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Time-dependent effects of psychosocial stress on the contextualization of neutral memories

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ABSTRACT

Memories about stressful experiences need to be both specific and generalizable to adequately guide future behavior. Memory strength is influenced by emotional significance, and contextualization (i.e., encoding experiences with their contextual details) enables selective context-dependent retrieval and protects against overgeneralization. The current randomized-controlled study investigated how the early and late phase of the endogenous stress response affects the contextualization of neutral and negative information. One hundred healthy male participants were randomly divided into three experimental groups that performed encoding either 1) without stress (control), 2) immediately after acute stress (early) or 3) two hours after acute stress (late). Stress was induced via the Trier Social Stress Test and salivary alpha-amylase and cortisol levels were measured throughout the experiment. In the Memory Contextualization Task, neutral and angry faces (items) were depicted against unique context pictures during encoding. During testing 24 h later, context-dependent recognition memory of the items was assessed by presenting these in either congruent or incongruent contexts (relative to encoding). Multilevel analyses revealed that neutral information was more contextualized when encoding took place two hours after psychosocial stress, than immediately after the stressor. Results suggest that the late effects in the unique, time-dependent sequence of a healthy endogenous stress response, could complement reduced contextualization immediately after stress. The contextualization of negative information was not influenced by psychosocial stress, as opposed to earlier reported effects of exogenous hydrocortisone administration. An imbalance between the early and late effects of the endogenous stress response could increase vulnerability for stress-related psychopathology.

1. Introduction

Stressful encounters are unavoidable in daily life. Memorizing such events is highly adaptive as it facilitates adequate responses to future challenges (De Quervain et al., 2017; Joëls et al., 2011; Roozendaal et al., 2009). The well-known phenomenon that emotionally significant experiences are remembered better than neutral events, due to evoked arousal, is therefore not surprising (De Quervain et al., 2017; Ferré et al., 2015; Kensinger, 2009; Roozendaal et al., 2009). Memories for negative stimuli are strengthened by recruitment of limbic brain areas during encoding and consolidation, in particular the amygdala (De Quervain et al., 2017; Joëls et al., 2011). These effects are mediated by hormones released in response to stress. Within minutes after confrontation with a stressor, catecholamine release is enhanced by fast activation of the autonomic nervous system (ANS) (Joëls et al., 2011; Quaedflieg and Schwabe, 2018; Sheldon et al., 2018; Wolf et al., 2016). Catecholamines rapidly increase connectivity in the salience network, including the amygdala, thereby preparing the brain for threat detection (Quaedflieg and Schwabe, 2018). Several minutes after the confrontation, the hypothalamic-pituitary-adrenal (HPA) axis is activated, causing enhanced levels of corticosteroids (for 1–2 hours) (De Quervain et al., 2017; Joëls et al., 2011; Quaedflieg and Schwabe, 2018; Sheldon et al., 2018), which bind to receptors expressed in limbic regions (De Quervain et al., 2017; Joëls et al., 2011). Corticosteroids can evoke rapid, non-genomic effects; 60–90 minutes later, these effects are complemented with delayed genomic effects (Joëls et al., 2011; Quaedflieg and Schwabe, 2018). Interestingly, various experiments showed that the immediate and delayed response to these stress

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hormones affect learning and memory in a time-dependent, sometimes opposing, manner (Joëls et al., 2011; Quaedflieg and Schwabe, 2018; van Ast et al., 2013). Taken together the findings suggest that the rapid effects promote a 'memory formation modus' (facilitating encoding and early consolidation), while the delayed effects seem to promote a 'memory storage modus' (thereby suppressing the encoding of new material that is not part of the original learning context) (Quaedflieg and Schwabe, 2018).

Thorough encoding of negative stimuli is a highly adaptive, healthy, mechanism that aids the recognition of danger signals in novel environments. However, inappropriate retrieval of emotional aspects of stressful episodes in safe environments is undesirable and suggested to predispose individuals to pathological conditions such as panic disorder (Kheirbek et al., 2012; Lissek et al., 2010), phobias (De Quervain et al., 2017), posttraumatic stress disorder (PTSD) (Garfinkel et al., 2014; Kheirbek et al., 2012; Liberzon and Abelson, 2016; Maren et al., 2013; van Rooij et al., 2014), or generalized anxiety disorder (GAD) (Lissek et al., 2014). Adequate retrieval of neutral aspects that were associated with a stressful experience is just as important, as it allows distinction from comparable experiences (e.g. trees might help to discriminate between a lion in the jungle and a lion in the zoo) (Javanbakht, 2019; Ventura-Bort et al., 2016). It is frequently reported that memory retrieval is enhanced in environments with similarities to the original encoding context (Bouton and Moody, 2004; Godden and Baddeley, 1975; Ranganath, 2010; Smith and Vela, 2001; van Ast et al., 2013; Zhang et al., 2018). Such context-dependent memories are likely to be achieved by binding event-related information with implicit details from the surrounding circumstances during encoding. Such *memory contextualization* may aid to enable subsequent selective retrieval, prevent overgeneralization (Maren et al., 2013; Meyer et al., 2017; van Ast et al., 2013; Zhang et al., 2018), and guide instrumental behavior (Bouton and Todd, 2014). The neurocircuitry that is suggested to underlie memory contextualization includes the hippocampus, amygdala, and (medial) prefrontal cortex (Maren et al., 2013; Zhang et al., 2018). Contextualization depends on the emotional significance (or valence) of information, as encoding can be reduced in the presence of negative valence, most likely due to differences in arousal intensity (Berkers et al., 2016; Bisby and Burgess, 2017; van Ast et al., 2013). This clearly illustrates that adaptive encoding of stressful experiences involves a complex interaction between memorizing emotional significance and contextual details. Brain areas involved in valence and context encoding (i.e. amygdala, hippocampus and (medial) prefrontal cortex), are highly sensitive to catecholamines as well as glucocorticoids (Joëls et al., 2018; Maren et al., 2013; Roozendaal et al., 2009).

