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Memories in context: On the role of cortisol

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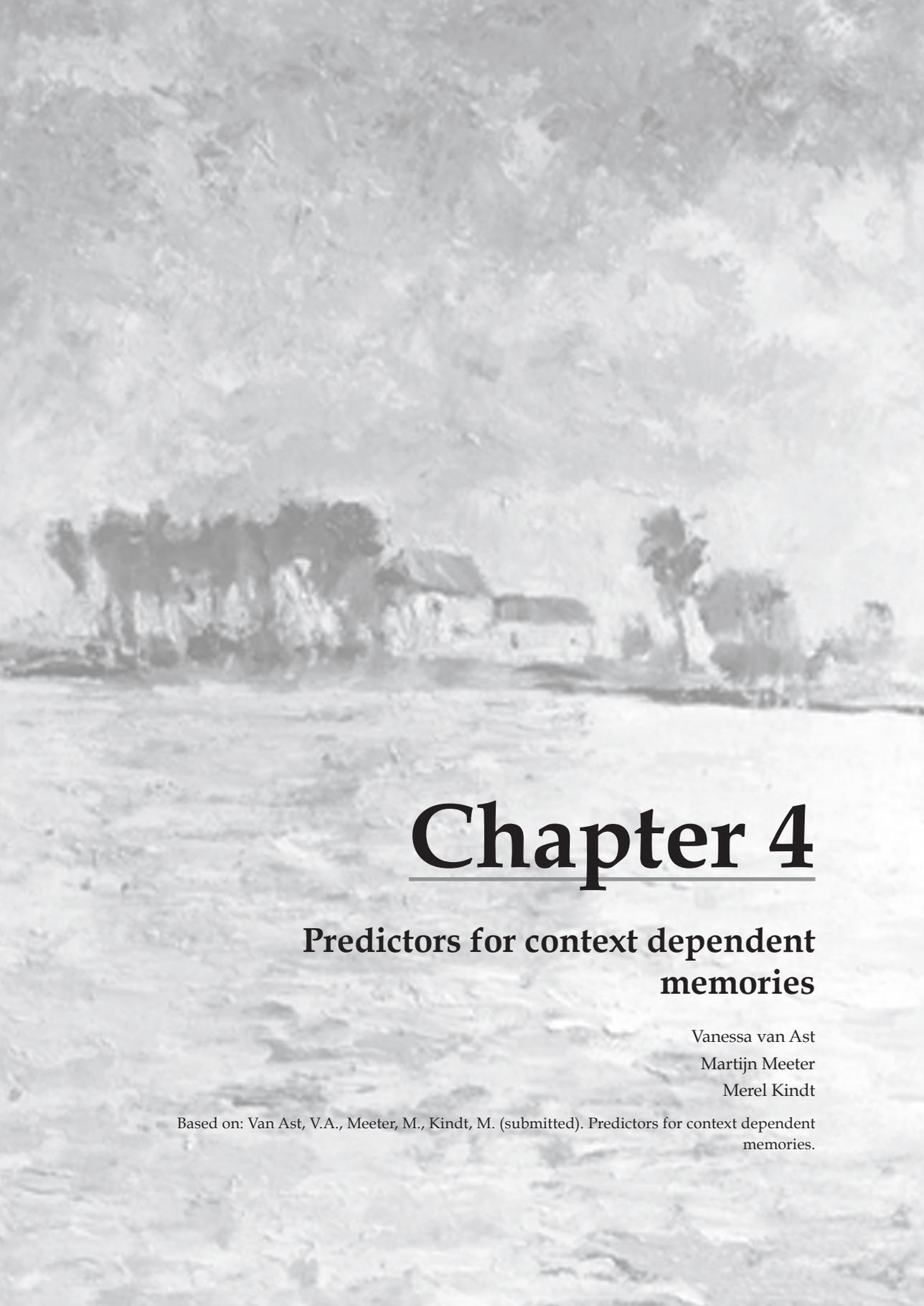
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A grayscale impressionistic painting of a coastal scene. In the foreground, there's a body of water with visible ripples. In the middle ground, a small house with a dark roof is nestled among trees. The background shows a hazy, textured sky. The overall style is soft and painterly.

Chapter 4

Predictors for context dependent memories

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Based on: Van Ast, V.A., Meeter, M., Kindt, M. (submitted). Predictors for context dependent memories.

SUMMARY

By flexibly enabling the disambiguation of certain cues in the environment and altering the accessibility of memories, contexts are indispensable for adaptive behavior in an ever-changing environment. Indeed, the incapability to store memories into their original encoding context (i.e., memory contextualization) has been suggested to be a vulnerability factor for posttraumatic stress disorder (PTSD). Here we examined whether other known vulnerabilities for PTSD such as trait anxiety, chronic stress, depression and alterations in baseline cortisol are related to alterations in memory contextualization. During encoding, participants were presented with pictures of faces displaying neutral and fearful expressions, against unique background pictures. Approximately 24 hours later, context dependency of memory for these faces was assessed. The results revealed that trait anxiety was related to weakened memory contextualization of both neutral and emotional faces, while chronic stress seemed to enhance memory contextualization. Depression, and trait anxiety too, were associated with enhanced memory for faces by previously seen contexts, independent of context congruency (i.e., non-specific contextualization). No effects were found for cortisol. In conclusion, the results presented here shed a closer view on which individual differences are related to enhanced versus impaired alterations in clearly defined aspects of memory. Overall, the findings support a model in which alterations in the usage of context to shape behavior form an endophenotype that is related to psychological dysfunction.

1. INTRODUCTION

After a specific threatening situation, somebody suffering from posttraumatic stress disorder (PTSD) may subsequently experience intense fear in situations that bear similar attributes as the original experience, but that are non-threatening in nature. Thus, instead of generalizing fear across contexts, an adaptive mechanism would be to compare present experiences to stored specific representations, so that fear or anxiety should only be evoked by cues that truly predict danger. In this respect, the context surrounding encoding and retrieval of central (fear) memories plays an imperative role in whether (and how) these memories are remembered, and can thereby protect against memory generalization. Indeed, memory retrieval is generally enhanced when the encoding context and retrieval context are similar (Godden and Baddeley, 1975). This implies that items and contexts are bound together during encoding (i.e., memory *contextualization*), such that the reinstatement of the initial context at test improves memory retrieval. This ability is highly adaptive as it aids in subsequently retrieving memories that are likely to be appropriate in a specific context. By flexibly enabling the disambiguation of certain cues in the environments and altering the accessibility of memories, contexts are indispensable for adaptive behavior in an ever-changing environment. Therefore, it is not surprising that impairments in contextualization processes may be associated with several forms of psychopathology, including PTSD, schizophrenia and substance abuse disorders (Davidson et al., 2000; Maren et al., 2013; Talamini et al., 2010).

