-transformed, and the area-under-the-curve increase from pre-stress to peak (+30 min relative to TSST onset) was used. For systolic blood pressure the absolute change between pre-stress and peak (during TSST) was used. To counteract the problem of multiple comparisons, holm correction (Holm, 1979) was applied. Accordingly, corrected p-values are reported.

All data analyses were performed with R version 3.3.6 (R Core Team, 2017). All reported *p*-values are two-tailed and Greenhouse-Geisser correction was applied if required. Significant ANOVA results were followed up by appropriate post-hoc tests. Prior to inference statistical procedures, data were checked for normal distribution (Shapiro-Wilk Test), homogeneity of variance (Levene-Test) as well as outliers.

2.4. Structural MRI acquisition

MRI measurements were obtained on a 3 T Siemens Magnetom Prisma scanner, equipped with a 32-channel head coil. A high-resolution T1-weighted anatomical image (voxel size = 1 × 1 × 1 mm) was acquired for later source-analysis of the MEG data.

2.5. MEG data acquisition

MEG was acquired at a rate of 1200 Hz, with a 275-channel whole-head system (Omega 2000, CTF Systems Inc.), housed in an electrically and magnetically shielded room. Additional Ag/AgCl-electrodes were applied to measure horizontal and vertical electrooculogram (EOG) and electrocardiogram (ECG). The head position relative to MEG sensors was monitored online during the whole recording and corrected as soon as the movement exceeded 5 mm using three fiducial points (nasion, left and right external ear canal).

2.6. MEG data processing

All analyses of the MEG data were conducted in MatLab (version R2017b; The MathWorks) using either custom made scripts or functions from the FieldTrip toolbox (Oostenveld et al., 2011).

2.6.1. Preprocessing

Data were imported to MatLab and filtered between 0.5 and 120 Hz (BUT Filter, Low-pass filter 4th order, high-pass filter 3rd order), and specifically filtered for line-noise using band-stop filters for relevant frequency intervals (49.5–50.5 Hz, 99.5–100.5 Hz). Signals were subsequently resampled to 400 Hz. Raw data were then divided into 6 s epochs (−2 to +4 s relative so stimulus onset). All Epochs were further demeaned based on the average signal of the whole trial. In order to remove artifacts related to SQUID jumps, muscle artifacts or external noise, we utilized semi-automatic detection based predefined thresholds (Quaedflieg et al., 2020). Following this procedure, on average 85% of all trials (SD = 10%) were retained in each dataset. In the next step, we calculated an extended infomax independent component analysis using the 'runica' command (ICA, stop criterion: weight change $<10^{-7}$) in order to identify and reject components related to eye-blinks or heartbeat. These components were identified by visual inspection of time courses and corresponding brain topographies. On average 5 (±SD: 1.6; range 2–10) components reflecting either cardiac or electro-ocular activity were removed before back-projecting the signals into

sensor-space.

2.6.2. Frequency analysis

Spectral decomposition of MEG data was performed using sliding Hanning windows (2–30 Hz, 1-Hz steps, five-cycle window, interval: −2 to 4 s relative to stimulus onset). The single trials were log-transformed (Grandchamp and Delorme, 2011; Smulders et al., 2018) and baseline corrected (absolute baseline correction −1 to 0 s relative to stimulus onset). The spectral data was then averaged per stimulus type (negative and neutral valence; remembered and not remembered) across participants of the experimental and control group, respectively.

2.6.3. Source analysis

Localization of frequency specific source activity was performed with the dynamic imaging of coherent sources (DICS; Gross et al., 2001) beamforming technique utilizing all 275 sensors (magnetometer and gradiometer). Volume conduction models were created using a single-shell volume conductor model (Nolte, 2003), based on the T1-weighted structural magnetic resonance image (MRI; Siemens Magnetom Prisma) from each participant. For three participants no T1 MR image was available, and consequentially the standard MNI 152 brain template was used. Individual MEG sensor positions were aligned to the MR images based on three fiducials (left and right acoustic meatus, nasion) using rigid body transformation. Segmentation of brain tissue was performed using the SPM12 software. Head models were derived from individual MR images using a single-shell volume conductor model (Nolte, 2003). A template grid of source positions was used (6 mm spacing). Following, leadfield matrices were calculated for each participant using the individual MEG sensor positions aligned to the individual head model and the source grid. Cross-spectral density matrices of the MEG data were computed for the time window and frequency which revealed a significant difference in the frequency data. The regularization parameter was set to $\lambda = 0.05$. Common spatial filters were computed by averaging the cross-spectral density matrices across all stimulus types and conditions. Power estimates in each source were estimated by multiplying the common filters with the cross-spectral density matrix of each stimulus type.

2.6.4. MEG analysis

All following statistical analyses of MEG data were centred around spectral and source power differences during immediate encoding (0–1 s). Contrast specific effects at whole-brain sensor and source level were tested with cluster-based permutation tests (10.000 permutations to correct for multiple comparisons; Maris and Oostenveld, 2007). This approach allows testing for statistical differences in large-scale data sets without the need for prior assumptions about the location of effects, while controlling for multiple comparisons. The samples were clustered at a level of $\alpha = 0.05$. Clusters with a Monte Carlo *p*-value of .05 and less are reported as significant. Prior to the statistical tests on source level, we parcellated the brain space using an anatomical mask (AAL; Tzourio-Mazoyer et al., 2002) to reduce computational effort and increase interpretability.

In a first step, we compared spectral power differences between negative and neutral trials independent of group and memory performance in theta frequency range (4–7 Hz) using a dependent sample cluster-based permutation *t*-test. This way we were able to identify the exact time-windows of where a significant difference between both stimulus categories was present, and could simultaneously probe the distinct role of theta oscillations during emotional memory formation (Hsieh and Ranganath, 2014; Lega et al., 2012). Thereafter, data windows corresponding to significant frequency clusters were projected to the source level and averaged over Regions of Interest using the AAL Atlas. Source data was next compared with dependent sample cluster-based permutation t-tests.