Although the full interaction between endogenous stress, valence encoding and contextualization has not been revealed, specific elements have been addressed in earlier studies. With respect to implicit contextualization of differently valenced information, most studies have focused on rapid effects of stress. One study found that immediately after stress, contextualization of neutral visual material is reduced (compared to non-stressful encoding), while the encoding of negative material was unaffected by stress or contextual details (Schwabe et al., 2009). Another study showed that neutral verbal information is more contextualized than negative information (van Ast et al., 2014). In this study, the endogenous stress-induced cortisol levels during encoding (but not subjective stress itself), positively predicted context-dependency of verbal memories, regardless of emotional significance (van Ast et al., 2014). The immediate effects of stress have also been found to impact the context-dependency of emotional material, indexed by reduced acquisition of contextual fear (McGlade et al., 2019). Only one study investigated both the immediate and delayed effects of cortisol on contextualization of neutral and emotional material, using exogenous administration of hydrocortisone (van Ast et al., 2013). Interestingly, this approach did not alter the strong context-dependency of neutral verbal memories, yet affected the contextualization of negative verbal information (van Ast et al., 2013). More specifically, the rapid effects of cortisol reduced contextualization of negative information, whereas the delayed effects of cortisol enhanced this process (van Ast et al., 2013). Possibly, the conflicting results are explained by the fact that the latter study involved exogenous administration of cortisol only, i.e. one of many hormones released after stress.

The current study was performed to elucidate the time-dependent effects of an endogenous stress response on memory contextualization of neutral and negative material in healthy male individuals. Only male participants were included because HPA-axis reactivity to acute stress varies greatly between men and women (Kajantie and Phillips, 2006) and the earlier study with hydrocortisone was carried out in males (van Ast et al., 2013). Three experimental groups performed a memory contextualization task either 1) without stress (control), 2) immediately after acute stress (early phase) or 3) two hours after acute stress (late phase). Based on previous research, we hypothesized that the ability to contextualize information would be hampered immediately after stress and enhanced during the late phases of the stress response, resulting in reduced and enhanced context-dependent memories, respectively. We expected this effect to be the strongest for negative information (compared to neutral information), based on the findings with hydrocortisone.

2. Methods

2.1. Participants

Healthy male participants were included in this randomized controlled trial (n = 120). Twenty participants (delayed-stress (n = 2), immediate-stress (n = 8), no-stress (n = 10)) were excluded from the analyses because MCT data was not available, due to errors in task code (n = 13), recording errors (n = 4), incompatible versions of encoding and retrieval task (n = 1) and subject withdrawal (n = 1). Data of 100 participants (age: M = 25.23, SD = 7.03, Range = 18.25–49.43) was available for the current analyses. There were no differences in age, BMI, education, marital status, profession, substance use and disturbed sleep rhythm between participants in the experimental groups (Table A.1.1). A priori power calculations, based on previously reported effect sizes, were made to establish the required sample size (Faul et al., 2009; van Ast et al., 2013). Participants were recruited via online platforms (e.g. the university student portal Blackboard, www.proefbunny.nl, Facebook) and via flyers at the campus of Utrecht University. All participants gave written informed consent and had normal or corrected-to-normal vision, normal uncorrected hearing, and a body mass index between 18.5 and 30. Inclusion/exclusion criteria were checked via a screening questionnaire. Participants were excluded if they had a past or present psychiatric or neurological condition (including substance abuse or addition), any somatic or endocrine disease (e.g., acute asthma), were taking any medication known to influence central nervous system or endocrine systems, had speech impairments, were not fluent in the Dutch language, or suffered from color blindness. Appointments were rescheduled if participants had any acute illness, fever or a severe cold, insufficient sleep during previous night, smoked within the last 2 h, drank anything other than water or ate within the last 2 h, ingested coffee or any caffeine-containing drink within the last 4 h, used alcohol within the last 24 h, had physical exercise within the last 12 h; or used any recreational drugs within the last 3 days; these acute exclusion criteria were checked upon arrival at the institute. Participants received €48,- for their participation.

2.2. Stress and control manipulations

As stress manipulation, the Trier Social Stress Test (TSST) (Kirschbaum et al., 1993) was used. This intervention took around 15 min and consisted of a preparation period (3 min), a free speech simulating a job interview (5 min), as well as a mental arithmetic task (3 min). The speech and mental arithmetic task took place while

standing in front of a nonresponsive three-person audience (usually one man and two women, in exceptional cases three women), while being video- and audio-taped. As control manipulation the placebo version of the TSST was used (Het et al., 2009), which is specifically designed to resemble important modulating variables such as physical (e.g., participants are standing in both conditions) or cognitive load of the TSST, but leaves out the uncontrollability and social-evaluative threat central to the TSST (Het et al., 2009). During the control manipulation, the participant was alone in a room, while performing the tasks. The TSST and placebo-TSST were always performed in different experimental rooms, to limit contextual similarities between the manipulations.

2.3. SNS and HPA (re)activity

Salivary alpha-amylase (sAA) and cortisol are frequently used measures of SNS and HPA activity, respectively (Kudielka et al., 2004; Nater and Rohleder, 2009). Saliva samples were obtained using Salivettes® (Sarstedt, Nümbrecht, Germany) at 14 time points during the experimental protocol (Fig. 2) and subsequently stored at -80 degrees Celsius. Samples were delivered in batches to the University Medical Center Utrecht LKHC laboratory for biochemical analysis. sAA was measured on a Beckman-Coulter AU5811 chemistry analyzer (Beckman-Coulter Inc, Brea, CA). Cortisol was measured without extraction using an in-house competitive radio-immunoassay employing a polyclonal anticortisol-antibody (K7348). [1,2–3 H(N)]-Hydrocortisone (PerkinElmer NET396250UC) was used as a tracer. The lower limit of detection was 1.0 nmol/l.

