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*Published in:*  
European Journal of Neuroscience

*DOI:*  
[10.1111/ejn.15067](https://doi.org/10.1111/ejn.15067)

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*Document Version*  
Publisher's PDF, also known as Version of record

*Publication date:*  
2020

[Link to publication in University of Groningen/UMCG research database](#)

*Citation for published version (APA):*

Sep, M. S. C., Joels, M., & Geuze, E. (2020). Individual differences in the encoding of contextual details following acute stress: An explorative study. *European Journal of Neuroscience*, 1-25.  
<https://doi.org/10.1111/ejn.15067>

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# Individual differences in the encoding of contextual details following acute stress: An explorative study

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## Funding information

Dutch Ministry of Defence; The Netherlands Organization of Scientific Research, Grant/Award Number: #022.003.003

[Correction added on 8 January 2021 after first online publication: Typo in “HPA” of the Abbreviations section is corrected; Shading in Table 1 and updated Figure 1.]

## Abstract

Information processing under stressful circumstances depends on many experimental conditions, like the information valence or the point in time at which brain function is probed. This also holds true for memorizing contextual details (or ‘memory contextualization’). Moreover, large interindividual differences appear to exist in (context-dependent) memory formation after stress, but it is mostly unknown which individual characteristics are essential. Various characteristics were explored from a theory-driven and data-driven perspective, in 120 healthy men. In the theory-driven model, we postulated that life adversity and trait anxiety shape the stress response, which impacts memory contextualization following acute stress. This was indeed largely supported by linear regression analyses, showing significant interactions depending on valence and time point after stress. Thus, during the *acute phase* of the stress response, reduced neutral memory contextualization was related to salivary cortisol level; moreover, certain individual characteristics correlated with memory contextualization of negatively valenced material: (a) life adversity, (b)  $\alpha$ -amylase reactivity in those with low life adversity and (c) cortisol reactivity in those with low trait anxiety. Better neutral memory contextualization during the *recovery phase* of the stress response was associated with (a) cortisol in individuals with low life adversity and (b)  $\alpha$ -amylase in individuals with high life adversity. The data-driven Random Forest-based variable selection also pointed to (early) life adversity—during the *acute phase*—and (moderate)  $\alpha$ -amylase reactivity—during the *recovery phase*—as individual characteristics related to better memory contextualization. Newly identified characteristics sparked novel hypotheses about non-anxious personality traits, age, mood and states during retrieval of context-related information.

## KEYWORDS

life adversity, linear regression analysis, random forest analysis, SAM-axis, HPA-axis

**Abbreviations:** AUCg, area under the curve with respect to ground; AUCi, area under the curve with respect to increase; AVP, arginine vasopressin; BLA, basolateral amygdala; BMI, body mass index; EME, estimated marginal effects; FC, fear contextualization; FGI, fear generalization index; FGT, fear generalization task; FPS, fear-potentiated startle; HPA, Hypothalamus-pituitary-adrenal; iU, inverted U-shaped; LM, linear regression models; MC, memory contextualization; MCT, memory contextualization task; MI, multiple imputations; MR, mineralocorticoid receptor; OT, oxytocin; PFC, prefrontal cortex; RF, random forest classifier; RMSE, root mean square error; sAA, salivary  $\alpha$ -amylase; SAM, sympathetic-adreno-medullary; TSST, trier social stress test; U, U-shaped.

Edited by Carmen Sandi

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## 1 | INTRODUCTION

It is widely known that acute stress affects memory formation, but the direction of the effect depends on situational characteristics, including information valence and the delay between the stressor and the encoding of information (De Quervain et al., 2017; Joëls et al., 2011, 2018). Rapidly after a stressful experience, activation of the sympathetic-adreno-medullary (SAM) axis and the hypothalamus-pituitary-adrenal (HPA) axis leads to noradrenaline and cortisol release, respectively (Godoy et al., 2018). Together they promote activity in the basolateral amygdala (BLA) and synaptic plasticity in the hippocampus (CA1), to facilitate memory encoding directly after stress (“acute phase”) (De Quervain et al., 2017; Joëls et al., 2018). This effect is stronger for emotional compared to neutral information, which evokes additional noradrenaline release in the BLA (Daviu et al., 2019; Roozendaal et al., 2009). Cortisol levels in the brain are likely elevated for 1–2 hr after an acute stressor (Joëls et al., 2011). More than 1h after the stressor (here referred to as the ‘*recovery phase*’), the genomic effects of cortisol (and the absence of noradrenaline or—potentially—reversed, late effects of noradrenaline) suppress activity in the BLA, likely to avoid the encoding of new information; and to promote rationalization and contextualization, through activation of the hippocampus and prefrontal cortex (PFC) (De Quervain et al., 2017; Joëls et al., 2018; Karst & Joëls, 2016). These differential effects of stress also determine the extent to which contextual details are embedded in episodic memory (i.e. memory contextualization; MC). The effects of the acute phase reduce MC, while the effects of the recovery phase increase MC (Sep, van Ast et al., 2019; van Ast et al., 2013). Context-impoverished memories are prone to maladaptive overgeneralization and (potentially incorrect) updating during recall (Zinn et al., 2020). Overgeneralization of stressful memories has been linked to development and treatability of fear- and anxiety-related disorders, like post-traumatic stress disorder (Bouton et al., 2006; Dymond et al., 2015; Javanbakht, 2019; Liberzon & Abelson, 2016; Maren et al., 2013).

In addition to situational characteristics, interindividual differences in stress responsivity and (contextual) learning abilities are substantial (Berkers et al., 2016; Haas & Canli, 2008; Kudielka et al., 2009). For example, the impact of stress on an individual depends partially on personality factors, such as trait anxiety (van Reedt Dortland et al., 2012; Weger & Sandi, 2018). Neuroticism and introversion were shown to affect salivary cortisol responses (Hauner et al., 2008), and neuroticism is associated with context-dependent fear expression (Craske et al., 2009). Besides, human and animal studies have shown that cumulative stress exposure during life may alter HPA-axis function and behavioural responses to stressful situations (Del Giudice et al., 2011; Horovitz et al., 2012; Joëls et al., 2018). As MC is implicated in the pathology and treatability of pathological fear

and anxiety, understanding individual characteristics that modulate MC can help to understand individual differences in vulnerability and treatment response. Therefore, it is of particular importance to understand these interindividual differences for both prevention and personalized medicine.

This study explored to what extent a variety of individual differences contribute to MC after stress; more specifically, the contextualization of neutral, emotional and fearful valenced material—assessed with a face recognition and fear conditioning task—at 30 min (‘acute phase’) or 2 hr (‘recovery phase’) after psychosocial stress or control conditions, in 120 healthy male individuals. Note, the recovery phase was probed at 2 hr to specifically target the late—potentially genomic—effects of cortisol and avoid confounding effects due to rapid actions of elevated cortisol levels in the brain (Joëls et al., 2011). We adopted two complementary strategies to answer the question at hand: (a) a theory-driven and (b) a data-driven approach (Hulsen et al., 2019). Where a theory-driven strategy aims to understand a relation between variables, a data-driven approach aims to reveal hidden relationships that can lead to new hypotheses (Elragal & Klischewski, 2017; Hulsen et al., 2019). With our theory-driven approach, we tested the hypothesis that MC is determined by the individual’s responsivity of the SAM-axis and HPA-axis, and that reactivity of these systems, in turn, is shaped by an individual’s trait anxiety and cumulative exposure to life adversity. For the theoretical rationale and specific hypotheses, see Box 1. With the data-driven approach we explored a variety of other variables that could be relevant for the prediction of MC at the level of an individual. For this purpose, variables were taken into account that have been associated with broader cognitive and psychological functioning, but are generally not studied as main drivers of individual differences in learning after acute stress; this includes variables like personality traits, life adversity and psychological or physiological states during encoding and retrieval.

The individual characteristics, identified by each method, will be interpreted in the results section. In the discussion we will reflect on the integration of both approaches and the overall findings of this explorative study.