The hippocampus has been suggested to underlie context effects on memory (e.g. O'Reilly and Rudy, 2000), as it binds together multiple elements of an experience into a novel conjunctive representation (Eichenbaum, 2004; O'Reilly and Rudy, 2000). Interestingly, there is a range of known individual differences related to alterations in hippocampal function (or structure) as well as altered memory function. And these factors seem to be associated with vulnerability for PTSD as well. One such factor is trait anxiety (Chambers et al., 2004), which has been shown to predict symptom severity in PTSD (Richman and Frueh, 1997). An influential neuroanatomical theory of anxiety (Gray and McNaughton, 2000) has claimed a crucial role for the hippocampal formation in anxiety behavior. Animal research indeed has revealed a negative relationship with trait anxiety and hippocampal volume in otherwise healthy rats (Kalisch et al., 2005). Also, reduced hippocampal neurogenesis appeared to be associated with heightened behavioral inhibition to naturally aversive situations (Earnheart et al., 2007). In humans positive (Rusch et al., 2001) as well as negative relations (Gallinat et al., 2005) with trait anxiety (or harm avoidance, Yamasue et al., 2007) and hippocampal volume has been revealed.

Secondly, we have previously shown that stress-induced cortisol can enhance memory contextualization (Van Ast et al., 2014), while very high cortisol levels by a hydrocortisone manipulation impaired it (Van Ast et al., 2013). Cortisol thus seems to be an important agent in altering memory (contextualization) processes, but the role of baseline cortisol has not been tested. Hypocortisolism has been related to PTSD, such that individuals with PTSD experience lower resting levels of peripheral cortisol and enhanced negative feedback mechanisms (Yehuda and LeDoux, 2007). Prospective studies have revealed that low cortisol responses early after trauma predicted increased risk for PTSD symptoms (McFarlane, 1989), while cortisol administration reduced risk (Schelling et al., 2004). Therefore, it has been suggested that lower baseline cortisol may confer risk for PTSD (Yehuda et al., 2000). Possibly in line with this idea, cumulative exposure to high glucocorticoid levels (resulting in an overshoot-reaction that is characteristic of a feedback response to a disturbance in homeostatic control; Sapolsky, 2003) throughout life leads to atrophy of hippocampal neurons (Kim and Diamond, 2002). Indeed, chronic stress has been shown to modulate learning strategies (Schwabe et al., 2008b) and it has been related to psychiatric disorders such as PTSD as well (e.g., Willner, 1997).

A fourth and final variable of interest is depression. Structural abnormalities of the hippocampus have been extensively investigated with respect to major depression: Reduced hippocampal volume was found to relate to depression severity (Videbech and Ravnkilde, 2004) and high-risk individuals with subclinical depression showed a smaller hippocampal volume as well (Dedovic et al., 2010). One study assessed hippocampal function using a virtual-reality spatial memory navigation task and found that depressed subjects performed significantly worse than controls (Gould et al., 2007), providing more specific evidence for hippocampal-dependent memory alterations. In accord, a rare fMRI study on hippocampal functioning during associative memory encoding found a dysregulation of the normal relationship between hippocampal activation and encoding success in an MDD sample (Fairhall et al., 2010).

Summarizing the above, trait anxiety, depression, chronic stress, and baseline cortisol have all strong links with alterations in hippocampus-dependent memory and PTSD, but it is unclear whether these factors also alter the ability to contextualize memories – hypothetically closely related to memory specific impairments in PTSD. Furthermore, since amygdala recruitment during emotional arousal is proposed to modulate other medial temporal lobe (MTL) structures to facilitate encoding and consolidation of emotional material (Dolcos et al., 2004), it can be predicted that these effects are strongest for emotional material. This is in line with theoretical models

predicting that emotional experiences weaken context dependent memory, resulting in impaired associations between items and their context (Brewin et al., 2010).

To induce neutral versus emotional memories, participants were presented with faces of individuals displaying neutral and fearful facial expressions depicted against unique background pictures. Approximately 24 hours later, memory contextualization was assessed; a subset of the faces was tested in intact face-context combination, while another subset was tested in a rearranged context-combination (see **Figure 1**). Enhanced memory performance in intact relative to rearranged combinations represents stronger *specific* contextualization; memory is enhanced because of the original unique face-context combination. Another possibility is that, relative to an old face in a new context, the tendency to recognize a face in a rearranged combination is enhanced by the mere presence of an old context, even though that specific face-context combination has not been seen before. To measure this second effect of context - which we will refer to as non-specific context sensitivity, we included a condition with old faces depicted in new contexts as control condition. In summary, during recognition, subsets of old faces were presented in either one out of three possible face-context combinations: 'intact', 'rearranged', or 'oldface' (and new context). The difference in memory between the intact and rearranged conditions represents specific memory contextualization, while the difference between the rearranged and oldface condition represents non-specific context sensitivity. To control for the old faces presented in either old contexts (intact and rearranged conditions) or new contexts (oldface condition), foil (new) faces were presented against old or new contexts. Further, we added an associative memory test to the design where we explicitly tested memory for the association between the face and the background image. It is presently unclear how context effects on recognition relate to associative memory. We tested our hypotheses by regressing the specific contextualization and non-specific context sensitivity indices on measures of trait anxiety, chronic stress, depression and baseline cortisol. For explorative purposes, similar analyses were run with difference scores in associative memory. Finally, in addition to objective alterations in memory performance, we also conducted exploratory analyses to test for changes in the subjective quality of memories (Yonelinas, 2002).