2.4. Memory contextualization

The Memory Contextualization Task (MCT; Fig. 1) was specifically designed to measure the influence of implicit contextual details on participants' memory for neutral and negative valenced, item-related information (i.e. context-dependent memory of negative and neutral items after contextualization). The task was modelled after previous versions (Staudigl and Hanslmayr, 2013; Talamini et al., 2010; Tambini et al., 2010; Tsivilis et al., 2001; van Ast et al., 2014, 2013, 2012; Zhang et al., 2018), and programmed in Presentation Version 18.1 (Neurobehavioral Systems, Inc, RRID:SCR_002521). Clipped-out images of 240 unique Caucasian faces (50% female; 530 × 750 pixels), with a neutral (50%) or angry (50%) facial expression, were derived from three validated databases (Goeleven et al., 2008; Langner et al., 2010; Minear and Park, 2004). The images were distributed in two groups, counterbalanced for gender and valence (i.e. facial expression): 120 stimuli served as items to remember and 120 stimuli were used as lures during the recognition phase. The contextual details were provided by 120 visually rich images of various indoor and outdoor locations (e.g. living rooms, restaurants, city landscapes, natural scenes; 1280 × 768 pixels). The background pictures were counterbalanced between task categories and most images were also used in previous tasks (van Ast et al., 2014, 2013, 2012). The task consisted of two phases: memory encoding and surprise recognition of the faces, 24 h apart (Fig. 2). During encoding, every single item to remember was paired with a unique location image (i.e. context); altogether these were shown in 120 trials (Fig. 1). Trial order was shuffled in blocks of 4 trials, in which all four combinations of context (to-be congruent or incongruent) and valence (neutral or negative) type were presented once, while identical context or valence categories never succeeded each other more than 2 times. Each trial started with presentation of the context alone, 1 s later the face appeared as oval overlay and the pair remained visible for 3 s. To ensure attention for the presented stimuli and stimulate rich encoding (van Ast et al., 2013; Zhang et al., 2018), participants were told that they had to perform in a task on imagination ability, and instructed to form a vivid mental image of the person (face) interacting with the depicted background (context). Note that to mimic real-life memory formation and prevent explicit associative learning between face and context, participants were not instructed to actively memorize the stimuli (combinations) (Zhang et al., 2018). After a 1 s delay, the response window popped up and participants had 1 s to rate how well they managed to form this image on a 4-point Likert scale (cf. Zhang et al., 2018). In the surprise recognition phase the next day, the old faces (i.e. items to remember) were presented once again, intermixed with 120 new faces (i.e. the lures that were not presented during encoding; Fig. 1). Both old and new faces were paired with the previously shown context images (i.e. each context was shown twice). Trial order was shuffled in blocks of 8, in which 4 old and 4 new faces were presented. For the old faces, each combination of context (congruent or incongruent) and valence (neutral or negative) type was presented once, for the new faces each valence category was presented twice. Again, identical context or valence categories never succeeded each other more than 2 times. The test was self-paced and participants had to indicate if they had seen the face during encoding and how certain they were of their answer, on a 6-point Likert scale (new, sure – new, probably – new, guess – old, guess – old, probably – old, sure). Importantly, no explicit reference was made

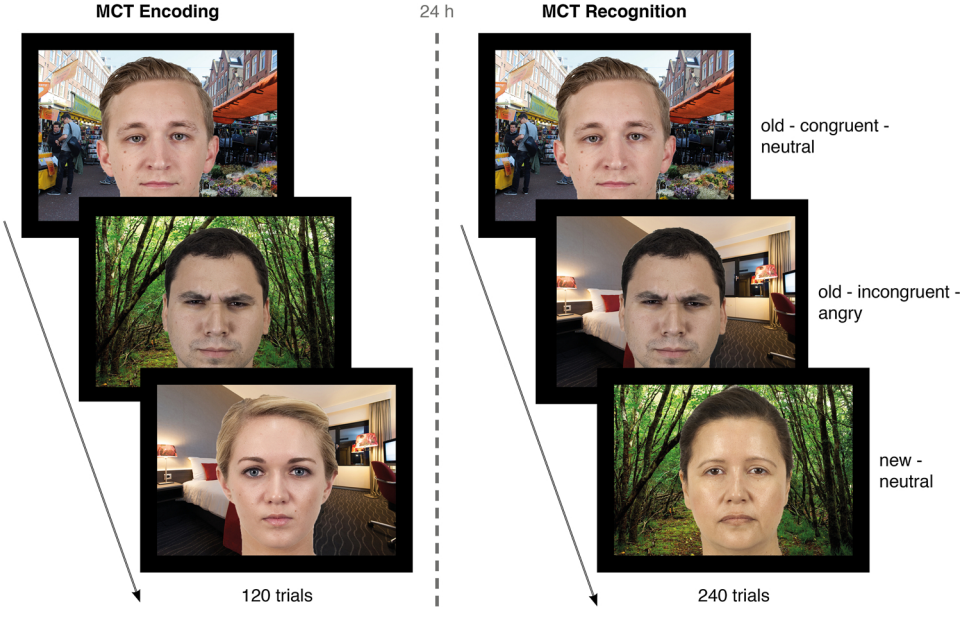

Fig. 1. Memory Contextualization Task (MCT). On the first day participants completed the encoding phase of the MCT. In this phase, unique combinations of (neutral and angry) faces and contexts were shown in 120 trials. Twenty-four hours later, participants completed the recognition phase of the MCT, in which all the 120 old faces were presented again together with 120 new faces. To assess context-dependency of memories (after contextualization), 60 old faces were presented with their original context (old - congruent) and 60 old faces were presented with a different context (old – incongruent).