In a next step, we performed a subsequent memory analysis, in order to relate the neural signature of picture encoding on day 1 to the actual memory performance on day 2. We therefore divided the data of the day 2 recognition task for valence, and whether pictures were correctly recognized or not. The MEG data were afterwards divided accordingly, in order to organize the MEG data of each participant in the following categories: Negative_remembered, Negative_forgotten, Neutral_remembered and Neutral_forgotten. As the initial analysis revealed a significant difference of spectral theta power between negative and neutral trials, further analyses were also primarily focussed on the theta frequency range (4–7 Hz). We subtracted the theta power of forgotten trials from remembered trials in order to retain brain activity associated with remembering. Next, we extended the analysis by adding the factor *group* (stress vs. control), and subsequently compared spectral power differences of negative (remembered-forgotten) and neutral (remembered-forgotten) trials separately between stress and control groups. Independent sample cluster-based permutation t-tests were calculated to find the exact time-window of were a significant difference between both stimulus categories was present. Data windows corresponding to significant frequency clusters were projected to the source level and averaged over Regions of Interest using the AAL Atlas. Source data was next compared with cluster-based permutation t-tests on the source level.

3. Results

3.1. Successful stress induction

Shortly before the picture encoding in the MEG on day 1, participants underwent either the TSST ($n = 28$) or a non-stressful control manipulation ($n = 25$). Significant increases in subjective stress ratings, blood pressure, and salivary cortisol confirmed the successful stress induction through the TSST. Participants in the stress condition experienced the experimental manipulation as significantly more stressful ($t_{(51)} = -6.893$, $p < .001$, $d = 1.896$), unpleasant ($t_{(51)} = -6.275$, $p < .001$, $d = 1.726$), and difficult ($t_{(51)} = -10.476$. $p < .001$, $d = 2.883$) than participants in the control condition (Table 2). Negative mood state, as measured with the negative affect subscale of the PANAS, increased significantly in response to the TSST but not after the control manipulation (*time* × *group* interaction: $F_{(1,77)} = 12.45$, $p < .001$, $\eta^2_p = .203$; Table 1). Post-hoc tests revealed significantly higher negative affect ratings in the stress group compared to the control group after the experimental manipulation ($t_{(49)} = -5.676$, $p < .001$, $d = 1.597$), whereas groups did not differ in their negative affect score at baseline ($t_{(51)} = -1.779$, $p = .081$, $d = 0.489$).

Systolic and diastolic blood pressure increased significantly in the stress group compared to controls, as reflected in a significant *time* × *group* interaction (systolic: $F_{(3,182)} = 19.68$, $p < .001$, $\eta^2_p = .282$; diastolic: ($F_{(3,182)} = 8.92$, $p < .001$, $\eta^2_p = .151$; Fig. 1A and B)). Post-hoc tests revealed that participants exposed to the TSST had significantly higher blood pressure than participants in the control group during the experimental manipulation (systolic: $t_{(51)} = -5.011$, $p < .001$, $d =$

Table 1
Subjective stress ratings.

	Stress	Control
Stressfulness	62.25 (23.53)***	23.08 (16.83)
Unpleasantness	57.64 (25.06)***	19.40 (18.29)
Difficulty	61.42 (17.24)***	16.40 (13.56)
Baseline NA	12.78 (3.08)	11.52 (1.87)
Pre-stress NA	11.75 (2.11)	10.64 (0.99)
Post-stress NA	15.07 (3.60)***	10.65 (1.02)

Subjective stress ratings reflected by the items 'stressfulness', 'unpleasantness' and 'painfulness' were rated on a scale from 0 ('not at all') to 100 ('very much') immediately after the TSST/Control procedure.
NA: Negative Affect was measured with the PANAS questionnaire for positive and negative mood states. Data represent means (±SD); *$p < .05$, **$p < .01$, ***$p < .001$.

Table 2
Negative affect and physiological stress parameters on day 2.

	Stress	Control
Heart rate (beats per minute)	80.53 (13.79)	86.40 (12.55)
Systolic blood pressure (mmHg)	120.85 (14.11)	118.50 (15.00)
Diastolic blood pressure (mmHg)	81.07 (7.37)	81.64 (8.44)
Cortisol (nmol/l)	4.34 (2.84)	4.69 (3.77)
Negative affect	11.00 (1.58)	10.72 (1.54)

Subjective and physiological parameters of participants on day 2. All parameters were taken at the beginning of day 2 and revealed no significant difference in either subjective or physiological stress parameters between stress and control groups. Data represent means (±SD).

1.379; diastolic: $t_{(51)} = -3.801$, $p < .001$, $d = 1.046$) and directly after the experimental manipulation (systolic: $t_{(51)} = -3.603$, $p < .001$, $d = 0.991$; diastolic: $t_{(51)} = -3.239$, $p = .002$, $d = 0.891$), whereas groups did not at baseline (systolic: $t_{(51)} = -0.921$, $p = .361$, d = 0.253; diastolic: $t_{(51)} = -0.841$, $p = .404$, $d = 0.231$). Furthermore, there was a significant *time* × *group* interaction for heart rate ($F_{(4,182)} = 5.89$, $p = .001$, $\eta^2_p = .105$; Fig. 1C). Post hoc tests indicated that the heart rate increased significantly from baseline to post-treatment in the stress group ($t_{(27)} = 3.357$, $p = .002$, $d = 0.597$), whereas there was no such increase in control participants ($t_{(24)} = -0.911$, $p = .371$, $d = 0.102$).