## 2 | MATERIALS AND METHODS

### 2.1 | Dataset

Previously, our group investigated the time-dependent effects of psychological stress on MC at group-level in a large randomized controlled trial. The primary and secondary outcome measures from this study are used for the explorative analysis presented here. 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.

## Box 1 Theoretical model: Hypothesized factors contributing to individual variation in memory contextualization following acute stress

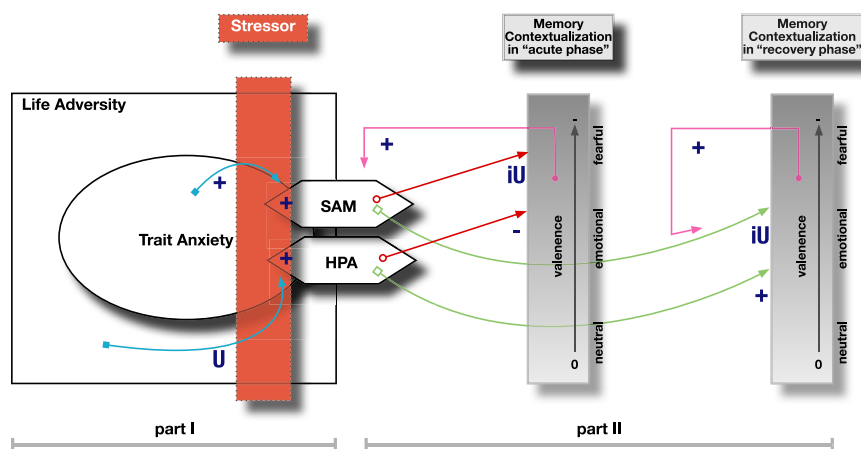
### Part I. Predictors of SAM-axis and HPA-axis reactivity to acute stress

We included three elements in Part I of the theoretical model (Figure 1). First, it has been shown that life adversity—especially early in life—impacts brain development, including central regulation of the SAM-axis and HPA-axis (reviewed in Joëls et al., 2018). The *Adaptive Calibration Model* suggests that life adversity asserts its effects on the SAM- and HPA-axis after mild acute stressors according to an U-shaped curve (U) (Del Giudice et al., 2011): low stress reactivity following moderate levels of life adversity, and high stress reactivity following either low or high levels of life adversity (of note, exposure to more severe or traumatic stress is expected to reduce stress reactivity in men and increase reactivity in women). Recent empirical studies have provided support for this model (Lin et al., 2020; Shakiba et al., 2020). This non-linear relation might explain why earlier studies have found both reduced and increased stress reactivity following life adversity (Carpenter et al., 2007; Ioannidis et al., 2020; Shields & Slavich, 2017). The second element of the model relates to the observation that life adversity does not impact all individuals equally: the *neurocognitive model* suggests that a large part of this variation is explained by trait anxiety (Weger & Sandi, 2018). Trait anxiety is mostly shown to increase SAM-axis and HPA-axis reactivity to acute stress (Weger & Sandi, 2018), although opposite effects have also been observed (Jezova et al., 2004). As a third element of the model, we expect that life adversity exerts its effects partly via trait anxiety; for example, life adversity is known to influence the development of stress-related psychopathology via trait anxiety (e.g. posttraumatic stress disorder; Kok et al., 2016).

### Part II. SAM-axis and HPA-axis reactivity and MC

For the second part of the theoretical model (Figure 1), we expect that SAM-axis reactivity, via noradrenaline, affects memory contextualization following an inverted-U-shaped (iU) curve, directly after acute stress. The hippocampus is important for MC (Maren et al., 2013) and it has been shown that noradrenaline can both enhance and impair LTP in this area (Giustino & Maren, 2018). Moreover, it has been shown that a moderate level of noradrenaline is needed for the consolidation of fearful contexts (Giustino & Maren, 2018). Regarding HPA-axis reactivity in this part of the theoretical model, differential time-dependent effects have been observed: the immediate effects impair MC, while the delayed effects (~2 hr) improve context dependency (van Ast et al., 2013).

To summarize, we expect that activity in the SAM-axis and HPA-axis, following acute stress, funnels the influence of life adversity and trait anxiety on memory contextualization (Figure 1). We expect no effects in the absence of acute stress. The interactions and main effects that will be statistically evaluated to test the hypothesized relations in Theoretical Model are summarized in Table 1.



**FIGURE 1** Schematic overview of the hypothesized theoretical model that underlies individual variation in memory contextualization following an acute stressor. Blue arrows indicate the influence of trait anxiety and life adversity on SAM- and HPA-axis reactivity following acute stress. Exposure to an acute stressor is postulated as a prerequisite to trigger the hypothesized effects in this scheme. Red and green arrows indicate how these systems affect memory contextualization during the acute and recovery phase, respectively. Information valence is indicated with the grey gradient (light: neutral valence, darker: more negative valence). The pink arrows represent SAM-axis activation by negative valence. The hypothesized directions of the effects are indicated: positive (+), negative (-), U-shaped (U), inverted U-shaped (iU)

**TABLE 1** Statistically tested interactions to evaluate the Theoretical Model

Hypothesized relations
Trait Anxiety × SAM-axis at learning × HPA-axis at learning
Life Adversity × SAM-axis at learning × HPA-axis at learning
Life Adversity × SAM-axis at learning
Life Adversity × HPA-axis at learning
Trait Anxiety × SAM-axis at learning
Trait Anxiety × HPA-axis at learning
SAM-axis at learning
HPA-axis at learning
Additional terms
Life Adversity × Trait Anxiety
Life Adversity
Trait Anxiety

Note: In this study,  $\alpha$ -amylase is measured as proxy for SAM-axis reactivity and cortisol is measured as proxy for HPA-axis reactivity.

Participant and methodological characteristics and group-level findings have been described in detail before (Sep, Gorter et al., 2019; Sep, van Ast et al., 2019), and are briefly summarized below. At a group-level, we found that the acute phase of the stress response reduced neutral MC, while the recovery phase of the stress response improved MC of neutral information (Sep, van Ast et al., 2019). These time-dependent effects of acute stress were not observed at group level for emotional or fearful information (Sep, Gorter, et al., 2019; Sep, van Ast et al., 2019).

## 2.2 | Participants

The dataset comprises data from 120 healthy male participants (age:  $M(SD)=24.91(6.68)$ , range = 18.08–49.34). Sample size is based on a priori power calculations for the primary research questions (Sep, Gorter, et al., 2019; Sep, van Ast et al., 2019) and absence of neurological / psychiatric illnesses was verified. Participants were randomly assigned to one of three experimental groups (Figure 2). For other demographics, see pp. 6–13 of the Supporting Information (II.A).

## 2.3 | Psychosocial stress and placebo manipulations

Psychological stress was induced using the Trier Social Stress Test (TSST) (Kirschbaum et al., 1993), a placebo version of the TSST was used as a control condition (Het et al., 2009).