2. MATERIALS AND METHODS

2.1. Participants

In total 13 men with a mean age of 21.31 years ($SD=4.71$, $range=18-36$) and 34 women with a mean age of 19.97 ($SD=2.23$, $range=18-27$) gave written informed consent and completed the study. Inclusion criteria as assessed by self-report were: no past or

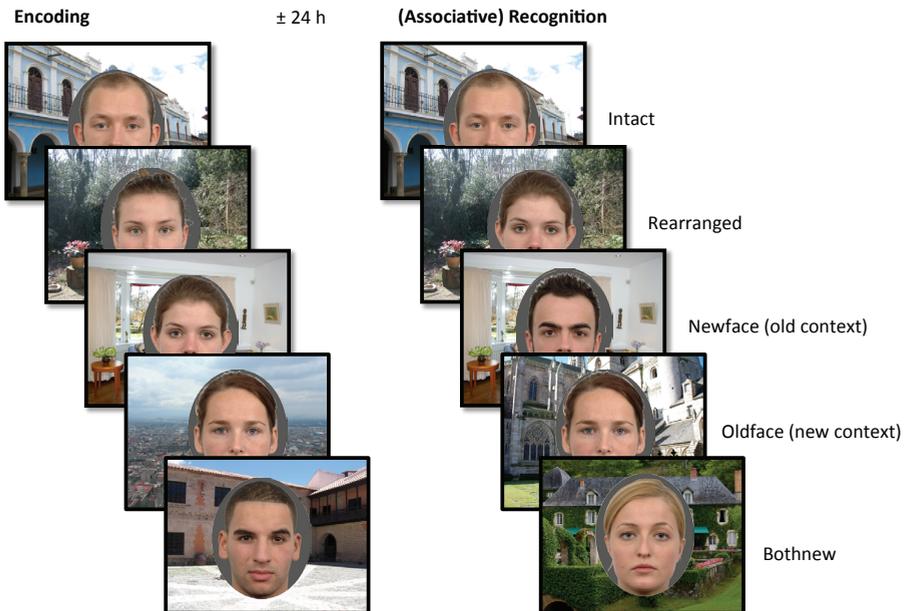


Figure 1. Experimental paradigm. During encoding participants were shown 72 unique faces, half of which were individuals with a neutral facial expression and half of which had a fearful facial expression. Each face was shown against a unique color picture. Participants were instructed to vividly imagine the depicted individual in the background by for example thinking of the way the person would feel there, or what the person would be doing, etc. During the recognition test 24 face-context sets from the encoding session remained intact (“intact”), 24 sets were presented in a rearranged combination (“rearranged”), and the contexts out of the 24 remaining encoding sets were presented with a new face and old context (“newface”) while the old faces were presented with a new context (“oldface”). Finally, 24 entirely new face-context sets were presented as well (“bothnew”). Here, faces and contexts were not presented partly sequential, but in parallel. In each condition, half of the 24 face-context combinations were with fearful faces and the other half with neutral faces. In total, 120 recognition trials were presented. Subjects were instructed to indicate whether or not they recognized the face as having seen during the encoding task. After their first response, participants were asked to indicate how sure they were of their response on a 5-point scale ranging from 1 “very unsure” to 5 “very sure”. The trial ended with an intertrial interval of 1 second. After Face Recognition, the same 120 trials from the recognition test were presented again for associative recognition. Participants were asked whether the face-context *combination* had been presented the day before.

present psychiatric or neurological condition, and age between 18 and 40 years. Participants having any somatic or endocrine disease (e.g., acute asthma), or taking any medication known to influence central nervous system or endocrine systems were excluded from participation. Further, participants were asked to refrain from taking any drugs three days prior to participation, and to get a night of proper sleep, refrain from heavy exercise, alcohol and caffeine intake 12 hours prior to participation, and

not to eat, drink, smoke or brush teeth two hours before participation. Participants were rewarded for their participation with course credits or paid € 24,-. The local ethical committee of the University of Amsterdam approved the study, which was performed in accordance with the Helsinki declaration.

2.2. Memory task

The memory task consisted of an encoding phase on day 1, and a face recognition phase and an associative recognition phase on day 2 that followed immediately after one-another. All tasks were programmed in presentation (Neurobehavioral Systems Inc., San Francisco, CA, USA).

2.2.1. Encoding

During encoding participants were shown 72 unique faces, half of which were individuals with a neutral facial expression (36; 18 males) and half of which displayed a fearful facial expression (36; 18 males). Faces were shown in a gray oval that was presented against unique color pictures depicting for example natural scenes or city landscapes (see **Figure 1**). Faces were drawn from the the Karolinska Directed Emotional Faces dataset (KDEF; Lundqvist et al., 1998), the Radboud Faces Database (RaFD; Langner et al., 2010) and the NimStim set of facial expressions (Tottenham et al., 2009). Care was taken to select those individuals that were rated as best suiting the intended facial expression from each dataset. Background pictures were selected from personal collection. The images contained no distinguishing objects, thus distinctiveness of the contexts relied on their unique spatial configuration. Participants were instructed to vividly imagine the depicted individual in the background by for example thinking of the way the person would feel there, or what the person would be doing, etc. These instructions were given to promote 1) deep encoding (Craik and Lockhart, 1972), 2) to effectively bind the face within its unique context, 3) as an incentive to encode the face-context combinations since otherwise no explicit instructions to remember the stimuli were given and 4) to create a complete and rich ecologically valid episodic memory. A typical trial (see **Figure 2**) commenced with the onset of a context picture for 1 second, followed by a window of 4 seconds where both the context and face were presented together. Then, the context disappeared, and the face was still visible for 1 second. By using this shifted trial set-up, we ensured that the context-face combination had to be actively bound together, instead of being encoded as one single compound (Staresina and Davachi, 2010). Half a second after face offset participants evaluated their mental image on arousal and valence dimensions using self-assessment manikins (SAM; Bradley and Lang, 1994) in a fixed time window of 4 seconds for each rating, with 1 second in between

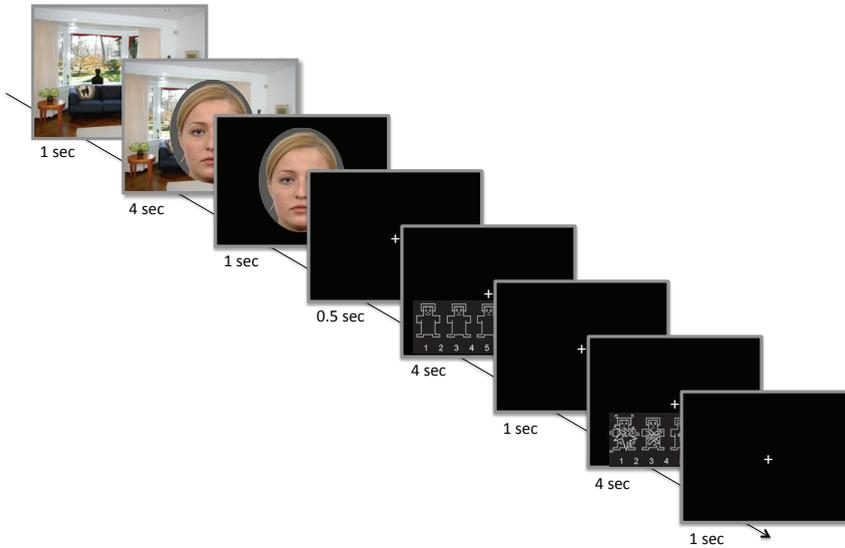


Figure 2. A typical trial commenced with the onset of a context picture for 1 second, followed by a window of 4 seconds where both the context and faced were presented together. Then, the context disappeared, and the face was still visible for 1 second. Half a second after face offset participants evaluated their mental image on arousal and valence dimensions using self-assessment manikins (SAM; Bradley and Lang, 1994) in a fixed time window of 4 seconds for each rating, with 1 second in between the ratings. In between trials a black screen with a fixation cross was presented for 1 second.

the ratings. In between trials a black screen with a fixation cross was presented for 1 second. Context-face combinations were randomized within 24 blocks of three different to-be trial types (i.e., “intact”, “rearranged”, and “oldface” or “newface”, see below for further description) to prevent any unwanted order effects on memory the following day.