Finally, salivary cortisol increased in response to the TSST but not after the control procedure (*time* × *group* interaction: $F_{(2,96)} = 10.67$, $p < .001$, $\eta^2_p = .179$; Fig. 1D). The stress group had significantly higher cortisol concentrations than controls immediately before the encoding task started (i.e., 20 min after TSST onset: $t_{(51)} = -3.046$, $p = .004$, $d =$

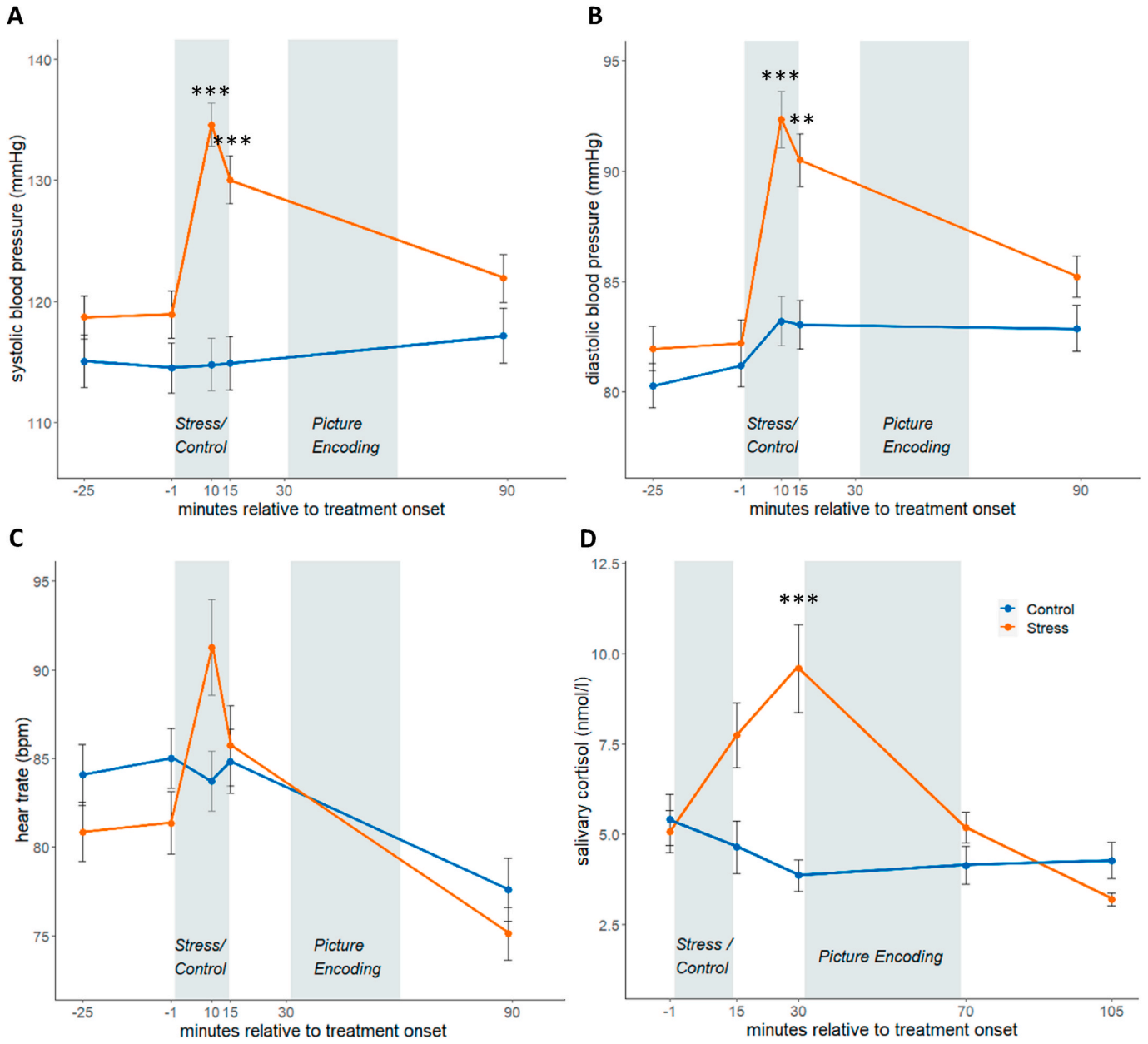

Fig. 1. Physiological stress response to the TSST/Control procedure. ***A***, Significant increases in systolic and ***B,*** diastolic blood pressure as well as ***C,*** heart rate. ***D***, The stress group further showed a significant increase in concentrations of salivary cortisol prior to the picture encoding task. Grey shades indicate the periods of the TSST/Control procedure as well as the picture encoding task. Data represent means (±SE); *$p < .05$, **$p < .01$, ***$p < .001$. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

0.838). Groups did not differ in cortisol concentrations before the experimental manipulation ($t_{(51)} = 0.250$, $p = .803$, $d = 0.068$), immediately after the experimental manipulation ($t_{(51)} = -1.900$, $p = .063$, $d = 0.522$), and 55 min after the experimental manipulation ($t_{(48)} = -1.482$, $p = .144$, $d = 0.304$).

3.2. Emotional memory enhancement

To assess stress-related changes in emotional memory and its neural underpinnings, participants encoded 150 neutral and 150 negative items in the MEG scanner. On day 1, during the picture encoding task, participants were asked to rate the intensity of each presented stimulus. As expected, negative pictures were experienced as significantly more intense (stress: 2.13 ± 0.36, control: 2.24 ± 0.43) than neutral pictures (stress: 0.42 ± 0.26, control: 0.37 ± 0.20; main effect emotionality: $F_{(1,50)} = 1389.35$, $p < .001$, $\eta^2_p = .965$). Importantly, the stress and control groups did not differ in the emotional intensity ratings (all main and interaction effects including the factor *group*: all $F < 1.10$, all $p > .313$, all $\eta^2_p < .020$).

About 24 h after encoding, participants returned to the lab for a surprise recognition test. Importantly, groups did not differ in negative affect levels, autonomic measures, or salivary cortisol before this memory test (all $t < 1.613$, all $p > .112$, all $d < 0.440$; Table 2). Overall, participants recognized 68.25 percent of the pictures encoded on day 1 correctly as 'old' (hits), whereas only 10.25 percent of the new pictures were classified as 'old' (false alarms), thus indicating very good memory performance. Accordingly, the signal detection theory-based sensitivity measure *dprime* yielded on average a high score of 1.71.