## 2.4 | Primary outcome measures: Memory contextualization

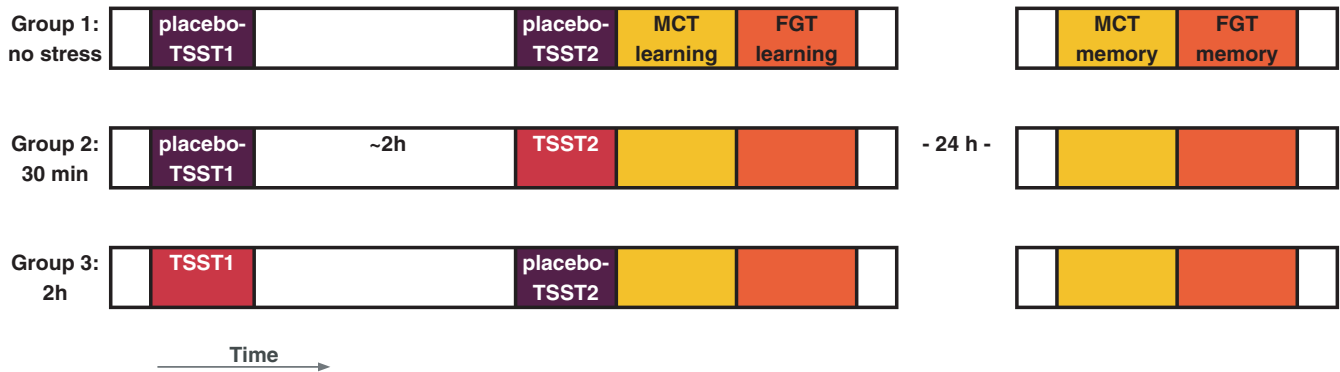
Participants received the encoding phase of two memory contextualization tasks (one based on face recognition and one based on fear conditioning) either directly after the TSST (Figure 2: group 2) or ~2 hr after the TSST (Figure 2: group 3); a placebo version of the TSST was used as control in these groups and in an overall control group (Figure 2: group 1). The two computer tasks were programmed in Presentation Version 18.1 (Neuro-behavioral Systems, Inc, RRID:SCR\_002521). In both tasks, surprise retrieval was measured 24 hr after encoding (i.e. participants were surprised with an unannounced memory test).

### 2.4.1 | Context-dependency neutral and emotional memories

Memory contextualization of neutral and emotional material was measured using the Memory Contextualization Task (MCT) (Sep, van Ast, et al., 2019; van Ast et al., 2013, 2014; Zhang et al., 2018). During encoding, 120 faces with neutral and angry facial expressions (from validated databases) were presented as overlay to visually rich images of indoor and outdoor environments. In each trial participants had to form a vivid mental image of the person (face) interacting with the environment (context). During the recognition phase, these faces were shown again (50% with the same background image (=congruent context) and 50% with a different background image (=incongruent context)), mixed with 120 new faces, making use of the same backgrounds. For each valence and context category, memory performance was measured according to the signal detection theory ( $d' = Z(\text{hit rate}) - Z(\text{false alarm rate})$ ). Subsequently, the contextualization index was calculated for each valence category ( $\Delta d' = d' \text{ congruent} - d' \text{ incongruent}$ ). Note, a higher contextualization score indicates more context dependency.

### 2.4.2 | Context-dependency fear memories

Contextualization of fearful information was measured using the Fear Generalization Task (FGT) (Mühlberger et al., 2014; Sep, Gorter, et al., 2019). In this task, three different contexts (i.e. three images of different office rooms that served as threat (CTX+), safe (CTX-) and new (G-CTX) context) modulated the meaning of the conditioned stimulus (CS, an image of a man with a neutral facial expression (CUE)). Fear was measured as (fear-potentiated) startle responses (FPS) to a startle probe (40 ms burst of white noise of 104 dB delivered via headphones). During encoding, only CUE.CTX+ and CUE.CTX- trials were presented. In this phase, the CUE.



**FIGURE 2** Experimental design. Participants were randomized in three experimental conditions: group 1 ( $n = 42$ ) performed the learning phase of the Memory Contextualization Task (face recognition based) and the Fear Generalization Task (fear conditioning based) following a placebo-version of the Trier Social Stress Test (TSST), as shown in the figure; group 2 ( $n = 42$ ) performed these tasks directly after the TSST, and group 3 ( $n = 36$ ) ~2 hr after the TSST. Participants completed the surprise memory phase of both tasks 24 hr after encoding

CTX+ trials co-terminated with the unconditioned stimulus (US; an electric pulse (200 ms, 100–400 V, intensity individually calibrated to “highly uncomfortable, but not painful” ( $M: 27.98$ ,  $SD: 22.93$ ; range: 3–99.9 mA)). During retrieval, CUE.CTX+, CUE.CTX- and CUE.G-CTX trials were presented (without US delivery). The FPS responses during retrieval were used to determine the fear generalization index (FGI) as fear to the CUE in the new context (corrected for the FPS to this CUE in the safe context), and as proportion of fear for the CUE in the threat context. The inverted FGI represents fear contextualization (FC), that is,  $FC = -((\text{mean FPS}_{G-CTX} - \text{mean FPS}_{CTX-}) / \text{mean FPS}_{CTX+})$ . Here, higher FC values represent more context dependency.

## 2.5 | Secondary outcome measures: Potential modulators of memory contextualization following stress

Demographics, personality traits, stressful life events and a symptom checklist (as check for the absence of psychopathology) were collected prior to the experiment. During the experiment, neuroendocrinological and self-report markers of state arousal and mood were measured before, during and after the TSST, as well as before and after each memory task. Salivary  $\alpha$ -amylase (sAA) and cortisol levels were measured as biomarkers for activation of the SAM-axis (Nater & Rohleder, 2009) and HPA-axis (Kudielka et al., 2004), respectively. In total, 14 saliva samples were collected (Figure 3). Details on the group-level analyses of these endocrine measures have been published before (Sep, Gorter, et al., 2019; Sep, van Ast, et al., 2019). All questionnaires were scored according to their manuals. Note, only continuous questionnaire scores (not cut-off scores) were included in the exploratory analyses. A detailed description of all outcome measures is provided on pp. 2–3 of the Supporting Information.