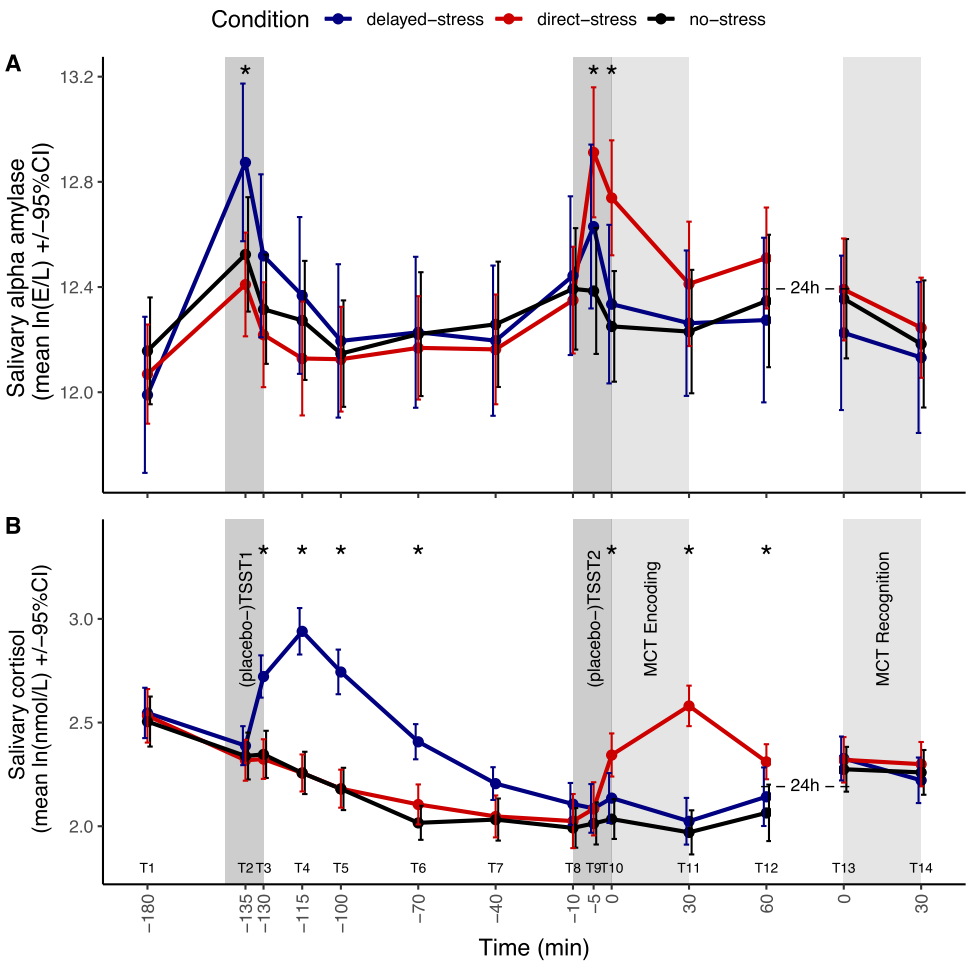

Fig. 2. The experimental timeline with salivary alpha-amylase and cortisol levels.
Mean salivary alpha-amylase (A) and cortisol (B) are shown per experimental condition, error bars represent 95% confidence intervals. Natural logarithms were used to transform the endocrine data. Samples T1-T12 were collected at day 1 and samples T13 and T14 were collected at day 2. Eight minutes before T2 (i.e. 143 min before encoding), participants were exposed to the (placebo-)TSST1, at T8 (i.e. 10 min before encoding) participants performed the (placebo-)TSST2. Significant Tukey adjusted post-hoc pairwise comparisons between experimental groups ($p < .05$) are indicated with *.

to the background image in the instructions of this task phase, to measure the implicit influence of contextual details on memory performance. Crucially, to investigate participants' ability to contextualize information, 60 old faces (30 neutral, 30 angry) were presented with their original encoding context (congruent context) and 60 (30 neutral, 30 angry) were presented with a different context (incongruent context). If recognition of the old faces was better in the congruent context compared to the incongruent context, it can be inferred that the contextual details during encoding were bound to the item-related information (contextualization) and thereby, improved participants' subsequent memory.

2.5. Experimental design and procedure

In a randomized-controlled, single-blind study design, participants were randomly allocated to one of the three experimental conditions (delayed-stress (n = 34), immediate-stress (n = 34), no-stress (n = 32)) using an a priori generated list from the random sequence generator at www.random.org. The three experimental conditions were induced via unique combinations of the stress and control manipulations (Fig. 2; delayed-stress: TSST1 & placebo-TSST2; immediate-stress: placebo-TSST1 & TSST2; no-stress: placebo-TSST1 & placebo-TSST2). Prior and during study participation, all participants were blind to the study aims and experimental conditions. Participants visited the lab twice (24 h apart) and all experimental procedures were performed between 12 pm and 7 pm, when cortisol levels are quite low due to circadian rhythmicity (Dickerson and Kemeny, 2004; Kudielka et al., 2004). The first visit commenced with the collection of informed consent and the baseline measures (T1, Fig. 2). After a waiting period, participants were subjected to the (placebo-)TSST1. Approximately 120 min later participants were exposed to (placebo-)TSST2 and subsequently conducted the encoding phase of the MCT (Fig. 2). The next day participants came back to the lab for their second visit and were confronted with the surprise recognition phase of the MCT (Fig. 2). At the end of day two, after completion of the experiment, participants were debriefed about the study aims and experimental conditions. Because this study was part of a larger project, also investigating the time-dependent effects of psychological stress on fear-conditioned memories, participants performed another task (that did not included facial stimuli) between T11 and T12 in a different experimental room (Fig. 2). This study was approved by the Medical Ethics Committee of the University Medical Center Utrecht, and conducted in accordance with the ICH Guidelines for 'Good Clinical Practice' and the Declaration of Helsinki (World Medical Association, 2013).

2.6. Data analysis

Demographics were analyzed with a one-way ANOVA in SPSS, version 25 (IBM, 2017). R was used for the statistical analysis of the endocrine measures and MCT performance with linear mixed-effect models (LMM) (R core team, 2018). LMM assumptions were checked using the influence.ME (Nieuwenhuis et al., 2012) and moments (Komsta and Novomestky, 2015) packages for R. The lme4 (Bates et al., 2015), LMERConvienceFunction (Tremblay and Ransijn, 2015) and lmerTest (Kuznetsova et al., 2017) packages for R were used to fit and test the linear mixed-effect models (LMMs). P-values were obtained by likelihood ratio tests of the full model with the effect in question against the model without the effect ($\alpha = 0.05$). The emmeans package (Lenth, 2018) for R was used for the post-hoc pairwise comparisons. P-values were Tukey adjusted for multiple family wise comparisons. Effect sizes

for the Tukey adjusted post-hoc pairwise comparisons on endocrine measures and MCT performance were calculated using Cohen's d, which is calculated by dividing 2 times the t-value by the square root of the degrees of freedom (Rosenthal and Rosnow, 1991). For the within factors valence and context in the MCT, Cohen's d was calculated by dividing the t-value by the square root of the degrees of freedom (Rosenthal, 1991). Figures were made with the ggplot2 (Wickham, 2016) and ggpubr (Kassambara, 2018) packages for R. Data and code available via Open Science Framework (https://osf.io/g93f4/).

2.6.1. Endocrine measures

For the manipulation check of stress-induction, LMMs were fitted to the alpha-amylase as well as to the cortisol data, to assess the endocrine levels over the course of the experiment in all experimental conditions. Condition, time and their interaction were entered as fixed effects, and intercepts for participants were entered as random effects in both LMMs (Eq.(B.1) in Appendix B). For the sAA analyses two data points (of 1400) were missing, for the cortisol analysis, one data point (of 1400) was missing. Missing values were excluded from the analyses. Cortisol and sAA values were log-transformed to ensure normality of the residuals. Visual inspection of residual plots did not reveal any obvious deviations from homoscedasticity or normality. For the cortisol analysis, one case (no-stress condition) was considered to be an influential point (Cooks distance was 0.71 in the log-transformed cortisol data, which was well above the cutoff of .40 (Nieuwenhuis et al., 2012)) and excluded from the cortisol analysis. The lab results revealed that the high values of this subject were most likely caused by corticosteroid use. No cases were excluded from sAA analysis. Tukey adjusted post-hoc pairwise comparisons were used to compare the levels between experimental conditions at each timepoint, and to compare the increase in cortisol levels (indexed with the estimated marginal mean (EMM) differences between baseline and peak) following TSST1 (in the delayed-stress condition) and TSST2 (in the immediate-stress condition).