Memory was overall significantly better for negative than for neutral items, as reflected in an increased hit rate (main effect *valence*: $F_{(1,45)} = 87.82$, $p < .001$, $\eta^2_p = .661$; Fig. 2A) and a significantly higher *dprime* (main effect *valence*: $F_{(1,48)} = 10.24$, $p = .002$, $\eta^2_p = .176$; Fig. 2C),

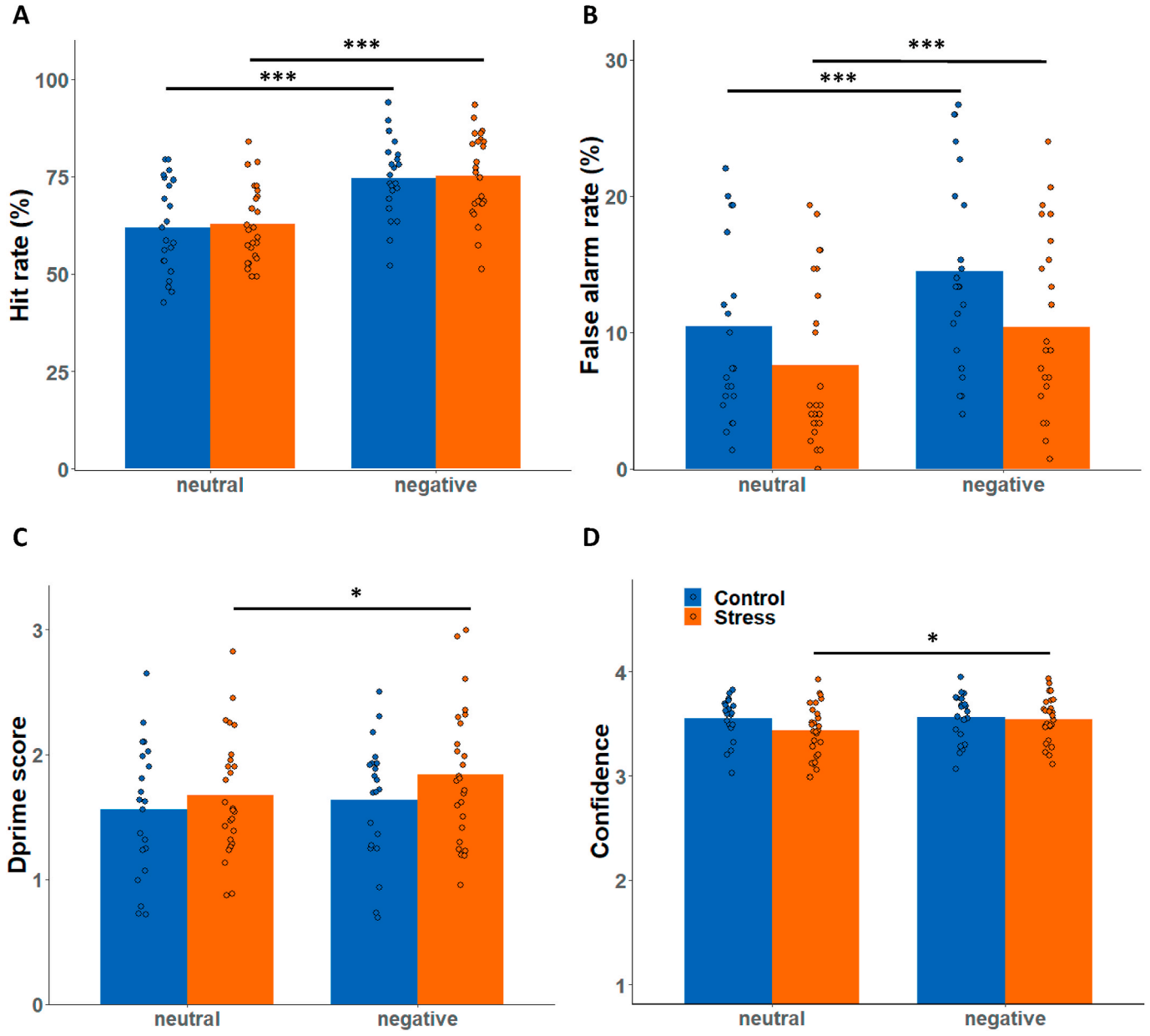

Fig. 2. Memory performance on day 2. ***A***, The hit rate reflected a high memory performance, with significantly better memory for negative than for neutral stimuli. ***B***, False alarm rates were also higher for negative than for neutral pictures. ***C***, Dprime scores further confirmed the overall good memory performance and the emotional memory enhancement. ***D,*** Memory confidence scores showed that whereas confidence was comparable for neutral and negative stimuli in control participants, negative items were recognized with higher confidence than neutral items when participants were stressed before encoding; *$p < .05$, ***$p < .001$.

although the false alarm rate was also elevated for negative compared to neutral items (main effect *valence*: $F_{(1,45)} = 36.95$ $p < .001$, $\eta^2_p = .451$; Fig. 2B). Results from the 2 × 2 ANOVA indicated that the stress and control groups did not significantly differ in recognition memory performance expressed as *dprime* (all main and interaction effects including the factor *group*: all $F < 0.50$, all $p > .485$, all $\eta^2_p < .010$; for hits and false alarms: all $F < 3.52$, all $p > .067$, all $\eta^2_p < .073$). Finally, we compared the relative differences in recognition performance between negative and neutral stimuli within each group. Results from paired t-tests revealed a significantly increased hit rate for emotional compared to neutral items (stress: $t_{(24)} = 8.022$, $p < .001$, $d = 1.210$; control: $t_{(21)} = 5.621$, $p < .001$, $d = 1.147$) and more false alarms for negative compared to neutral stimuli in both groups (stress: $t_{(23)} = 4.187$, $p < .001$, $d = 0.442$; control: $t_{(22)} = 4.419$, $p < .001$, $d = 0.593$). For the sensitivity parameter *dprime,* only the stress group showed a significantly higher performance for negative compared to neutral stimuli ($t_{(25)} = 2.590$, $p = .015$, $d = 0.331$), whereas this difference was not significant in the control group ($t_{(23)} = 1.953$, $p = .063$, $d = 0.247$). This difference, however, needs to be interpreted with great caution given the non-significant interaction effects reported above. Explorative analyses of the correlations of memory performance (*hits*, *false alarms*, *dprime*) with changes in cortisol (AUCi), systolic blood pressure (peak-baseline), and negative PANAS scale (post-pre) did not reveal a significant association (all $r < 0.359$, all $p_{corrected} > .160$).