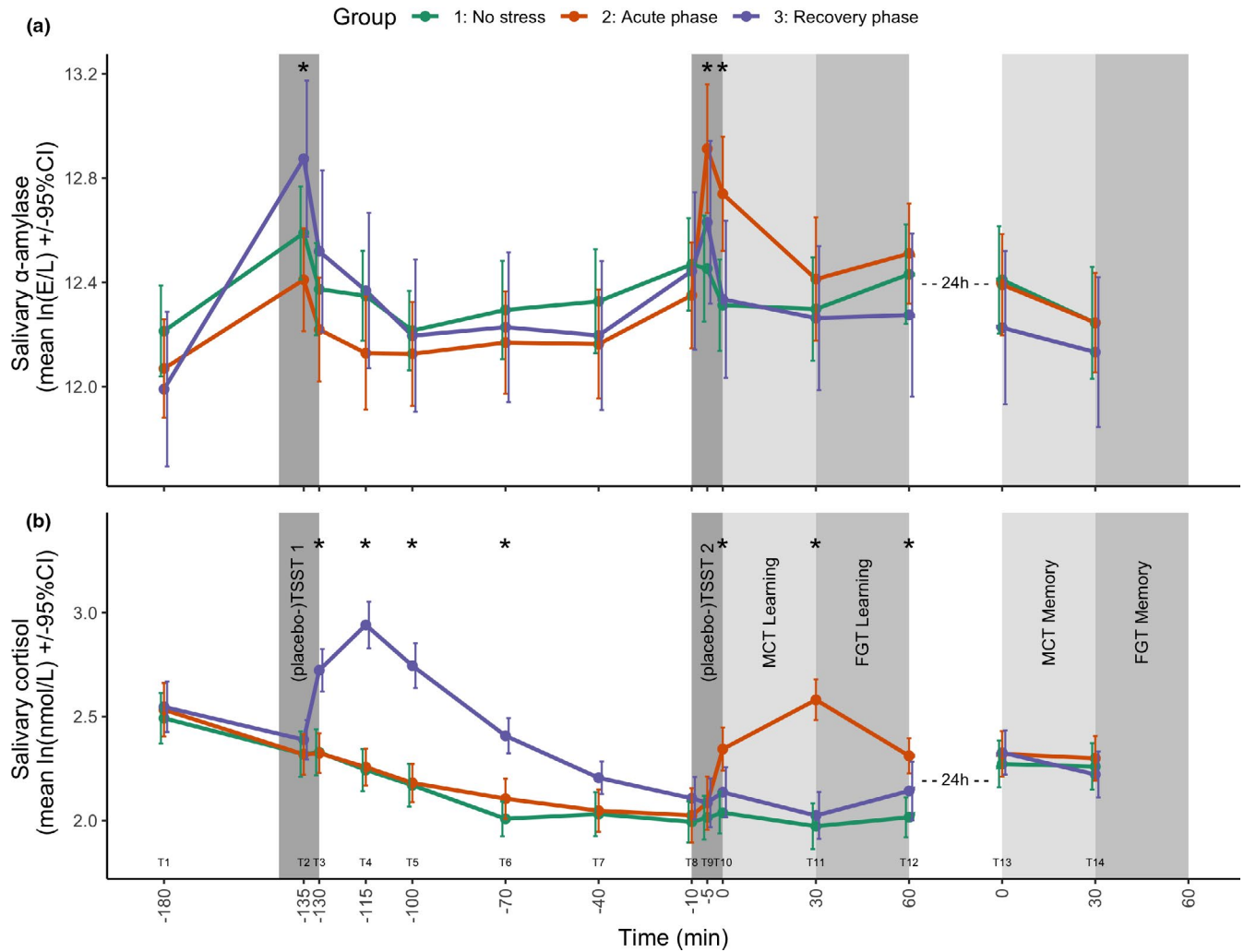
## 2.6 | Data analysis

MCT and FGT scores were preprocessed in Matlab (MATLAB, RRID:SCR\_001622), all other preprocessing steps and analyses were performed in R (R Core Team, 2019), data and code available via Open Science Framework (<https://osf.io/6kf34/>). The complete analyses pipeline is depicted on p. 3 of the Supporting Information.

### 2.6.1 | (passive) Multiple imputation

On average, there were 3.20% missing values per composite variable (i.e. questionnaire total scores, area under the curve scores, etc.). At least one composite variable was missing for 27 participants (22.50%). (Passive) Multiple imputations (MI) were used to deal with missing values in questionnaire, endocrine and FGT scores (using the *Multivariate Imputation by Chained Equations (MICE)* package in R (Buuren & Groothuis-Oudshoorn, 2011), with 10 MI using 15 iterations). MI reduced missing values to 0.57% on average per composite variable. After imputation, 20 participants had at least one missing composite variable (16.67%). Note, MCT scores were not imputed as we considered imputation for this variable invalid: missing values originated from participants without any measures for this task due to technical errors, so there was no information available on neutral and emotional memory performance in this group. As MCT scores were not available for all participants, this variable was also not included in the imputation models for other variables.

MI of item scores from multi-item questionnaires is preferred over direct imputation of the total scores (Eekhout et al., 2018). To avoid too many predictors in the imputation model (because many multiple-item questionnaires were used), passive imputation was used for participants with <70% missing items for a questionnaire (Eekhout et al., 2018). In



**FIGURE 3** The experimental timeline with salivary  $\alpha$ -amylase and cortisol levels. Mean salivary  $\alpha$ -amylase (a) and cortisol (b) levels 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 \*. MCT: Memory Contextualization Task; FGT: Fear Generalization Task; TSST: Trier Social Stress Test; CI: confidence interval. Figure adapted from Sep, Gorter et al. (2019) and Sep, van Ast et al. (2019). For details on the analyses, see these references

this adaptation to the imputation model, item scores are imputed and total scores are updated by recently imputed item scores (Eekhout et al., 2018). For each item score, a unique imputation model was created including all item scores of that questionnaire and the total scores of the other scales (collected at that time point; Eekhout et al., 2018). The FPS responses in the FGT were also imputed using passive imputation, to preserve the relation between raw FPS responses and the FC score. For details on passive imputation models, see Supporting Information p. 4 (Table I.C). If >70% of items/scores were missing, total scores were imputed directly via an imputation model including covariates (body mass index, BMI, age, experimental condition), the total scores of other questionnaires (Personality, life adversity, State-Trait Anxiety Inventory State scale, Positive and Negative Affect

Scale) and FC scores. Raw endocrine measures were imputed directly by the covariates, total scores of personality and life adversity questionnaires, other raw endocrine measures and FC scores.

### 2.6.2 | Preprocessing: Variable reduction and standardization

To reduce the number of variables for the explorative analyses, the 'Area under the curve with respect to increase' (AUCi) and 'Area under the curve with respect to ground' (AUCg) were calculated for the repeated perceived arousal, mood and endocrine measures, for day 1 (encoding) and day 2 (retrieval) separately. Both the AUCi and AUCg were calculated, as

they reflect different aspects of the stress response (Khoury et al., 2015; Pruessner et al., 2003). Subsequently all variables were transformed to *z*-scores. A cumulative life adversity measure was composed as sum of the *z*-transformed Child Trauma Questionnaire and Life Stressor Checklist Revised total scores (Kok et al., 2016; Vinkers et al., 2014). Finally, the data were split by experimental condition in three separate datasets.

### 2.6.3 | Theory-driven analysis: Linear regression models

To test the hypotheses postulated by the theoretical model, linear regression models (LM) were fitted to the (a) neutral, (b) emotional and (c) fear contextualization indices within each experimental condition (the equation of the full model is provided on p. 5 of the Supporting Information). Visual inspection of the Residuals versus Fitted, Normal Q-Q, Scale-Location and Residuals versus Leverage plots did not reveal any influential cases or obvious deviation from normality of the residuals and homoscedasticity. Assumption checks and LM analyses were performed within each imputed dataset, using the R-packages *stats* (R Core Team, 2019), *MICE* (Buuren & Groothuis-Oudshoorn, 2011) and *mitools* (Lumley, 2019). The Variance Inflation Factors (VFI) did not indicate collinearity in the main effects model (VFI: range 1.0068–2.4963) (O'Brien, 2007). Note, we tested data collinearity (in the main effect models without interaction effects), as interaction terms are generally highly correlated with their main effects (Olvera Astivia & Kroc, 2019), and the within-model estimated *p*-values for main and interaction effects in higher-order models—sensitive to biased standard errors due to high correlation (Dormann et al., 2013)—were not used to test our hypotheses. Multivariate Wald tests (D1) were used to compare the full model with the effect in question against the model without the effect ( $\alpha < 0.05$ ) (Meng & Rubin, 1992). As the nature of this study is explorative, we will also discuss marginal significant effects ( $\alpha = 0.05$ – $0.08$ ) and do not correct for multiple testing (3 outcome measures in 3 groups). Significant main or interaction effects were not followed by post-hoc analysis, but their estimated marginal effects (with 95% confidence intervals) were visualized using R-packages *ggplot2* (Wickham, 2016), *ggeffects* (Lüdtke, 2018) and *ggpubr* (Kassambara, 2020).

### 2.6.4 | Data-driven analysis: Boruta Random Forest–based variable selection

For the data-driven approach, the Boruta algorithm was used to select variables that significantly outperform ‘noise’ in predicting an outcome variable. Boruta is a wrapper algorithm around the Random Forest classifier (RF) that compares the

original RF variable importance scores to variable importance achieved ‘at random’ (estimated using permuted copies of the variables in the dataset) (Kursa & Rudnicki, 2010). The RF parameters were tuned to  $m.try = 2$  and  $n.tree = 1,500$ , with 5-fold cross validation on the 10th imputed dataset using R-packages *randomForest* (Liaw & Wiener, 2002) and *caret* (Kuhn, 2020). Boruta variable selection was performed with maximal 1,000 runs, using the R-package *boruta* (Kursa & Rudnicki, 2010). Separate algorithms were run for neutral, emotional and fear memory contextualization, in each experimental group (within each imputed dataset). Results from the imputed datasets were pooled using majority voting (i.e. only variables that were selected in six or more of the ten imputed datasets were considered important). Random permutation statistics were used to test—in each imputed dataset—if the variance explained by a RF model with the Boruta selected variables (pseudo- $R^2$ ) was >95th percentile of the null distribution ( $p < .05$ ) created by 1,000 randomization of the observed MC values using R-package *rfUtilities* (Murphy et al., 2010). Only the selected variables of RF models that were significant in all imputed datasets were further evaluated (note, the random permutation tests reached the same conclusions in each imputed dataset; see Supporting Information, p. 18). Partial dependence (PD) plots and accumulated local effects (ALE) plots are used to explore how the selected variables—in significant RF models—affect memory contextualization within each imputed dataset, using the R-package *DALEX* (Biecek, 2018). For a detailed description of both plots see Apley and Zhu (2020). In brief, PD plots are the most widely used tool to explore how predictions of black box supervised learning models change, if the value of one predictor variable is changed, while the values of other predictor variables in the model are kept constant (Apley & Zhu, 2020). ALE plots are an alternative to PD plots, and provide a more accurate representation of the relation if the predictor variables in a model are highly correlated (Apley & Zhu, 2020).