2.6.2. MCT performance

Performance on the MCT was scored according to the signal detection theory (Stanislaw and Todorov, 1999; van Ast et al., 2013; Zhang et al., 2018), with a custom-build Matlab script (MATLAB, RRID:SCR_001622). Participants' answers did not differ in certainty level between experimental conditions (data not shown), therefore answers of all certainty levels were pooled per answer category (i.e. old and new) for the scoring of MCT performance. The proportion of correct answers to old faces (i.e. hit rate) and incorrect answers to new faces (i.e. false alarm rate) were calculated for both neutral and angry faces, in the congruent and incongruent context. For each valence and context category, participants' ability to discriminate between old and new faces was indexed via the d-prime sensitivity index (d' = Z(hit rate) − Z(false alarm rate) (Stanislaw and Todorov, 1999)). The differences (Δ) in d' between the congruent and incongruent context, for both levels of valence, served as contextualization indices (van Ast et al., 2013; Zhang et al., 2018). Thus, a larger contextualization score, indicates higher context-dependency of memories.

To assess the influence of experimental condition, valence and context on the specificity of retrieved memories, LMMs were fitted to the d-prime sensitivity (d') and contextualization (Δd') indices. Condition, valence, context and their interactions were entered as fixed effects, the random effects contained intercepts for all participants and random slopes for valence and context (Eq.(B.2) in Appendix B). There were no missing data. LMM assumptions were checked and satisfied after removing one influential case (delayed-stress condition). This subject showed a very high false alarm rate (73.3%) compared to his hit rate (47.5%), which suggest that task instructions were misunderstood and the response categories were switched. Tukey adjusted post-hoc pairwise comparisons were used to follow-up main effects or interaction-effects. In addition to d-prime indices, hit rates and false alarm rates were analyzed, results are reported in appendix A (sections A.4 and A.5).

3. Results

3.1. Manipulation check stress induction: sAA and cortisol responses

As expected, the LMMs on salivary ln(sAA) levels revealed a significant time*condition interaction ($\chi2(26) = 211.144$, $p < .000$) and a significant main effect of time ($\chi2(13) = 336.421$, $p < .000$; Table A.2.1). Tukey adjusted post-hoc pairwise comparisons of the experimental conditions at each timepoint showed that TSST reliably increased sAA levels (Fig. 2A, Table A.2.2). At T2, i.e. the moment in time that individuals were subjected to the first (placebo-)TSST (=TSST1), the group that underwent the TSST (delayed-stress condition) had higher ln(sAA) levels than the immediate-stress condition that was subjected to placebo treatment ($t(143.138) = 2.729$, $p = .019$, $d = .456$). The same pattern was observed when participants were subjected to the second (placebo-)TSST (=TSST2). At this time, the group that was subjected to the TSST (immediate-stress condition) had significantly higher ln(sAA) levels than the groups that were subjected to the placebo-TSST (delayed-stress condition (T10: $t(143.138) = -2.376$, $p = .049$, $d = -0.397$) and no-stress condition (T9: $t(143.138) = 2.992$, $p = .009$, $d = .499$; T10: $t(143.138) = 2.830$, $p = .015$, $d = .473$). There were no significant differences in sAA levels between the experimental groups on the other time points (Fig. 2A, Table A.2.2).

The LMMs on ln(cortisol) levels also revealed a significant time*-condition interaction ($\chi2(26) = 417.676$, $p < .000$) and significant main effects of stress ($\chi2(2) = 14.743$, $p = .001$) and time ($\chi2(13) = 374.743$, $p < .000$; Table A.2.3). Tukey adjusted post-hoc pairwise comparisons of the experimental conditions at each timepoint revealed that the TSST led to increased cortisol levels (Fig. 2B, Table A.2.4). For one hour immediately after the TSST1 (T3-T6), cortisol levels in the delayed-stress condition were significantly higher than after the placebo-TSST1 in the immediate-stress condition and no-stress condition (all $p < .001$; see Table A.2.4). TSST2 exposure elevated cortisol levels in the immediate-stress condition, compared to placebo-TSST2 in the delayed-stress condition (T10 & T11, both $p < .01$, see Table A.2.4), and the no-stress condition (T10-T12, all $p < .01$, see Table A.2.4). The manipulation check showed that the relative increase (baseline-peak) in cortisol following the TSST1 in de delayed-stress condition (T2 – T4; EMM: -0.552, $t(1325.220) = -9.643$, $p < .001$, $d = -0.530$) did not differ from the relative increase in levels following the TSST2 in de immediate-stress condition (T9 – T11; EMM: -0.496, $t(1325.544) = -8.609$, $p < .001$, $d = -0.473$).

3.2. Time-dependent effects of stress on memory performance

Mean d-prime sensitivity indices for each experimental condition are depicted in Fig. 3A. The LMMs on the d-prime sensitivity indices (d') revealed a significant 3-way condition*valence*context interaction ($\chi2(2) = 6.930$, $p = 0.031$; Table A.3.1). In addition there were a marginal significant interaction between valence and context ($\chi2(1) = 3.594$, $p = 0.058$; Table A.3.1) and main effect of context ($\chi2(1) = 3.832$, $p = 0.050$; Table A.3.1). Together this indicates that there is contextualization of item memory (main effect context), which is marginally different for neutral and negative items (interaction valence*context), and significantly influenced by the stress manipulation (valence*context*stress interaction). Results of the follow-up Tukey adjusted post-hoc pairwise comparisons (Fig. 3A; Tables A.3.2–4) show that the delayed-stress group specifically recognized neutral faces in the congruent context 1) better than in the incongruent context ($t(193.514) = 3.852$, $p < 0.001$; Table A.3.3) and 2) better than the control group ($t(158.195) = 2.801$; $p = 0.016$; Table A.3.2) This indicates that the delayed-stress condition has a specific effect on neutral memory contextualization.