If participants classified a picture as 'old', they further had to indicate the confidence of their decision. Overall, participants were very confident in their choices as reflected by an average confidence rating of 3.52 (±0.21). Negative pictures were overall remembered with higher confidence than neutral pictures (main effect *emotionality*: $F_{(1,46)} = 8.49$, $p < .006$, $\eta^2_p = .156$). Interestingly, whereas the confidence ratings were comparable for neutral and negative items in controls ($t_{(20)} = 0.233$, $p = .818$, $d = 0.034$), participants in the stress group recognized negative items with significantly higher confidence than neutral items ($t_{(26)} = 4.552$, $p < .001$, $d = 0.455$; *group* × *valence* interaction: $F_{(1,46)} = 6.39$, $p = .015$, $\eta^2_p = .122$; main effect *group*: $F_{(1,46)} = 0.99$, $p < .236$, $\eta^2_p = .021$; Fig. 2D).

Explorative analyses of the correlations of memory confidence with changes in cortisol (AUCi), systolic blood pressure (peak-baseline), and negative PANAS scale (post-pre) did not reveal significant direct associations (all $r < 0.329$, all $p_{corrected} > .560$).

3.3. Explorative analyses of sex differences

Although the present study did not focus on potential sex differences and was therefore not sufficiently powered to detect such effects, we ran an explorative analysis testing for potential differences in the impact of stress on emotional memory in men and women. While the sensitivity parameter *dprime* indicated an overall increase in memory performance in women compared to men (main effect *sex*: $F_{(1,46)} = 10.774$, $p = .002$, $\eta^2_p = .190$; $t_{(90)} = 4.205$, $p < .001$, $d = 0.854$), participants' sex did not modulate the influence of stress on memory for neutral and negative events, neither for *dprime*, nor for *hits*, *false alarms* or *confidence* (*group* × *valence* × *sex* interactions: *all* $F < 1.576$, all $p > .211$, all $\eta^2_p < .033$), thus suggesting that the impact of stress on emotional memory formation did not differ between men and women.

3.4. Stress increases theta power in medial temporal and occipito-parietal regions during emotional memory formation

In a next step, we asked whether stress affected the neural processes through which emotional memories are formed. In a first step, we analysed spectral power associated with the encoding of negative and neutral stimuli on sensor level, contrasting sensor level theta power (4–7 Hz) during negative and neutral trials. The cluster-based permutation *t*-test revealed a positive cluster of sensors, in which theta power was significantly increased in negative relative to neutral stimuli. From 0 to 0.9 s after stimulus onset, theta power was increased in frontal sensors ($p = .001$; *ci*-range = 0.001; std <0.001; Fig. 3A). Following source analysis, spectral data was averaged over ROIs of the AAL atlas and the subsequent cluster based permutation t-tests on ROI level revealed that the observed theta power difference related to the encoding of negative vs. neutral pictures originated from a cluster centred around frontal and temporoparietal brain regions ($p < .001$; *ci*-range < 0.001; std <0.001; Fig. 3B). These changes in source level theta power did not differ between the stress and control groups (no cluster-$p < 0.05$), suggesting that these changes may reflect general mechanisms of emotional processing that were not influenced by stress.

Next, we specifically focussed on the key question of our study, whether stress affected the mechanisms of emotional memory formation. To this end, we ran subsequent memory analyses (i.e. contrasted subsequently remembered vs. forgotten trials) for neutral and negative items, and investigated, whether the stress and control groups differed in the neural underpinnings of memory formation for negative relative to neutral stimuli. Cluster-based permutation tests on sensor level revealed that theta power was significantly increased during the encoding of negative stimuli (remembered – forgotten) in the stress group compared to controls ($p = .038$; *ci*-range = 0.004; *std* = 0.002; Fig. 4A and B; see supplementary Fig. S1 for a depiction separately in stressed and control participants) from 0 to 0.9 s relative to stimulus onset. Follow-up source analyses using cluster-based permutation tests on ROI level revealed that the observed theta power difference originated from a cluster of medial temporal lobe and occipito-parietal regions ($p = .026$; *ci*-range = 0.003, *std* = 0.002; Fig. 4C).

While stress impacted theta activity related to emotional memory formation in occipito-parietal and medial-temporal regions, theta power involved in the remembering of neutral stimuli did not differ between groups (sensor-level: no cluster-$p < .05$). Even when a more lenient threshold was used ($\alpha = 0.1$), there was no group difference in theta activity associated with the encoding of neutral stimuli. Explorative analyses of the correlations of theta activity with changes in cortisol (AUCi), systolic blood pressure (peak-baseline), and negative PANAS scale (post-pre) did not reveal significant direct associations (all $r < .447$, all $p_{corrected} > 0.156$).

3.5. Explorative analyses in additional frequency bands

In addition to our main analysis focussing on stress-induced changes in theta oscillation s related to emotional memory formation, we performed explorative analyses in the alpha (8–12 Hz) and beta (13–30 Hz) bands. In the alpha band, a signficant sensor cluster could be found, reflecting a decrease in alpha activity for negative compared to neutral stimuli, ranging from 0.6 to 1 s after stimulus onset ($p = .031$; *ci*-range = 0.065; std = 0.033). The subsequent cluster based permutation test on source level did however not reveal a significant cluster of alpha activity (no cluster-$p < .05$). In the beta band, a signficant cluster of sensors was detected, ranging from 0.6 to 1 s after stimulus onset. Here, beta power was significantly decreased for negative compared to neutral stimuli ($p = .015$; *ci*-range = 0.044; std = 0.023). Source analysis revealed that the observed beta power difference associated with negative vs. neutral pictures originated from a wide-spread occipito-parietal cluster of brain regions ($p < .001$; *ci*-range < 0.001; std <0.001).