2.2.2. Face recognition

During the surprise recognition test 24 face-context sets from the encoding session remained intact (“intact”), 24 sets were presented in a rearranged combination (“rearranged”), and the contexts out of the 24 remaining encoding sets were presented with a new face and old context (“newface”) while the old faces were presented with a new context (“oldface”). Finally, 24 entirely new face-context sets were presented as well (“bothnew”). Unlike the encoding phase, faces and contexts were not presented partly sequential, but in parallel. In each condition, half of the 24 face-context combinations were with fearful faces and the other half with neutral faces. Gender of the depicted individuals was equally divided over fearful and neutral individuals. In total, 120 recognition trials were presented. Subjects were instructed to indicate

whether or not they recognized the face as having seen during the encoding task, by responding “old” (the letter ‘z’ on the keyboard) or “new” (letter ‘m’), respectively. In addition they were told that the background image may or may not be the same, but that they should focus on the faces. Reaction times of these responses were recorded. After their first response, participants were asked to indicate how sure they were of their response on a 5-point scale ranging from 1 “very unsure” to 5 “very sure”. The trial ended with an intertrial interval of 1 second. The entire test was self-paced.

2.2.3. Associative recognition

After Face Recognition, the same 120 trials from the recognition test were presented again for associative recognition. Now, instead of focusing on the face, participants were asked whether the face-context *combination* had been presented during encoding. During presentation of the face-context combination three response options appeared: 1) “intact”, 2) “rearranged”, 3) “new”. If participants responded with “new” they were further probed to indicate whether 1) the face, 2) the background, or 3) both the face and the background were new. The response options corresponded with keyboard numbers. The test was again self-paced.

2.3. Salivary cortisol

Saliva samples were obtained using Salivette devices (Sarstedt, Nümbrecht, Germany) at 3 time points spread throughout the experiment (**Figure 3**). After testing, the salivettes were stored at -25°C . Upon completion of the entire study, samples were sent out to the Technische Universität Dresden, Germany for biochemical analysis. Salivary free cortisol concentrations were assessed using a commercially available

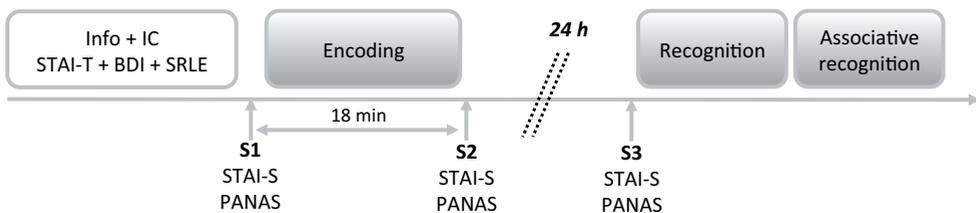


Figure 3. Timeline of the experiment. Upon arrival, participants filled out the informed consent (IC) followed by personality questionnaires assessing trait anxiety (STAI-T), depression inventory (BDI) and chronic stress (SRLE). Prior to memory encoding baseline mood questionnaires (PANAS and STAI-S) along with a baseline saliva sample (S1) were taken. After memory encoding, the mood questionnaires were again filled out along with a second saliva sample (S2). Memory testing took place approximately 24 hours after encoding. This session commenced with the mood questionnaires and a third saliva sample (S3), followed by the recognition and associative recognition tests.

chemiluminescence immuno-assay (CLIA) with high sensitivity of 0.16 ng/ml (IBL, Hamburg, Germany).

2.4. Subjective measures

2.4.1. SRLE

The survey of recent life experiences (SRLE; de Jong et al., 1996) assessed daily stress hassles in the last month, and consists of 41 questions that have been shown by factor analysis to load on 6 moderately independent subscales: 1) social and cultural difficulties, 2) work, 3) time pressure, 4) finances, 5) social acceptability, 6) social victimization.

2.4.2. BDI

The Beck depression inventory (BDI; Beck et al., 1988) is a 21-item self-report measure of depressive symptomatology. Subjects rate whether they have experienced each symptom during the past few days. The BDI is commonly used to assess mild to moderate levels of depression.

2.4.3. STAI-T/S

The Spielberger State-Trait Anxiety Inventory (STAI-Trait; Spielberger et al., 1979), are 20-item self-report questionnaires assessing anxiety proneness for current state and trait anxiety. All items are rated on a Likert-scale ranging from 1 (not at all) to 4 (very much) and are summed up to produce a total score (20 – 80), with higher scores indicating more trait anxiety.

2.4.4. PANAS

To assess possible changes in mood, the Dutch version of the Positive and Negative Affect Scale (Watson et al., 1988) is used. The PANAS is a 20-item self-report measure consisting of two mood scales, one assessing positive and one assessing negative affect. Items are rated on a 5-point scale ranging from 1 (*very slightly or not at all*) to 5 (*extremely*), reflecting how participants feel at the very moment.

2.5. Procedure

A schematic outline of the experimental procedure is depicted in **Figure 3**. Testing took place in between 1 pm and 7 pm, when endogenous cortisol levels are stable and relatively low (Pruessner et al., 1997). Upon arrival, participants read the information brochure, were screened by means of an interview to assess eligibility for participation and signed the informed consent, followed by completion of the

trait scale of the STAI-T, SRLE and BDI. Along with baseline mood questionnaires (PANAS and STAI-S) a baseline saliva sample (S1) was taken. Then, instructions for the encoding task were given orally, which were repeated on screen directly before encoding. After encoding a second saliva sample (S2) was taken along with the mood questionnaires (PANAS and STAI-S). To allow for sufficient consolidation time, memory testing took place approximately 24 hours later. The second test session commenced with the mood questionnaires (PANAS, VAS and STAI-S; T6), BP and HR measurement followed by the cued retrieval and recognition tests. Finally, the exit questionnaire was filled out and the experimenter debriefed the participant.