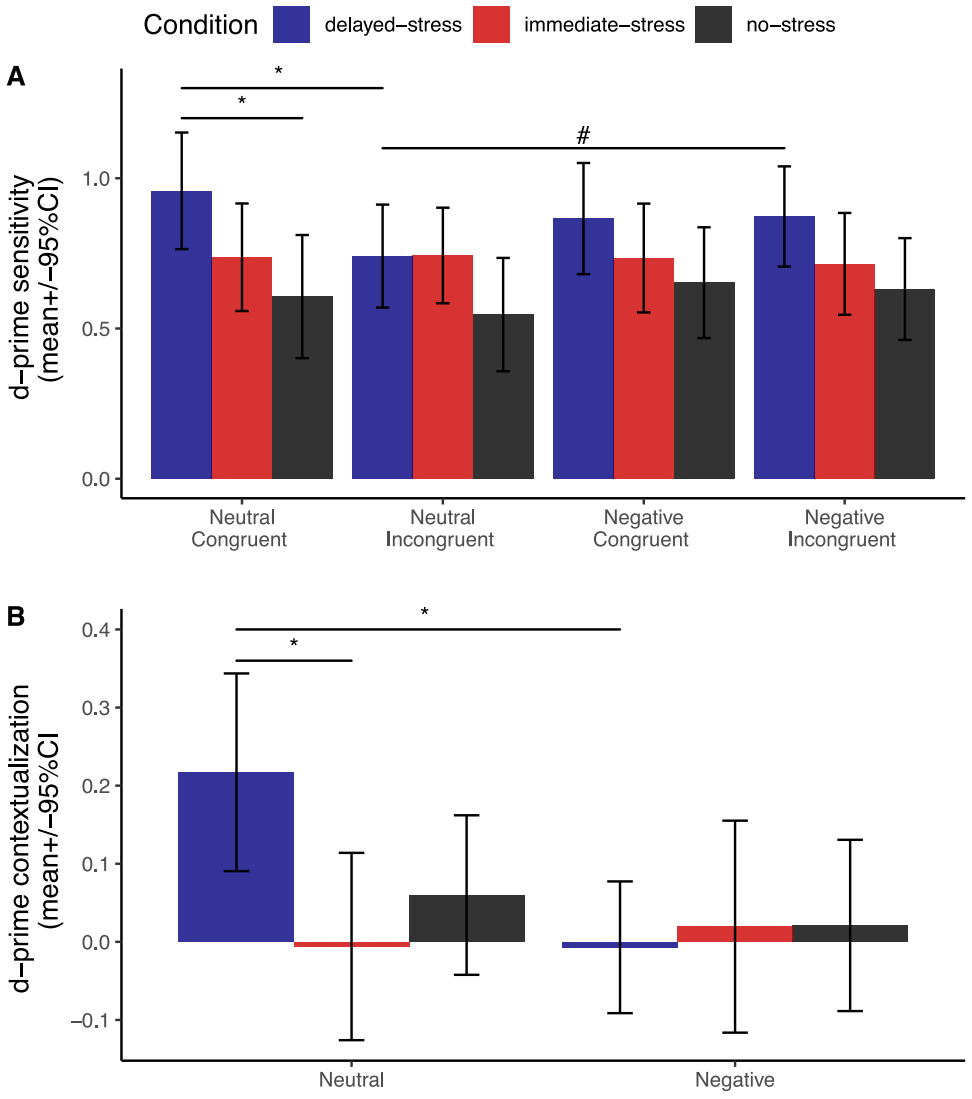

Fig. 3. Memory performance: sensitivity and contextualization indices.
Mean memory sensitivity (d'; A) and memory contextualization (Δd'; B) indices for each context and valence category, per experimental group. Error bars represent 95% confidence intervals. Memories about neutral information were more contextualized by participants in the delayed-stress condition, compared to participants in the immediate-stress condition. Significant Tukey adjusted post-hoc pairwise comparisons ($p < .05$) are indicated with * (#: $p = .05$).

To explore the three-way interaction, LMMs were fitted to the contextualization indices, which represent the factor 'context', using condition, valence and their interaction as fixed effects, and intercepts per subject as random factor. Mean d-prime contextualization indices are shown in Fig. 3B. There was a significant condition*valence interaction ($\chi2(2) = 6.930$, $p = 0.031$; Table A.3.5) and a marginal significant main effect of valence ($\chi2(1) = 3.594$, $p = 0.058$; Table A.3.5). No main effect of condition was observed. Tukey adjusted post-hoc pairwise comparisons revealed that the delayed-stress condition had a higher contextualization index for neutral faces than the immediate-stress condition ($t(193.514) = 2.819$, $p = 0.015$, $d = .405$; Table A.3.6). Note, for this valence category, contextualization indices of both stress conditions did not differ significantly from the no-stress condition (immediate-stress: $t(193.514) = -0.826$, $p = .687$, $d = -.119$; delayed-stress: $t(193.514) = 1.957$, $p = .126$, $d = .281$; Table A.3.6). Furthermore, experimental condition had no significant influence on the contextualization of faces with negative valence (i.e. angry faces) (Table A.3.6). Tukey adjusted post-hoc pairwise comparisons between valence categories are shown in Table A.3.7. Additional analyses of hit rates revealed similar results as the d-prime analyses (Appendix A., section A.4). Experimental condition had no effect on the false alarm rates (Appendix A., section A.5).

4. Discussion

The aim of the current study was to investigate possible time-dependent effects of psychosocial stress on memory contextualization of neutral and negative information in healthy male participants.

4.1. Stress manipulation

The TSST reliably increased sAA and cortisol levels in our study while the placebo-TSST did not, independent of the order in which participants performed these manipulation tasks. Also, the relative increase (baseline-peak) in cortisol levels, due to the TSST, was similar in both stress groups. Our analyses showed that participants in the immediate-stress condition performed encoding in the presence of increased sAA and cortisol levels, while the participants in de delayed-stress group performed encoding approximately 2 h after sAA and cortisol levels were increased; in the latter group the cortisol levels

remained high for some time but, notably, were comparable to placebo treatment at the time of encoding. Importantly, the endocrine levels of the experimental groups did not differ during the recognition test, this confirms that we selectively investigated the time-dependent effects of the endogenous stress response on memory encoding only.