### 2.6.5 | Comparisons of model performance measures

As LM and RF modelling adopt different methodologies, their conventional ‘goodness-of-fit’ parameters cannot be used as comparable indicators of model performance. The accuracy of the predicted values by each model can be used as an alternative indicator for goodness of model fit (Biecek & Burzykowski, 2020; Smith et al., 2013). More specifically, we used the accuracy of the predicted values to evaluate how well the study data was explained by (a) the identified variables from the theoretical model, (b) the variables selected by the data-driven approach and (c) their combination in ensemble models. The ensemble models



were LMs including (a) the significant (linear) terms from the theoretical model and (b) linear, quadratic or cubic polynomial terms for the Boruta selected variables from significant RF models. To select the appropriate polynomial term, the PD and ALE plots were visually inspected to identify the lowest-order polynomial term. Importantly, the use of LMs and polynomial Boruta variables critically improves the interpretability of the relation between these variables and memory contextualization (compared to RF), which is essential for generating new hypotheses. With the ensemble models, we specifically aimed to estimate the goodness of fit of the *interpreted* theoretical (LM) and data-driven (Boruta) models and not the maximal goodness of fit of these variables in a non-linear black box model, like RF.

Model performance was estimated (in each imputed dataset) via the goodness-of-fit measures  $R^2$  and Root Mean Square Error (RMSE, i.e. the standard deviation of the residuals) for the predicted values by (a) LM including *only* the significant terms, (b) significant RFs including *only* the Boruta selected variables and (c) ensemble models. These measures were subsequently averaged across the 10 imputed datasets. Note, the complete sample size was used for model development *and* performance evaluation, since (a) our primary aim was to explain the current data, rather than assess predictive performance on new data, and (b) the size of the experimental groups did not allow us to split the dataset in separate training, test and validation sets. All predictions were performed by 10 times 5-fold cross validation in the R-package *caret* (Kuhn, 2020), as a bias-correction strategy from evaluating model performance on the training data (Biecek & Burzykowski, 2020).

## 3 | RESULTS

### 3.1 | Theory-driven analysis

The (marginal) significant relations that were identified by the theoretical approach are indicated in grey in Table 2. Only these effects are discussed below for reasons of clarity, the complete (including non-significant) statistics are provided in the Supporting Information (pp. 13–17). The estimated marginal effects (and their 95% confidence intervals) of all the significant term are depicted in Figure 4.

#### 3.1.1 | Memory contextualization following acute stress

Directly after acute stress, individuals who experienced more life adversity contextualized emotional material better (main

effect life adversity:  $DI(1, 25.20) = 5.35, p = .03$ ; Figure 4a). In contrast to the theoretical model, this effect was not facilitated by SAM-axis or HPA-axis reactivity, here (and below) represented as proxy by sAA and cortisol AUCi, respectively. However, the observation that life adversity improves memory contextualization of negative valenced material corresponds to earlier observations in rodents where (early) life adversity improved contextual fear conditioning (Champagne et al., 2008; Oomen et al., 2010). This might reflect a resilient phenotype. A recent review showed that resilient individuals, without psychopathology following (early) life adversity, show similar stress responsivity as unexposed or susceptible (i.e. with psychopathology following (early) life adversity) individuals, but more effectively modulate this response when faced with cognitively challenging tasks (Moreno-López et al., 2020).

In the next sections, the effects of (interactions with) SAM-axis or HPA-axis reactivity on memory contextualization are described. Note, the classifications ‘high’ and ‘low’ refer to 1SD above and 1SD below the sample mean, respectively.

##### 3.1.1.1 | SAM-axis reactivity (-amylase) and memory contextualization

During the acute phase of the stress response, sAA (AUCi) was positively related to increased fear contextualization in individuals with low levels of life adversity (two-way interaction life adversity  $\times$  sAA:  $DI(1, 27.63) = 4.74, p = .04$ ; Figure 4c). This effect can be explained by the postulated relation among life adversity, SAM-axis reactivity and memory contextualization. According to theory, moderate SAM-axis responses would improve memory contextualization directly after stress. Increased SAM-axis reactivity to acute stress—here correlated with lower levels of life adversity—and negative valence (of fearful material), likely evoked more optimal noradrenaline levels in these individuals; that is, the presence of both acute stress and negative valence promoted contextualization in individuals with low levels of life adversity. This also suggests that the reduced SAM-axis responsivity following more life adversity leads to noradrenaline levels that no longer promote contextualization.

While a stronger sAA response to acute stress was related to increased fear contextualization directly after stress in individuals with low levels of life adversity (Figure 4c), it correlated with reduced contextualization of neutral information during the recovery phase of the stress response in these individuals (Figure 4e). This contrasting effect was also observed for individuals with high life adversity: sAA did not relate to better fear contextualization directly after stress (Figure 4c), but it was related to increased context dependency of neutral material during the recovery phase (two-way interaction life adversity  $\times$  sAA:  $DI(1,$

**TABLE 2** Results from the theory-driven approach

Stress-response phase	Significant models per information valence type and stress-response phase											
	Acute phase			Recovery phase			No stress					
	Neutral	Emotional	Fearful	Neutral	Emotional	Fearful	Neutral	Emotional	Fearful	Neutral	Emotional	Fearful
Information Valence:												
Trait Anxiety × sAA (AUCi) at learning × Cortisol (AUCi) at learning <sup>a</sup>												4G*
Life Adversity × sAA (AUCi) at learning × Cortisol (AUCi) at learning <sup>a</sup>												
Life Adversity × sAA (AUCi) at learning <sup>b</sup>			4C*			4E*						
Life Adversity × Cortisol (AUCi) at learning <sup>b</sup>						4F*						
Trait Anxiety × sAA (AUCi) at learning <sup>b</sup>												
Trait Anxiety × Cortisol (AUCi) at learning <sup>b</sup>						4D#						
sAA (AUCi) at learning <sup>c</sup>												
Cortisol (AUCi) at learning <sup>c</sup>						4B#						
Life Adversity × Trait Anxiety <sup>b</sup>												
Life adversity <sup>c</sup>											4A*	
Trait anxiety <sup>c</sup>												

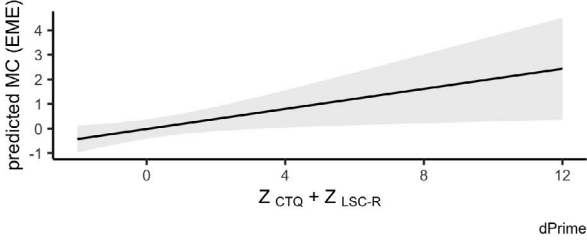
Note: Grey cells indicate significant models (\*  $p < .05$ ; #  $p < .08$ ). Non-shaded cells indicate non-significant models. The number-letter combinations indicate the subplot in Figure 4 that shows the estimated marginal effects from the interaction. Salivary  $\alpha$ -amylase (sAA) is indexed as proxy for SAM-axis reactivity and cortisol as proxy for HPA-axis reactivity. AUCi = area under the curve with respect to increase.

<sup>a</sup>Compared to the full model.