To further uncover potential stress effects on the neural underpinnings of emotional memory formation, we exploratively compared spectral power of the alpha (8–12 Hz) and beta (13–30 Hz) bands during encoding of emotional stimuli between groups. We therefore again compared subsequent memory-related brain activity for negative and neutral items between groups. For negative trials, cluster-based permutation tests on sensor level revealed no difference in alpha power (no cluster-$p < .05$), yet a non-significant trend for a positive (stress > control) sensor cluster in the beta band from 0.4 to 0.8 s ($p = .063$; *ci*-range = 0.005; *std* = 0.002). Subsequent source analysis did however not reveal a significant cluster of activity (no cluster $p < .05$).

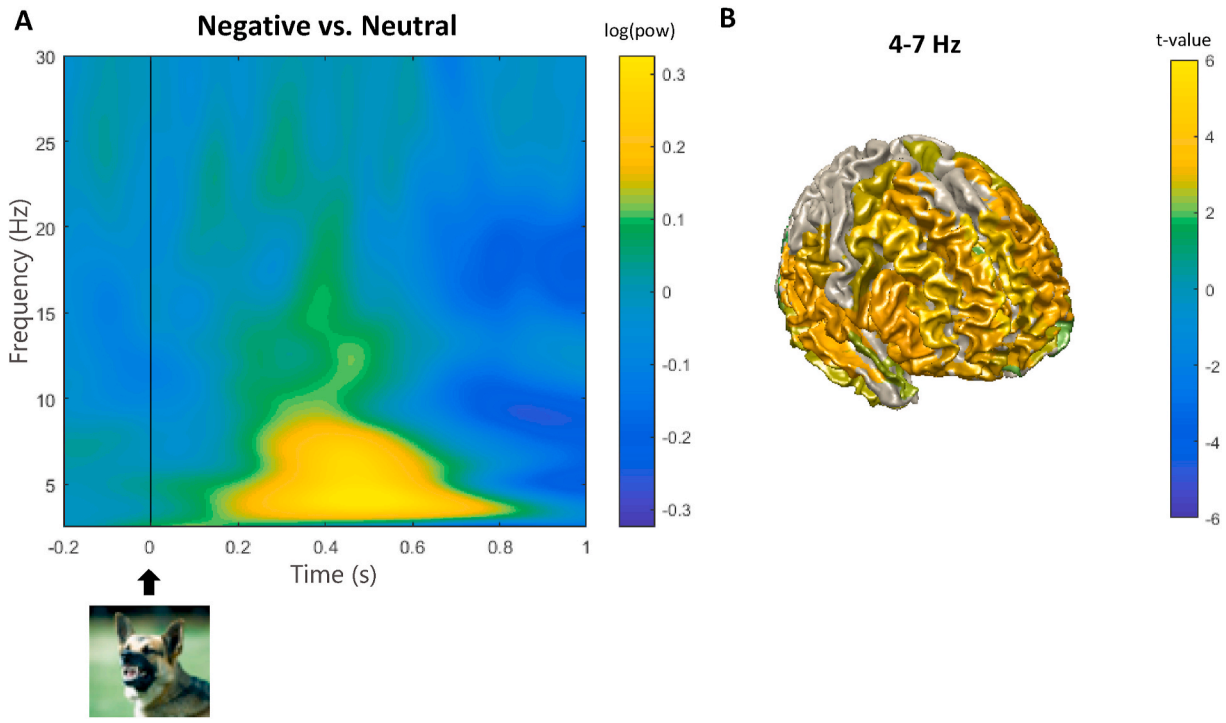

Fig. 3. Differences in spectral and source level data decompositions for negative versus neutral trials, independent of stress. ***A***, Time-Frequency representation, averaged over all sensors for illustrative purposes. ***B***, Regions with significant differences in the theta range (4–7 Hz, 0–0.9 s) resulting from the cluster-based permutation *t*-test (Negative > Neutral) on source level.

Alpha and Beta power involved in the remembering of neutral stimuli did also not differ between groups (sensor-level: no cluster-$p < .05$).

3.6. Control variables

We controlled for potential group differences in depressive mood as well as state and trait anxiety at the beginning of day 1 (Table 3). Importantly, the stress and control groups did not differ in any of these variables (depressive mood: $t_{(51)} = -0.345$, $p = .730$, $d = 0.095$, state anxiety: $t_{(51)} = -1.098$, $p = .277$, $d = 0.302$; trait anxiety: $t_{(51)} = -0.848$, $p = .399$, $d = 0.233$).

4. Discussion

Stress-induced changes in emotional memory formation are highly relevant for many contexts, including eyewitness testimony (Marr et al., 2021; Sauerland et al., 2016), educational settings (Vogel and Schwabe, 2016), or stress-related mental disorders (De Quervain et al., 2017; Pitman et al., 2012). Nevertheless, the neural mechanisms underlying changes in emotional memory formation under stress are not yet fully understood and, in particular, the temporal changes in mnemonic processing under stress remained elusive. Here, we used MEG to study the neural underpinnings of emotional memory formation under stress with high temporal and spatial resolution. At the behavioural level, we did not find a significant influence of stress on overall recognition performance but found that stress increased the influence of emotion on memory confidence. Even more importantly, our neural data revealed that stress increased memory-related theta activity in medial-temporal and occipito-parietal areas specifically for emotionally relevant material.

Theta activity is thought to act as 'glue' in memory formation and to bind brain regions during memory encoding through an increase in oscillatory power (Hanslmayr and Staudigl, 2014; Buzsáki and Moser, 2013; Nyhus and Curran, 2010). Specifically, episodic memories are comprised of multiple elements that are processed in distinct areas, which need to be integrated during memory formation (and during later retrieval). This binding relies on the precise timing of neural activity, which is assumed to be orchestrated through hippocampal theta activity (Clouter et al., 2017; Berens and Horner, 2017). From a neurophysiological perspective, theta oscillations are thought to act as a driving force in hippocampal neuronal plasticity, facilitating memory formation processes (Jutras et al., 2013; Huerta and Lisman, 1995). Our findings show that acute stress is accompanied by enhanced theta activity during memory formation, which may point to an improved binding of the separate elements of an episode under stress.