4.2. Time-dependent effects of stress on memory contextualization depend on emotional significance

Overall, we found that the early and late phase of the endogenous stress-response differentially affect the context-dependency of neutral memories. In line with our hypothesis, two hours after stress, neutral information was more contextualized than immediately after stress. Alterations in contextualization can be explained by changed memory performance in either the congruent or incongruent (or both) conditions, as previous literature shows that increasing context-dependency not only improves memory performance for 'old' items in (congruent) context, but also increases false alarms in familiar contexts (thereby hampering memory performance in the incongruent context) (Doss et al., 2018). This phenomenon could be explained by the role of the hippocampus in contextualization (Smith and Bulkin, 2014). There is evidence that contexts become associated with a unique ensemble of hippocampal neurons (that can be associated with memories and behaviors in a certain context) (Smith and Bulkin, 2014). This unique ensemble of neurons (and its association) is reactivated when a context is reencountered, via 'automatic re-expression', which facilitates the recognition of previously associated items, potentially at the cost of 1) recognizing non-associated items and 2) memory specificity (i.e. increasing false alarms) (Smith and Bulkin, 2014). Importantly, in contrast to our hypothesis, the contextualization of neutral material by participants in both stressed groups (i.e. immediate-stress and delayed-stress condition) was not significantly different from the non-stressed participants (i.e. no-stress condition). This could suggest that the time-dependent sequence of non-genomic (during the early phase) and genomic (during the late phase) effects of endogenous stress response fulfil complementary functions, where the late effects could complement the reduction in contextualization caused by the immediate effects.

These findings are in line with the idea that the *early phase* of the stress response improves memory for cues, or central parts of the event, at the cost of contextual information. It has been hypothesized that during negative experiences, upregulation of amygdala activity facilitates item encoding, while downregulation of hippocampal activity reduces contextual binding (Bisby and Burgess, 2017). This phenomenon is in line with previously described observations (McGlade et al., 2019; van Ast et al., 2013; Wiemers et al., 2013) and also known in the literature as attentional narrowing (Kensinger, 2004; Quaedflieg and Schwabe, 2018). The *late phase* of the stress response has been less investigated. Data from our study show that the late effects of stress enhance contextualization of neutral information, compared to the early effects. This suggests that the late effects of the endogenous stress response during encoding facilitate later selective recognition of neutral information in relevant situations.

The observed time-dependent effects on memory contextualization partly follow the pattern of earlier findings with exogenously administered hydrocortisone (van Ast et al., 2013). Here however, emotional significance had a remarkable different influence: endogenous stress only affected the encoding of contextual details from neutral information, whereas hydrocortisone administration only influenced memory contextualization of negative material (van Ast et al., 2013). There are several explanations that might account for this discrepancy. First, exposure to psychosocial stress in the current study activated both the SNS and the HPA-axis; as a consequence memory encoding was studied after the release of catecholamines, corticosteroids and other stress mediators (Joëls et al., 2011; Quaedflieg and Schwabe, 2018). By contrast, van Ast et al. (2013) studied memory encoding by manipulating cortisol levels only (van Ast et al., 2013). Other studies have also shown that catecholamines and cortisol do not necessarily affect cognitive performance in the same direction (e.g. Margittai et al., 2018). Secondly, hydrocortisone administration led to higher cortisol concentrations than a psychosocial stress manipulation (van Ast et al., 2014), which could have caused different effects as the relation between stress levels and memory performance follows an inverted-U-shaped curve (Salehi et al., 2010). Thirdly, van Ast et al. (2013; 2014) used verbal material to study learning and memory (negative and neutral words) instead of faces. A recent study that used words to study explicit associative memories found that immediate pre-encoding stress enhanced memories for the association between high arousal words and neutral objects (Goldfarb et al., 2019). Although our paradigm is different from explicit association paradigms (see section 2.4), it could be argued that neutral and angry faces are biologically more salient, thereby more arousing stimuli than words (Zhang et al., 2018). Indeed, it has been shown that both neutral and emotional faces activate the amygdala, although the response is the strongest for emotional facial expressions (Costafreda et al., 2008; Sergerie et al., 2008; Zhang et al., 2018). As a consequence, our neutral stimuli might have been more arousing than the neutral stimuli used in the earlier study.

In line with our results, other studies have also shown that the immediate effects of stress reduce the context-dependency of neutral visual information, without affecting the contextualization of negative information (Schwabe et al., 2009). It is important to note that these selective effects of stress on neutral memory contextualization do not necessarily contradict previous idea's about the enhancing influence of stress on emotional *item* memory (Cahill et al., 2003; De Quervain et al., 2017; Ferré et al., 2015; Joëls et al., 2011; Payne et al., 2007). Rather, they add specific information on the influence of emotional significance on memory contextualization after pre-encoding stress. Our findings also align with earlier findings that negative information is, *in general*, less context dependent than neutral information (Bisby and Burgess, 2017). A phenomenon that has also been observed in emotional memory studies that adopted a classical fear condition paradigm (Dunsmoor et al., 2017; Starita et al., 2019). Besides, previous studies have shown that the enhancing effect of stress or emotion on memory is not always a common finding, but is greatly influenced by various factors like timing or subjective arousal (Bennion et al., 2013; Goldfarb et al., 2019; Shields et al., 2017).

4.3. Time-dependent neurobiological shift following stress

Our findings align with a growing body of literature on the time-dependent effects of stress (Henckens et al., 2012, 2010; Hermans et al., 2014; Joëls et al., 2012; van Ast et al., 2013; Vinkers et al., 2013, 2011). It has been described that the early phase of the stress response induces a shift from flexible, cognitive-controlled memory towards more habitual, stimulus-response memory (dorsal striatum), via – among others – catecholamines and rapid glucocorticoid effects (Quaedflieg and Schwabe, 2018). This shift is thought to facilitate immediate, efficient selection of well-established behavioral routines during a stressful event (Joëls et al., 2018; Quaedflieg and Schwabe, 2018). Delayed genomic effects of glucocorticoids are believed to restore executive functioning and cognitive control of memory (hippocampus and the prefrontal cortex), to ensure adequate interpretation and rationalization of the event (Joëls et al., 2018; Quaedflieg and Schwabe, 2018). Our finding that the contextualization of neutral memories is enhanced by the delayed genomic effects, might be caused by activation of the hippocampus and prefrontal cortex. A functional magnetic resonance imaging (fMRI) study on the neuronal underpinnings of memory contextualization of neutral faces (Zhang et al., 2018) showed that context-dependency was associated with stronger connectivity between the inferior frontal gyrus (IFG) and 1) amygdala, 2) fusiform gyrus (FG), and 3) parahippocampal gyrus (PHG). This suggests that the IFG in the prefrontal cortex integrates information about salience (amygdala),

facial details (FG) and place and contextual details (PHG) (Zhang et al., 2018). Indeed, it may have been likely that the delayed effects of cortisol have exerted their beneficial effects on contextualization by acting on this very network.