2.6. Data analysis

Statistical analysis was performed using the SPSS statistical software package (SPSS Inc., Chicago, Illinois). Arousal and valence ratings of the faces obtained during the encoding task on day 1 were analyzed by means of a repeated measures ANOVA with the repeated measure Emotion (emotional, neutral) as within-participant factor. Effects of mood (STAI and PANAS) were tested as covariates in this analysis). To test for possible influences of trait anxiety, cortisol, depression and chronic stress on memory ratings and to test the possibility that these ratings mediated their effects on memory measures the following day, we regressed the valence and arousal ratings on the predictors, and we regressed the memory contextualization measures on the subjective ratings, respectively.

For the recognition test of the faces hit rates (i.e., correct classification of previously presented faces as “old”) were calculated as a function of Context and Emotion (i.e., neutral intact, neutral rearranged, neutral oldface, emotional intact, emotional rearranged, emotional oldface). False alarm rates (i.e., misclassification of new words as “old”) were similarly calculated for all combinations (neutral newface, neutral both new, emotional newface, emotional bothnew). Using the hit and false alarm rates (collapsed over newface and bothnew) d-prime sensitivity index as a function of context and emotion was calculated, according to signal detection theory. For this goal hit rates were truncated at 0.975, and false alarm rates at 0.025 (Stanislaw and Todorov, 1999). Recognition d-prime data were analyzed by means of an omnibus ANOVA with the repeated measures factors Context (intact, rearranged, oldface) and Emotion (neutral, emotional).

Further, since recognition judgments are thought to be based on the contribution of a continuous familiarity dimension along with an independent recollection process that also contributes to memory performance (Yonelinas, 1997), we also calculated receiver-operating characteristics (ROC) for all conditions by calculating the relationships of hits and false alarms as a function of response confidence. A

least squares algorithm (Yonelinas, 1997) was used to estimate the intercept and the degree of curvilinearity observed in each ROC, which reflects recollection (R_0) and familiarity (d'), respectively. A Greenhouse-Geisser procedure was used in case of violation of the sphericity assumption in ANOVAs. Alpha level was set at .05 for all statistical analyses.

Specific memory contextualization indices for the several types of memory assessments (e.g., d -prime, recollection) were computed by subtracting measures of the rearranged condition from the intact condition. Thus, a larger specific contextualization index reflects greater *specific* contextual dependency of memories. To test for *non-specific* context sensitivity, we computed the difference between the rearranged and oldface condition. A bigger non-specific context sensitivity index represents enhanced sensitivity to use any old - *non-specific* to the original face-context combination - context to reinstate a memory. Finally, to test hypothesized predictors of the two types of context effects on memory, we regressed specific contextualization and non-specific context sensitivity indices against trait anxiety, cortisol, depression and chronic stress on memory contextualization using multiple regression. As a control analysis, we also regressed general memory performance on the predictors. That is, we used general memory performance take over the intact, rearranged and oldface condition, thereby disregarding the effect of context in the analysis, as the dependent variable.

For the associative recognition memory task we calculated associative accuracies for all conditions (i.e., intact, rearranged, oldface, newface, bothnew). Since our primary interest was the difference between associative hits for intact and rearranged combinations and the difference between associative hits for rearranged and oldface conditions, we calculated hit rates for the intact, rearranged and oldface conditions (i.e., correct classification of previously presented face-context combinations as "intact", "rearranged", or "oldface", respectively). We also calculated associative intact, rearranged or oldface false alarm rates (i.e., incorrect classification as "intact", "rearranged" or "oldface", of combinations on all conditions). With these terms d -prime sensitivity index was calculated for the three combinations for neutral and fearful times separately and collapsed over emotion.

3. RESULTS

3.1. Subjective ratings during memory encoding

To assess whether the induction of neutral versus emotional mental images was successful, we analyzed the neutral and emotional faces on ratings of valence and arousal obtained during the encoding task. Ratings are depicted in **Figure 4A**. As

expected, the fearful faces imagined in their respective contexts were rated significantly more negative ($F_{1,43} = 80.74, p < 0.001, \eta_p^2 = 0.652$) and significantly more arousing ($F_{1,43} = 149.64, p < 0.001, \eta_p^2 = 0.777$). Mood did not affect ratings (all $F_{1,41} < 2.551, all p > 0.118$). Trait anxiety, chronic stress, cortisol or depression did not predict ratings (all $p > 0.164$), neither did the neutral or fearful ratings predict any of the memory contextualization (all $p > 0.207$) or associative measures (all $p > 0.891$). Thus, the experienced intensity of the stimuli during encoding did not mediate possible effects of individual differences on subsequent memory (Baron and Kenny, 1986).

3.2. Context effects on memory recognition

3.2.1. Hit and false alarm rates

To assess context effects on hit and false alarm rates (see **Figure 4B**), we first subjected the hit rate data to a 2×2 repeated measures ANOVA with Context (intact, rearranged, oldface) and Emotion (neutral, emotional) as within-participant factors. As can be seen in the left panel of **Figure 4B**, Context exerted a strong influence on whether a face was recognized or not ($F_{2,88} = 15.08, p < 0.001, \eta_p^2 = 0.255$). Planned contrasts revealed that the hit rate was higher in intact contexts than rearranged contexts - demonstrating the presence of specific memory contextualization ($F_{1,44} = 7.13, p = 0.011, \eta_p^2 = 0.140$), and higher in rearranged contexts than in a new context - demonstrating non-specific context sensitivity ($F_{1,44} = 8.00, p = 0.007, \eta_p^2 = 0.154$). The interaction with- and/or main effect of Emotion did not reach significance (all $F < 1.82, all p > 0.169$). The false alarm rate data revealed that false alarms were higher when the context was old than when it was new ($F_{1,44} = 12.71, p = 0.001, \eta_p^2 = 0.224$), and when the facial expression was emotional than when it was neutral neutral ($F_{1,44} = 27.08, p < 0.001, \eta_p^2 = 0.381$). These two factors did not interact ($F_{1,44} = 2.55, p = 0.117$).

3.2.2. Confidence ratings

Analysis of confidence ratings (See **Figure 4C**) for the correctly identified old items revealed a main effect of context ($F_{2,88} = 4.64, p = 0.012, \eta_p^2 = 0.097$). Confidence ratings for the false alarms revealed a marginally significant main effect of Emotion ($F_{1,28} = 3.95, p = 0.069, \eta_p^2 = 0.114$), with more confidence for the fearful items. None of the other effects reached significance (All $F < 2.66, all p > 0.110$).