Importantly, the increase of theta power during memory formation was specific to negative stimuli and specifically present in medial temporal regions and occipito-parietal areas. This pattern of results is generally in line with prominent models of memory formation under stress, which assume that stress facilitates specifically the processing of emotionally-arousing, salient material closely linked to noradrenergic activation as well as the role of the medial temporal regions, the amygdala and the hippocampus in emotional memory formation under stress (Schwabe et al., 2012; Joëls et al., 2011; Roozendaal et al., 2009). Moreover, it is specifically hippocampal theta that has been linked to mnemonic binding (Lega et al., 2012; Tesche and Karhu, 2000). Beyond the hippocampus, however, there is also evidence that emotionally arousing stimuli lead to increased occipital activity (Phan et al., 2002; Herrmann et al., 2008), suggesting that emotional stimuli are prioritized already during early visual processing. Furthermore, there is evidence for a functional connection between the amygdala and areas involved in early visual processing (Tamietto, 2012; Amaral et al., 2003) and the effect of emotional stimuli on visual cortex activation is closely related to the amygdala's response (Furl et al., 2013; Morris et al., 2001). The stress-related increase in theta activity in the occipital cortex during emotional memory formation may, thus, further enhance the prioritization of emotionally salient information, as well as the binding of visual representations which may be particularly relevant during stressful threatening encounters. In addition to occipital cortex, memory-related theta activity was also significantly increased in parietal areas. Parietal

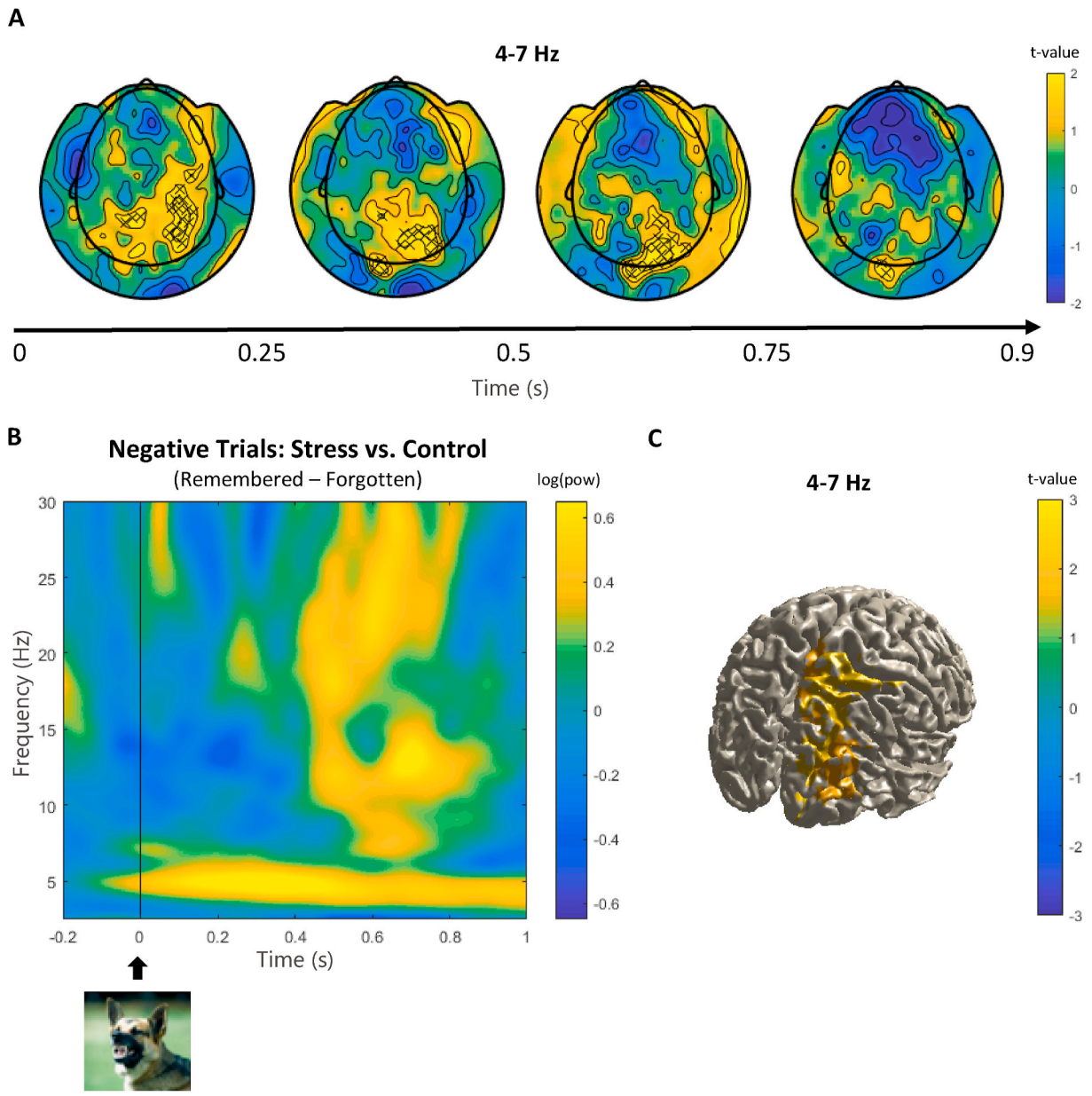

Fig. 4. Stress effects on theta power during the encoding of negative trials (remembered-forgotten). ***A***, Topography of theta activity differences (stress > control). Crosses indicate a significant cluster of sensors returned by the cluster-based permutation *t*-test. For illustrative purposes, data has been binned into four time-segments, ranging from 0 to 0.9 s relative to stimulus onset. ***B***, Averaged time-frequency representation (stress > control) of parieto-occipital sensors which were included in the significant sensor-cluster presented in A. ***C***, Brain regions with significantly higher theta activity during encoding of negative items in the stress (vs. control) group on source level.