4.4. Implications for the etiology and treatment of anxiety disorders

The differential early and late effects of stress on memory contextualization of neutral items, might play a role in the pathology of anxiety disorders. It has been hypothesized that an imbalance between the immediate and the delayed effects of stress on the brain increases vulnerability to psychopathology after traumatic or stressful events (Joëls et al., 2018). In line with this idea, it has been suggested that inflexible habit memory, promoted by the immediate effect of extreme stress, facilitates the formation of strong associations between trauma-related cues and emotional responses in PTSD (De Quervain et al., 2017). Linguistic research showed that trauma narratives are indeed dominated by emotional and sensory details (Crespo and Fernandez-Lansac, 2016). A revised version of the dual representation theory of PTSD proposes that flashbacks arise from an imbalance in encoding of sensory and contextual details of a traumatic event (Brewin and Burgess, 2014). Interestingly, the ability to contextualize memories - of which we here show that it can be improved by the delayed effects of stress - protected against intrusions from a distressing trauma film in healthy participants (Meyer et al., 2017).

Our findings not only shed light on the etiology of anxiety disorders, but can also inform strategies for their treatment. It has been shown that effectivity of an evidence-based treatment for anxiety disorders, cognitive-behavioral therapy (including exposure therapy) (Hofmann and Smits, 2008), is highly context-dependent (Podlesnik et al., 2017). Possibly due to the role of contexts in the acquisition and extinction of chained behaviors (which are hypothesized to play an important role in relapse after successful therapy) (Thrailkill and Bouton, 2017). Interestingly, there is evidence that cortisol administration prior to exposure therapy can increase therapy efficacy for anxiety disorders (De Quervain et al., 2017), while post-exposure cortisol does not (Raeder et al., 2019). This highlights the importance of timing for cortisol add-on therapies. Meir Drexler and colleges propose a model for the effects of stress and cortisol on context-dependency of (fear) extinction and relapse (Meir Drexler et al., 2019). In line with our findings that the immediate effects of stress reduce memory contextualization, they show that stress pre-extinction reduces context-dependency of extinction, thereby reducing the risk for relapse. This could point towards a shared mechanism for the influence of stress on memory contextualization and context-dependent fear-extinction (Meir Drexler et al., 2019). Following this reasoning, the delayed effects of stress, which enhance context-dependency as we show here, might counterintuitively reduce the efficacy of exposure therapy by preventing the generalization of exposure memories (Podlesnik et al., 2017; Thrailkill and Bouton, 2017).

4.5. Limitations

There are some limitations to our study. First, only male participants were included in this study. As it is known that sex influences stress and memory processes (Cornelisse et al., 2011; De Quervain et al., 2017; Wolf et al., 2001), our results are not generalizable to women. For example, the variability in HPA-reactivity to acute stress between men and women (Kajantie and Phillips, 2006) could change the interaction between contextual details, emotional significance and stress. To elaborate on the role of gender, future studies should include pre-menopausal women (corrected for the use of (oral) contraceptives, as these can blunt HPA-reactivity to acute stress (De Quervain et al., 2017)) and post-menopausal women too. Secondly, it has been reported that stress also influences attention and working memory (Henckens et al., 2012, 2011). For example, striatal activity (which is promoted by the immediate effects of stress (Quaedflieg and Schwabe, 2018)) guides attention based on learned stimulus-response associations, while hippocampal activity (promoted by the delayed effects of stress (Quaedflieg and Schwabe, 2018)) facilitates context-guided attention (Goldfarb et al., 2016). Unfortunately, we cannot distinguish these effects from memory encoding in our set-up. Thirdly, because our task included only neutral and negative stimuli, we cannot determine if the influence of emotional significance was due to differences in valence or arousal (Ford et al., 2012; Mickley Steinmetz and Kensinger, 2009; Roozendaal et al., 2009). Future studies could include positive stimuli to disentangle these effects. Fourthly, although we consider the used paradigm valid to measure memory contextualization based on previous studies (van Ast et al., 2014, 2013; Zhang et al., 2018) and we did find an overall effect of context on memory, memory performance in our study is lower than previously reported (although the rates are not uncommon in emotional memory research (Dunsmoor et al., 2015)). Task difficulty might have been influenced by the use of neutral and negative faces instead of words in mixed-lists might in our study (Tambini et al., 2017; Zhang et al., 2018). Performance could have also been influenced by the relative long experimental protocol as participants performed encoding after 3 h in the lab. Fifthly, although we used statistical methods to detect influential cases, we did not exclude trials or participants from the analyses based on individual performance criteria (e.g. significant memory performance). This might have increased 'noise' in our analysis, but also strengthens the validity of our analyses and results. Finally, the stressful event in the current study (TSST) was not part of the to-be-remembered material, which *is* the case in real-life situations. The reproducibility of the stress situation was essential to study the distinct influences of early and late phases of the stress response on encoding of neutral and negative material separately; however, it limits the generalizability of our findings to stressful experiences in real-life.

4.6. Conclusion

Our findings underline that the interplay between stress, emotional significance and contextual details during encoding is highly complex. Our study shows acute psychosocial stress evokes an endogenous stress response with differential early and late effects on the contextualization of neutral information. More specifically, two hours after stress, neutral information was more contextualized then immediately after stress. Our results suggest that the sequence of these time-dependent effects in a healthy endogenous stress response allows the late effects to complement the reduced contextualizaiton immediatly after stress. An imbalance between the early and late effects of the endogenous stress response could increase vulnerability for stress-related psychopathology. Ideally, this hypothesis should be tested in future research by means of a prospective study design.

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CRediT authorship contribution statement

Milou S.C. Sep: Conceptualization, Methodology, Software, Formal analysis, Investigation, Data curation, Writing - original draft, Visualization, Project administration, Funding acquisition. **Vanessa A. van Ast:** Conceptualization, Methodology, Writing - review & editing, Supervision. **Rosalie Gorter:** Methodology, Software, Formal analysis, Writing - review & editing. **Marian Joëls:** Conceptualization,

Methodology, Resources, Writing - review & editing, Supervision, Funding acquisition. **Elbert Geuze:** Conceptualization, Methodology, Resources, Writing - review & editing, Supervision, Funding acquisition.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.psyneuen.2019.06.021.

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