3.2.3. D-prime

Hit rates and false alarm rates were converted to d' , a measure of memory sensitivity (see **Figure 4D**). Context exerted a strong influence on whether a memory was recognized or not ($F_{2,88} = 15.97, p < 0.001, \eta_p^2 = 0.266$). Planned contrasts revealed

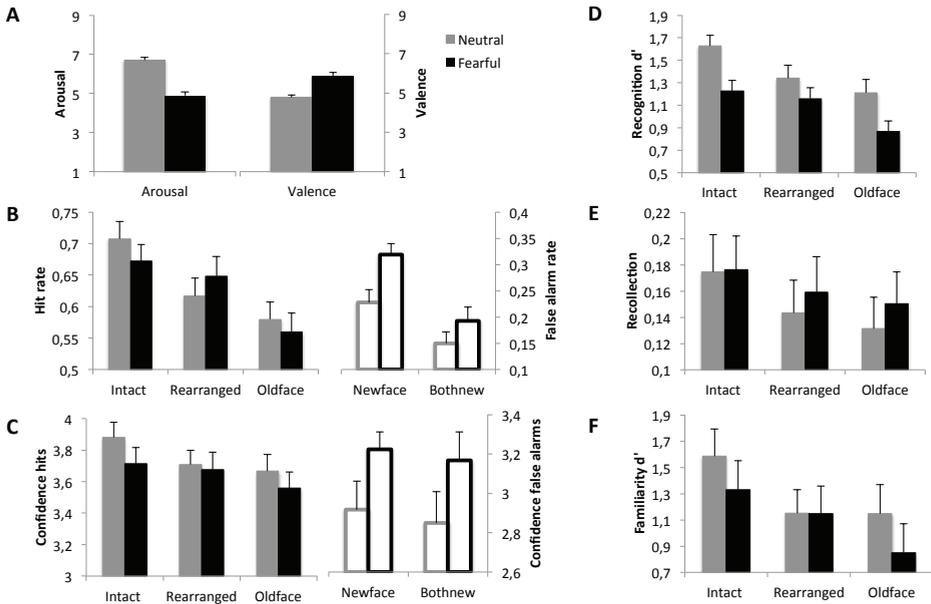


Figure 4. Arousal and valence ratings. **(A)** The graph depicts arousal and valence ratings of the mental images of the faces in contexts that participants formed during encoding at the first day of the experiment. **(B)** Hit rate during recognition testing. The graph depicts memory performance indexed by mean hits, as a function of context (intact, rearranged and oldface) and emotion (neutral or emotional). The right panel depicts false alarm rates as a function of emotion (neutral or fearful) and context (newface, bothnew). **(C)** Confidence ratings during recognition testing. The graph depicts mean confidence for hits, as a function of context (intact, rearranged and oldface) and emotion (neutral or emotional). The right panel confidence ratings for false alarm rates as a function of emotion (neutral or fearful) and context (newface, bothnew). **(D)** Recognition performance. Graphs depict memory performance indexed by D-prime as a function of Context and Emotion. **(E)** Subjective quality of memories. Mean recollection estimates (R_c) as a function of context and emotion. **(F)** Subjective quality of memories. Mean familiarity estimates (d') as a function of context and emotion. Error bars represent standard error of the mean (s.e.m.).

that memory in intact contexts was better than in rearranged contexts ($F_{1,44} = 6.69$, $p = 0.0031$, $\eta_p^2 = 0.132$) while recognition was better in rearranged contexts than in a new context ($F_{1,44} = 9.82$, $p = 0.003$, $\eta_p^2 = 0.184$), again demonstrating the presence of specific contextualization and non-specific context sensitivity. Out of all participants, 64% showed a specific memory context enhancement effect, and 62% displayed the non-specific effect. Finally, recognition performance was worse for negative faces ($F_{2,88} = 14.59$, $p < 0.001$, $\eta_p^2 = 0.249$), but Emotion and Context did not interact ($F_{2,88} = 1.91$, $p = 0.155$).

3.2.4. Subjective quality of memories

Analysis of the recollection estimates (**Figure 5** and **Figure 4E**) did not reveal any significant effects (all $F < 1.97$, all $p > 0.146$).

Analysis of the familiarity (**Figure 4F**) estimates revealed a main effect of Context ($F_{2,88} = 6.83$, $p = 0.002$, $\eta_p^2 = 0.134$). Planned contrasts revealed that memory familiarity with intact contexts was stronger than in rearranged contexts pointing out the existence of specific memory contextualization ($F_{1,44} = 4.442$, $p = 0.041$, $\eta_p^2 = 0.092$), but familiarity in rearranged contexts was not significantly stronger than in a new context ($F_{1,44} = 1.32$, $p = 0.257$).

3.3. Predictors of memory contextualization

3.3.1. Dependent variable: D-prime

Since none of the above analyses showed interactions with Emotion, we collapsed over emotion and calculated our specific contextualization measure (intact d' - rearranged d'), non-specific context sensitivity measure (rearranged d' - oldface d') and general memory measures (i.e., memory performance regardless of the context condition) that were used as the dependent variable in the regression analyses (see **Table 1**). Using depression, trait anxiety, baseline cortisol and chronic stress measures as predictors and the memory specific contextualization measure as the dependent

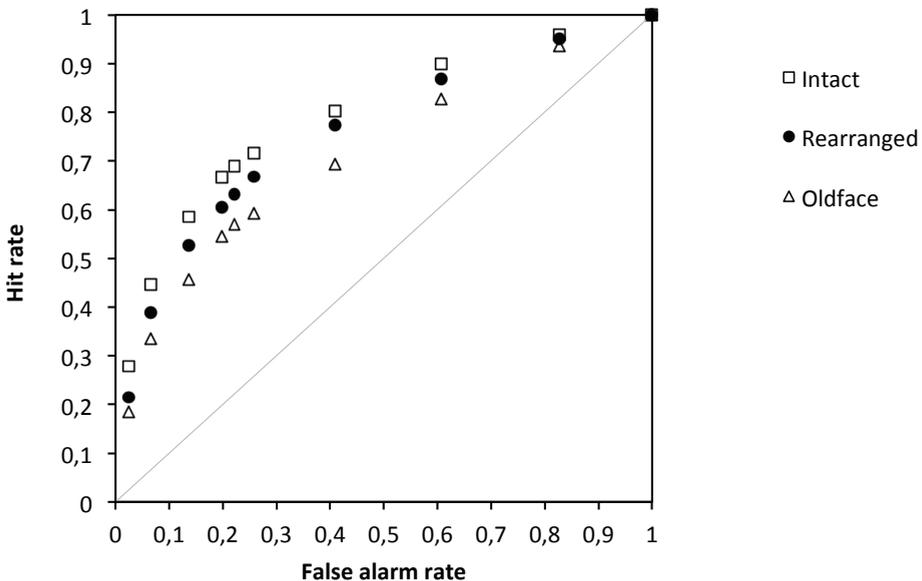


Figure 5. Receiver operating characteristic (ROC) curves as a function of hit rate, false alarm rate, and condition.