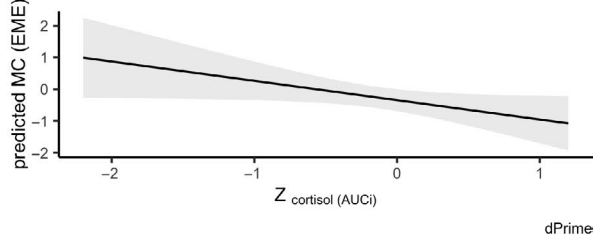
<sup>b</sup>Compared to the model without three-way interactions.

<sup>c</sup>compared to the model without three- and two-way interactions.

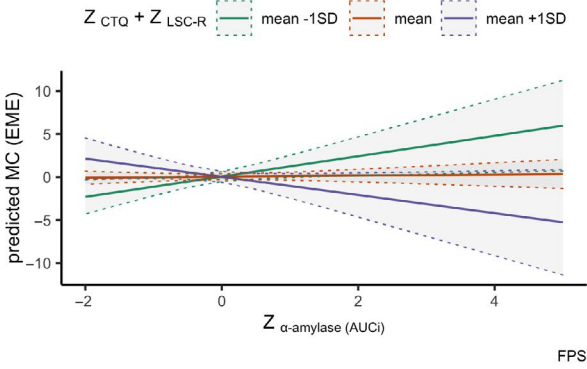
**(a)** Emotional MC ~ life adversity  
acute phase



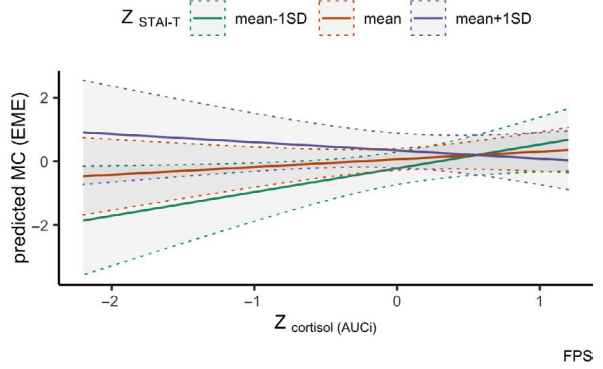
**(b)** Neutral MC ~ cortisol  
acute phase



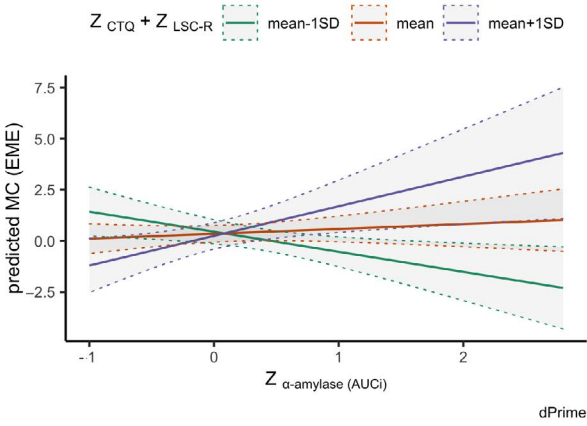
**(c)** Fearful MC ~ life adversity x  $\alpha$ -amylase  
acute phase



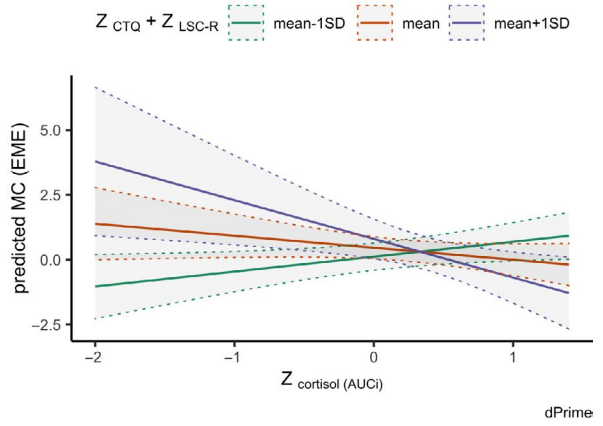
**(d)** Fearful MC ~ trait anxiety x cortisol  
acute phase



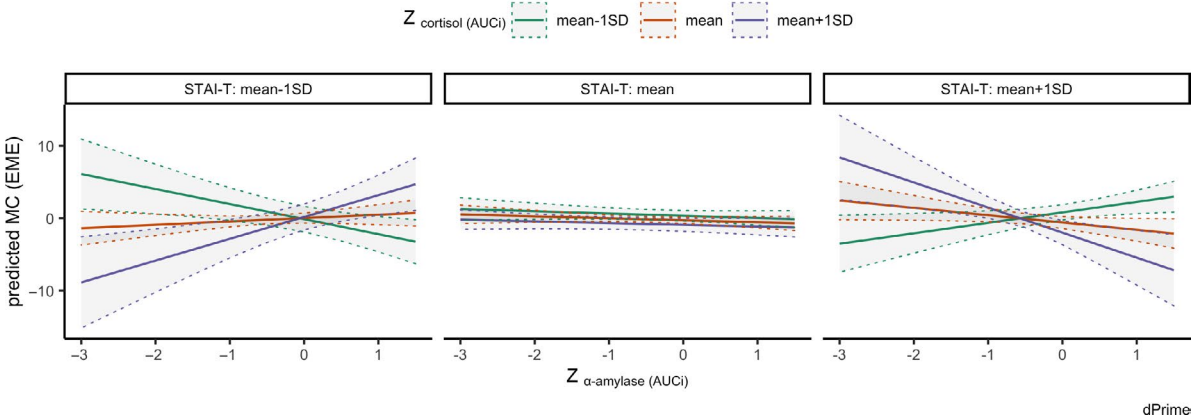
**(e)** Neutral MC ~ life adversity x  $\alpha$ -amylase  
recovery phase



**(f)** Neutral MC ~ life adversity x cortisol  
recovery phase



**(g)** Emotional MC ~ trait anxiety x cortisol x  $\alpha$ -amylase  
no stress (basal)



**FIGURE 4** Visualized estimated marginal effects of the associations identified by the theory-driven approach. The estimated marginal effects (EME) reflect the change in memory contextualization based on the value of a predictor variable in the model ( $x$ -axis). For two-way and three-way interactions the values of respectively one or two predictor variables are held constant at three levels: the (1) sample mean, (2) mean— $1SD$  and (3) mean +  $1SD$  (these levels are indicated with colours and panels). The  $y$ -axis shows the predicted memory contextualization (MC) based on these estimated marginal effects. The grey ribbons indicate the 95% confidence intervals of these predictions. Life adversity is measured with the Child Trauma Questionnaire (CTQ) and the Life Stressor Checklist Revised (LSC-R), trait anxiety is measured with the State-Trait Anxiety Inventory Trait scale (STAI-T). Salivary  $\alpha$ -amylase (sAA) is indexed as proxy for SAM-axis reactivity and cortisol as proxy for HPA-axis reactivity. AUCi: area under the curve with respect to increase, FPS: fear potentiated startle

20.24) = 8.64,  $p = .01$ ; Figure 4e). As absolute noradrenaline levels were presumably low during contextualization (inherent to the recovery phase of the stress response and the absence of negative valence), we expect that this observation cannot be explained by the acute effects of noradrenaline. It rather suggests that SAM-axis reactivity has a delayed effect on memory contextualization. Such a delayed effect can indeed be inferred from cellular studies in rodents (Karst & Joëls, 2016). More specifically, to explain this observation in the framework of the theoretical model, the model needs to be updated with a negative, delayed effect of SAM-axis reactivity on memory contextualization. Given the hypothesized U-shape relation between life adversity and SAM-axis reactivity to stress, that is, more SAM reactivity following less life adversity and less SAM reactivity following moderate life adversity, the updated model would simultaneously predict: (a) a reduction in memory contextualization in individuals with less life adversity—that is, more SAM reactivity leads to a stronger negative delayed effect and (b) an increase in memory contextualization following more life adversity, that is, less SAM reactivity leads to a weaker negative delayed effect.