Table 3
Participants state, and trait anxiety and depression scores.

	Stress	Control
State Anxiety	35.35 (4.93)	33.72 (5.91)
Trait Anxiety	35.21 (5.85)	33.52 (8.55)
Depression Score	3.96 (3.54)	3.60 (4.12)

State and Trait anxiety scores were measured with the State-Trait Anxiety Inventory. Depression Scores were determined utilizing the Beck Depression Inventory. Participants conducted both questionnaires at Baseline on day 1. Data represent means (±SD).

theta activity has been most commonly related to working memory (Riddle et al., 2020; Sauseng et al., 2004) and memory retrieval processes (Jacobs et al., 2006; Hebscher et al., 2019). Thus, the stress-related increase in parietal theta might represent a mechanism through which emotionally salient events are kept for longer in working memory, which may promote both the coping with the ongoing situation and the storage of the specific event in long-term memory. In sum, the stress-related increases of emotional memory-related theta power in medial temporal and occipito-parietal areas that we observed here might represent a mechanism that facilitates the mnemonic binding of elements of an episode within and across representational areas. The enhanced visual processing of salient events as well as their longer availability in short-term memory, may foster the prioritized storage of emotionally arousing events experienced in the context of a stressful encounter. Although there is evidence suggesting a causal link between theta and memory (Lang et al., 2019), it is at this point important to note that MEG studies are correlative in nature and that based on the present data as such the conclusion that changes in theta are a causal mechanism

underlying memory formation under stress may not be warranted.

How may stress have induced the observed increases in memory-related theta? Theta power reflects the strength of a specific oscillation of neuronal populations. In particular, theta oscillations are believed to be critical for formation of active neuronal ensembles and the modification of synaptic weights (Buzsáki, 2002). It thus seems reasonable that a modification of theta oscillations is directly linked to changes in synaptic plasticity. The exposure to acute stress triggers the release of a cocktail of hormones, peptides, and neurotransmitters, many of which exert a direct effect on neuronal activity (Joëls and Baram, 2009; Kim and Diamond, 2002). For instance, results from animal studies indicate that cortisol exerts a non-genomic effect on neurons by blocking the release of cAMP (Cyclic Adenosine Monophosphate; Vijayan et al., 2010), which plays a central role in mediating synaptic transmission (Duman and Nestler, 1999). Thus, stress mediators such as cortisol might have directly stimulated the activity of neurons generating theta-frequency oscillations. At the systems level, in particular concurrent glucocorticoid and noradrenergic activity is known to enhance amygdala activity which then modulates activity in other memory-related regions such as the hippocampus (Kim et al., 2015; Richter-Levin and Akirav, 2000). Further, stress mediators may induce a large-scale network reconfiguration in favour of a 'salience network' (Hermans et al., 2011, 2014), including, for instance, the amygdala which is closely connected to other medial temporal regions as well as to visual representation areas (Meier et al., 2021; Wendt et al., 2011; Sabatinelli et al., 2009). Thus, the orchestrated action of a multitude of different stress mediators may enhance activity in brain areas specialized in emotional memory formation and further promote the communication via a specific frequency band (i.e. theta) that appears to be particularly well suited for mnemonic binding of the elements of an episode. In line with the idea that multiple stress mediators drive neural and behavioural changes after stress in interaction, single stress mediators, such as cortisol or autonomic activity did not correlate significantly with changes in memory performance, confidence, or theta activity.

Although our imaging data show a significant effect of stress on the spatio-temporal neural underpinnings of emotional memory formation, it is important to note that 24 h-delayed recognition performance did not differ between the stress and control groups. One potential explanation for the latter may relate to the overall recognition performance in the present study. Participants' performance was overall high, particularly for emotionally negative pictures, which may have resulted in a ceiling effect, leaving not much space for an additional stress-related enhancement. Moreover, in contrast to a free recall test, which involves an active search process in memory, recognition tests require only a comparison process, which might be less sensitive to stress effects. At least, there are also several previous studies that did not find a significant effect of stress on recognition memory (Meier et al., 2020; Hidalgo et al., 2015; Li et al., 2014; Quaedflieg et al., 2013). Finally, the discrete old-new responses in the recognition test are considerably less fine-grained than our neural measures and may hence be less sensitive to stress effects. Indeed, when we analysed participants' confidence ratings, which did provide a more fine-grained analysis of memory performance, we observed that the influence of stimulus emotionality on memory confidence was significantly higher in stressed participants than in controls. Interestingly, this influence of stress was manifested in reduced confidence for neutral stimuli rather than in increased confidence in memory for emotional events. This finding suggests a stronger priorization of memory based on emotional salience after stress, which is generally in line with earlier findings suggesting that stress or arousal may not only enhance memory for central features of an episode but also reduce memory for more peripheral information (Kalbe et al., 2020; Kensinger et al., 2007).

Together, our data provide novel insights into the neural underpinnings through which stress may impact emotional memory formation. Specifically, we show that stress is accompanied by an increase in memory-related theta activity in medial temporal and occipito-parietal areas. Importantly, this effect was specifically observed during the encoding of emotionally arousing, but not neutral, stimuli. The present findings suggest that stress enhances neuronal oscillations that appear to be ideally suited for binding elements of an episode, in areas known to play a prominent role in emotional memory formation. Through this process, stress may facilitate the long-term storage of emotionally salient events encoded in the context of a stressful encounter, which may be highly adaptive for coping with similar future events, but could also contribute to the painful memory for aversive experiences in disorders such as PTSD.

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CRediT authorship contribution statement

Hendrik Heinbockel: Formal analysis, Methodology, Visualization, Writing – original draft. **Conny W.E.M. Quaedflieg:** Data curation, Writing – review & editing. **Till R. Schneider:** Methodology, Writing – review & editing. **Andreas K. Engel:** Resources, Validation, Funding acquisition, Writing – review & editing. **Lars Schwabe:** Conceptualization, Project administration, Writing – original draft, Writing – review & editing, Supervision.

Declaration of competing interest

None.

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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.2021.100383.

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