variable, a significant model emerged ($F_{4,44} = 2.91, p = 0.033$) that explained 23% ($R^2 = 0.226$) of the variance in specific memory contextualization. Trait anxiety emerged as a negative predictor ($b = -0.5, p = 0.019$) and chronic stress as a positive one ($b = 0.47, p = 0.019$) (Figure 6A,B). In a second model using memory non-specific context sensitivity as the dependent variable a marginally significant model emerged ($F_{4,44} = 2.398, p = 0.066$). Again trait anxiety was a significant predictor, but now a positive one ($b = 0.44, p = 0.042$), while depression now emerged as a significant negative predictor ($b = -0.42, p = 0.047$) (Figure 6C,D). These predictors only emerged for the specific and non-specific context sensitivity measures, since the model with general memory performance as the dependent variable was not significant ($F_{4,44} = 1.077, p = 0.381$).

Table 1. Predictors of the regressions

Variable	Mean	SD
STAI-T	39.9	9.9
SRLE	64.5	10.6
BDI	7.1	5.8
Mean cortisol	8.3	4.7

Means and standard deviations (SD) of the individual differences variables. STAI-T, Trait version of the Spielberger state trait anxiety inventory; SRLE, survey of recent life events; BDI, Beck Depression Inventory.

3.3.2. Dependent variable: Subjective quality of memories

Regression models with the specific contextualization of recollection as the dependent variable were not significant (All $F_{4,44} < 0.35$, all $p > 0.843$); neither was the model with non-specific context sensitivity measure of familiarity ($F_{4,44} = 1.98$, all $p = 0.116$). However, the model with specific contextualization of familiarity did reach significance ($F_{4,44} = 2.94, p = 0.032$). In this model trait anxiety ($b = -0.414, p = 0.05$) and chronic stress ($b = 0.567, p = 0.003$) were significant predictors, suggesting that the previously reported effects of these variables on memory contextualization may be mediated by alterations in familiarity, but not recollection.

3.4. Associative recognition

3.4.1. Context effects on memory associations

Analysis of the associative memory data (**Figure 6E**) revealed that memory for Association Type differed as a function of Emotion ($F_{2,88} = 4.52, p = 0.014, \eta_p^2 = 0.093$). The analysis revealed a main effect of Association Type ($F_{1,88} = 182.67, p < 0.001, \eta_p^2 = 0.806$) and Emotion as well ($F_{1,88} = 4.17, p = 0.047, \eta_p^2 = 0.087$). Planned contrasts revealed that associative memory for intact combinations was better than in rearranged combinations, while it was better in rearranged combinations than in combination with a new context (All $F_{1,44} > 13.60$, all $p < 0.001$), indicating that specific and non-specific memory contextualization existed on this measure as well.

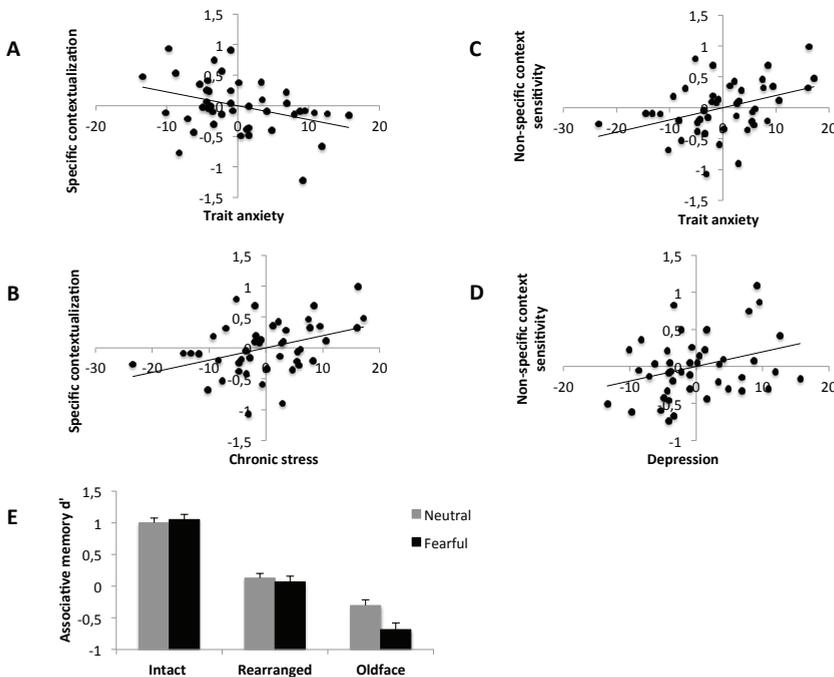


Figure 6. (A) Controlling for depression, chronic stress and cortisol a regression analysis revealed a significant negative relationship between trait anxiety and memory contextualization (intact - rearranged). (B) Controlling for depression, trait anxiety and cortisol a regression analysis revealed a significant positive relationship between chronic stress and memory contextualization (intact - rearranged). (C) In the second regression model a significant positive relationship between trait anxiety and the alternative memory contextualization (rearranged - oldface) measure was observed. (D) In the second regression model a significant positive relationship between depression and the alternative memory contextualization (rearranged - oldface) measure was observed. (E) Memory performance on associative recognition task. Error bars represent standard error of the mean.

3.4.2. Predictors of associative contextualization

Though the above analysis of associative memory performance revealed an interaction with Emotion, we collapsed over this condition for reasons of consistency. The two models with memory contextualization and the alternative memory contextualization were not significant (All $F_{4,44} < 1.41$, all $p > 0.249$). Interestingly, memory performance on associative contextualization measures did not correlate with any of the predictors (all $p > 0.144$).

4. DISCUSSION

By reinstating memories, contexts play a crucial role in memory function. When information is not properly contextualized, inaccurate memories accompanied by inappropriate responses may occur (Maren et al., 2013). For this reason, delineating which factors alter memory contextualization is vital for understanding how psychological dysfunction characterized by reduced memory contextualization may develop. Here we aimed to assess altered memory contextualization in individuals displaying trait vulnerabilities for the development of PTSD. The strongest finding of the present paper was that trait anxiety was related to weakened specific contextualization, but at the same time to inflated non-specific context sensitivity. In other words, though higher trait anxiety was associated with enhanced memory when the cue was paired with an old context (non-specific), it was associated with reduced memory performance with regard to the specific and unique original face-context combination. Depression seemed to inflate non-specific context sensitivity too. Further, chronic stress seemed to enhance specific memory contextualization, but baseline cortisol did not associate with any of our context measures. Finally, explorative analyses suggested that the specific contextualization effects may have originated from alterations in specific context induced familiarity of the faces. Context dependent recollection (on ROC estimates and associative memory) was however not related to any of our predictors, neither did these measures directly relate to any of the recognition measures. Taken together, trait anxiety, depression and the experience of chronic stress all seem to be capable in subtly altering the means by which central memories are integrated into their original encoding contexts.