### 3.1.1.2 | HPA-axis reactivity (cortisol) and memory contextualization

As predicted by the theoretical model, a stronger cortisol response related to decreased contextualization of neutral material directly after acute stress in all subjects (main effect cortisol:  $DI(1, 25.20) = 4.11, p = .05$ ; Figure 4b). In contrast to the hypothesized negative relation between HPA-axis reactivity and memory contextualization, cortisol correlated *positively* with fear contextualization in individuals with low trait anxiety levels but not in individuals with high trait anxiety (two-way interaction trait anxiety  $\times$  cortisol:  $DI(1, 27.94) = 3.61, p = .07$ ; Figure 4d). To explain this observation in the framework of the proposed theoretical model, the model needs two updates. Firstly, this observation implies that cortisol can improve memory contextualization in the presence of noradrenaline, here likely induced via acute stress and the negative valence. In other words, cortisol seems to enhance the effects of SAM reactivity in our model. This supports the idea that HPA-axis reactivity can boost memory processes, when synchronized with SAM-axis reactivity (De Quervain et al., 2017). Secondly, this observation suggests

that trait anxiety modulates the effect of HPA-axis reactivity on memory contextualization. Trait anxiety could exert this effect by modulation of glucocorticoid signalling via the mineralocorticoid receptor (MR; Weger & Sandi, 2018). In rodents, corticosteroids enhance glutamatergic transmission via the MR in two brain areas that are involved in memory contextualization: the BLA and the hippocampus (Karst et al., 2005, 2010; Maren et al., 2013); this may also be the case in humans (Maren et al., 2013). This enhanced excitability could facilitate emotional memory contextualization. Interestingly, it has been shown that high trait anxiety rats show less MR expression in the hippocampus compared to low trait anxiety rats (Herrero et al., 2006), which might imply that high trait anxiety individuals benefit less from enhanced MR signalling following exposure to cortisol. This could explain our observation that cortisol did not improve fear contextualization directly after acute stress in individuals with high trait anxiety. This observation also aligns with our recent meta-analyses where we showed that high trait anxiety is related to fear generalization (Sep et al., 2019).

During the recovery phase of the stress response, the delayed effects of cortisol related to increased contextualization of neutral material in individuals with low life adversity (Figure 4f; of note, this contrasts with the negative delayed effect of sAA in these individuals, shown in Figure 4e). High life adversity abolished this effect of cortisol (two-way interaction life adversity  $\times$  cortisol:  $DI(1, 20.24) = 8.31, p = .01$ ; Figure 4f). This observation follows the hypothesized model that predicted a stronger cortisol response in individuals with low life adversity, and a positive correlation between delayed actions of cortisol and memory contextualization.

### 3.1.2 | Memory contextualization without acute stress

As expected, basal sAA and cortisol activity did not correlate with emotional memory contextualization in individuals with an average trait anxiety level ('mean' across this sample), in the absence of acute stress. However, memory contextualization of stimuli that trigger noradrenaline release, that is, emotional valence, was affected by distinct interactions between sAA and cortisol in individuals with

**TABLE 3** Results data-driven approach. Boruta selected variables and random permutation statistics by information valence type and stress-response phase

Stress-response phase:	Acute phase			Recovery phase			No Stress		
	Neutral	Emotional	Fearful	Neutral	Emotional	Fearful	Neutral	Emotional	Fearful
<b>Information Valence:</b>									
Random permutation tests for RF models with Boruta selected variables <sup>a</sup> : <i>p</i> -values averaged across 10 imputed datasets <i>M</i> ( <i>SD</i> )	0.01 (0.00)	0.04 (0.00)	0.17 (0.06)	0.00 (0.00)	0.01 (0.00)	0.03 (0.01)	0.00 (0.00)	0.03 (0.01)	0.01 (0.01)
Variables included in RF									
Subject ID									
Body mass index (BMI)									
Age				5.B1					
Smoking									
Alcohol									
Recreational drugs									
History of mental illnesses									
History of physical illnesses									
Disrupted day/night rhythm									
SCL (total)									
CTQ (total)		5.A2							
LSC-R (total)									
Life adversity: z(CTQ)+ z(LSCR)	5.A1								
STAI-T (total)									
Honesty-humility (HEXACO subscale)		5.A3							5.C4
Emotionality (HEXACO subscale)									
Extraversion (HEXACO subscale)									
Agreeableness (HEXACO subscale)								5.C3	
Conscientiousness (HEXACO subscale)							5.C1		
Openness to Experience (HEXACO subscale)									
Novelty Seeking (TCI-SF subscale)									
Harm Avoidance (TCI-SF subscale)									
Reward Dependence (TCI-SF subscale)									
Persistence (TCI-SF subscale)									
Self-directedness (TCI-SF subscale)									
Cooperativeness (TCI-SF subscale)							5.C2		
Self-transcendence (TCI-SF subscale)									

(Continues)

TABLE 3 (Continued)

Stress-response phase: Information Valence:	Acute phase			Recovery phase			No Stress		
	Neutral	Emotional	Fearful	Neutral	Emotional	Fearful	Neutral	Emotional	Fearful
	Cortisol (AUCg) at learning								
sAA (AUCg) at learning									
Cortisol (AUCg) at retention									
sAA (AUCg) at retention									
Cortisol (AUCi) at learning									
sAA (AUCi) at learning									
Cortisol (AUCi) at retention									
sAA (AUCi) at retention									
sAA (AUCi) at retention									
VAS arousal (AUCg) at learning									
VAS mood (AUCg) at learning									
VAS arousal (AUCg) at retention									
VAS mood (AUCg) at retention									
VAS arousal (AUCi) at learning									
VAS mood (AUCi) at learning									
VAS arousal (AUCi) at retention									
VAS mood (AUCi) at retention									
STAI-S (AUCg) at learning									
STAI-S (AUCg) at retention									
STAI-S (AUCi) at learning									
STAI-S (AUCi) at retention									
PANAS Negative Affect (AUCg) at learning									
PANAS Positive Affect (AUCg) at learning									
PANAS Negative Affect (AUCg) at retention									
PANAS Positive Affect (AUCg) at retention									
PANAS Negative Affect (AUCi) at learning									
PANAS Positive Affect (AUCi) at learning									
PANAS Negative Affect (AUCi) at retention									
PANAS Positive Affect (AUCi) at retention									
Only for fear MC: fear acquisition									

Note: Grey cells indicated Bonferroni selected variables. Non-shaded cells indicate non-selected variables. The number-letter combinations indicate selected variables in significant RF models and refer to the subplots in Figures 5–7 that show how that variable was used by the RF model (via Partial-dependence (PD) plots and accumulated local effects (ALE) plots). The empty grey cells indicated Bonferroni selected variables in non-significant RF models. <sup>a</sup>A complete overview of the permutation statistics is provided on p. 18 of the Supporting Information.

relatively high or low trait anxiety levels (three-way interaction trait anxiety  $\times$  sAA  $\times$  cortisol:  $DI(1,14.34) = 5.01$ ,  $p = .04$ ; Figure 4g). More specifically, memory contextualization in individuals with low trait anxiety benefited from synchronized basal sAA and cortisol levels, while individuals with high trait anxiety showed improved memory contextualization when basal activity of the two systems was desynchronized.

The basal symmetry in individuals with low trait anxiety follows the pattern observed directly after acute stress, where memory processes benefit from synchronized SAM-axis and HPA-axis activity: directly after stress glucocorticoids promote noradrenaline effects (De Quervain et al., 2017; Krugers et al., 2012). The asymmetry in high trait anxiety individuals corresponds to observed desynchronized basal SAM-HPA activity in patients with generalized anxiety disorder (basal HPA < basal SAM) (Reeves et al., 2016). Trait anxiety increases the risk for anxiety disorders (Weger & Sandi, 2018), and asymmetric SAM-HPA activity could be one of the mechanisms. Our observation that basal HPA < basal SAM resulted in improved emotional memory contextualization in healthy individuals with relatively high trait anxiety (Figure 4g) could reflect a protective factor. A study with exogenous yohimbine and hydrocortisone administration has earlier shown that separately these compounds promote amygdala and hippocampus activity during encoding, much more so than when combined (van Stegeren et al., 2010). This suggests that either system alone could facilitate memory contextualization via activity in these brain areas, a situation that would occur when their activity is inversely related.