The most consistent finding of the present study was that trait anxiety seemed to reduce specific memory contextualization while inflating non-specific context sensitivity, of both neutral and emotional memories. These two types of context effects on memory are not entirely independent from each other, since any shift in memory performance in the rearranged condition affects both the difference score of specific and non-specific context effects on memory (provided these remain con-

stant). Indeed, the reduction of specific memory contextualization by higher trait anxiety is mirrored in inflated non-specific context sensitivity; two sides of the same coin. Recent influential theories on the etiology of anxiety disorders have postulated that impairments in pattern separation may underlie overgeneralization of fear in anxiety disorders (Kheirbek et al., 2012a). In distinguishing safe from threatening signals, contexts plays an imperative role (Maren et al., 2013). In line with these propositions, animal studies have shown that reduced plasticity in the hippocampal DG led to reduced discrimination among highly similar contexts, leading to enhanced freezing in an otherwise safe context (Kheirbek et al., 2012b). Also, high trait anxiety mice have been shown to be impaired in spatial learning abilities (Herrero et al., 2006). In humans, research linking trait anxiety and hippocampal dependent memory processing is rare. State anxiety though, as induced by threat of shock, has been shown to impair hippocampal-dependent associative memory, while it enhanced object memory (Bisby and Burgess, 2013). Importantly, the majority of animal studies investigating pattern separation abilities used stressful paradigms such as context fear conditioning. Similarly, research in humans focuses on alterations in memory due to emotionality. However, we did not find different effects of context for fearful or neutral faces, and trait anxiety seemed to be related to a more general reduction in memory contextualization. Together these findings suggest that higher trait anxiety biases an individual towards a tendency for reduced context discrimination in accessing certain memory traces, along with an inflated sensitivity to reactivate a memory in any previously seen environment.

Next, we found that chronic stress was positively related to memory contextualization, suggesting that those individuals who reported more daily hassles in the last month were better at contextualizing memories. This finding may be somewhat counterintuitive, since chronic stress - associated with cumulative exposure to high glucocorticoid levels - typically leads to atrophy and ultimately death of hippocampal neurons that can cause impairments in hippocampus-dependent learning and memory (Kim and Diamond, 2002). Generally, it is thought that stressors initially promote adaptation ("allostasis"), while a recovery after stress ("allostatic state") leads, if repeated often over time, to wear and tear on the body ("allostatic load") (McEwen, 2007). In the latter case, the hippocampus responds with decreased dendritic branching and reduction in number of neurons in the DG. However, it is rather unlikely that the reported chronic stress intensity of our healthy participants equal the intensity of the stressors that are typically tested in animal research. One underlying mechanism of the seemingly beneficial effects of chronic stress in this study may be that some hours after stress, slower long-lasting genomic corticosteroid actions develop (De Kloet et al., 2005; Wiegert et al., 2005). Such delayed effects of stress on

the brain are thought to restore homeostasis following stressful periods (Diamond et al., 2007; Joëls, 2006), and can enhance cognitive function (Oitzl et al., 2001). We have previously shown that delayed effects of cortisol can enhance specific memory contextualization (Van Ast et al., 2013) and hippocampal dependent trace-conditioning (Cornelisse et al., 2014). Causal conclusions on delayed stress effects for the present study are clearly not possible since the design is correlational in nature. For future studies it remains therefore an open question whether current reports of chronic stress have differential (or even opposing) effects on memory contextualization, and what the underlying mechanisms may be.

Depression seemed to be related to non-specific context sensitivity; the higher the depressive score, the more individuals recognized faces in a previously seen context that was not part of the original specific encoding episode. One line of relevant research into memory function in depression has focused on the relative inability of some patients to retrieve specific autobiographical memories. Patients suffering from depression seem to be impaired in doing so. Instead, they respond to cues with memories reflecting several occurrences at once, unable to remember a specific episode, thereby displaying overgeneral memories (Wessel et al., 2001). Perhaps even more reminiscent to the present observations is the finding that patients suffering from major depression display impaired source memory when having to discriminate between highly similar perceptual information (Degl'Innocenti and Backman, 1999). Though specific memory contextualization was not related to depressive symptoms, the present study adds to the idea that those individuals more dysphoric are not so much impaired in recognition itself, but are unable to use context to distinguish between similar old but unrelated memory episodes.

Though findings are still equivocal, pretrauma individual differences in HPA functioning appear to comprise one potential vulnerability factor for PTSD after experiencing trauma (Bomyea et al., 2012). Here, however, we did not find any relations with any of the memory measures and baseline cortisol. Though we used an average of cortisol samples surrounding encoding and all participants were tested after 1 pm, our measure may have nevertheless been too crude, since the use of morning cortisol awakening curves are highly recommended for baseline cortisol assessment (Pruessner et al., 1997).

Interestingly, trait anxiety, depression and chronic stress were only related to context effects on recognition, but not to recollection or the equivalents of specific and non-specific memory contextualization as assessed by associative memory. In line with this observation, memory contextualization and non-specific context sensitivity of memory measures were not correlated with their respective counterparts assessed by associative memory performance. Generally however, context effects on memory

are investigated by associative designs where participants have to indicate whether they recognized the cue, context, or the cue- context association (Bisby and Burgess, 2013; Schmidt et al., 2011; Uncapher et al., 2006). Recognition judgments in the present study were required only to the central word in the face–context pair. Since context effects on recognition and associative memory were not related, it seems that incidental context effects on recognition are supported by another mechanism than recollection or associative memory. Instead, explorative analyses showed that the trait anxiety and chronic stress effects on memory contextualization were paralleled in the contextualization of familiarity. It must be noted that the associative memory test always followed recognition testing, since it was not of our primary interest. The associative memory test is therefore not unbiased. Nevertheless, these findings are a replication of a series of experiments in which experimental manipulations affecting context effects on recognition were typically accompanied by alterations in familiarity, but not recollection (Van Ast et al., 2014; 2013).

In conclusion, the results presented here shed a closer view on which individual differences are related to enhanced versus impaired alterations in clearly defined aspects of memory. Overall, the findings support a model in which alterations in the usage of context to shape behavior form an endophenotype that is related to psychological dysfunction.