## 3.2 | Data-driven analysis

The theory-driven approach was complemented with an unbiased, data-driven approach to explore unpredicted relationships in the dataset. The Boruta algorithm revealed both expected (i.e. included in the theoretical model) and newly identified variables with relevance for the prediction of memory contextualization at an individual level (Table 3). Random permutation statistics indicated that RF models with Boruta selected variables significantly explained MC for almost all valence types and stress-response phases (Table 3), except for fearful MC during the acute phase ( $P_{\text{averaged across imputed datasets}} = 0.17$ ). Note, no variables were selected by Boruta for fearful MC during the recovery phase. An overview of all the permutation statistics is provided in Table 3 (all averaged  $p$ -values) and the Supporting Information (p. 18). The partial-dependence (PD) and accumulated local effects (ALE) plots of the Boruta selected variables from the significant RF models in each imputed dataset are used for the interpretation of the relations and depicted below (Figure 5: Traits; Figure 6: State during encoding; Figure 7: State during retrieval).

There were no indications for bias in the plots in Figure 5, 6 and 7, due to (a) high correlations between variables in the RF models (i.e. no obvious differences between the PD and ALE plots) or (b) multiple imputations (i.e. no difference between the imputed datasets). The expected and newly identified characteristics are described separately.

### 3.2.1 | Expected characteristics

In line with the results from the theory-driven approach, the data-driven analysis revealed that exposure to early life adversity was related to more contextualization of emotional information directly after acute stress (Figure 5.A2). Of note, unlike the theoretical findings, the data-driven results suggest that life adversity also relates to improvements of the contextualization of neutral material during the acute phase of the stress response (Figure 5.A1).

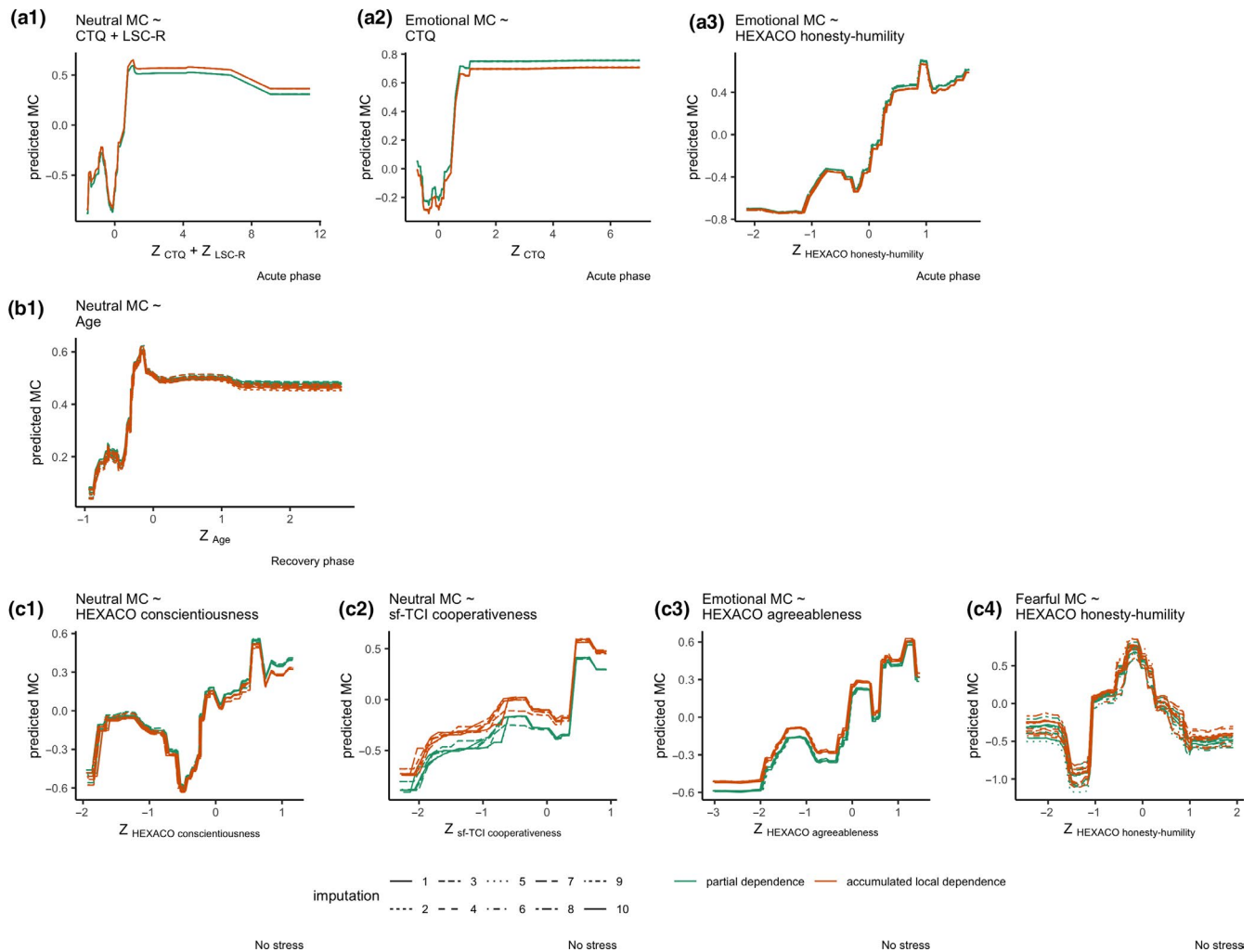
Like the theoretical model, the data-driven analysis implies that either weak or strong delayed effects of sAA hampered neutral memory contextualization during the recovery phase (Figure 6.A3). Of note, the theoretical model suggested that weak effects are beneficial in individuals with relatively low levels of life adversity, while stronger effects promote memory contextualization following more life adversity. Interestingly, the data-driven analysis also indicated that perceived arousal—which was not included in theoretical model—affects neutral memory contextualization during the recovery phase in the same direction as physiological arousal (for which we used sAA as a proxy) (Figure 6.A2). This illustrates that a moderate level of the delayed effects of arousal facilitates neutral memory contextualization during the recovery phase of the stress response.

### 3.2.2 | Newly identified characteristics

#### 3.2.2.1 | Non-anxious traits

3.2.2.1.1 | *Conscientiousness, cooperativeness and agreeableness.* Without acute stress, the personality traits conscientiousness and cooperativeness (Pearson's  $r = .33$ ) were, respectively, cubic and linear related to increased context dependency of neutral information processing (Figure 5.C1-C2), and agreeableness was related to better emotional memory contextualization (Figure 5.C3). Together, these explorative analyses lead to the hypothesis that, without stress, the context dependency of neutral and slightly emotional (but not fearful) information is not only affected by high and low trait anxiety, as the theory-driven results indicated, but also by personality traits that are more cognitive (e.g. conscientiousness) or social (e.g. cooperativeness, agreeableness) in nature. Conscientiousness and cooperativeness have been positively

A: acute phase, B: recovery phase, C: no stress (basal),



**FIGURE 5** Memory contextualization by significant Boruta selected 'personality traits and life adversity' variables. Partial dependence (PD; green) and accumulated local effects (ALE; orange) plots show how levels of the x-as variables are expected to change memory contextualization -in each imputed dataset-, based on their function in the corresponding Random Forest model. The similarities between the PD and ALE plot suggest that the plots are not biased by highly correlated variables in the Random Forest models. The similarities between the imputations also suggest no bias due to multiple imputation. CTQ: child trauma questionnaire; LSC-R: life stressor checklist revised; TCI-SF: short-form version of the temperament and character inventory

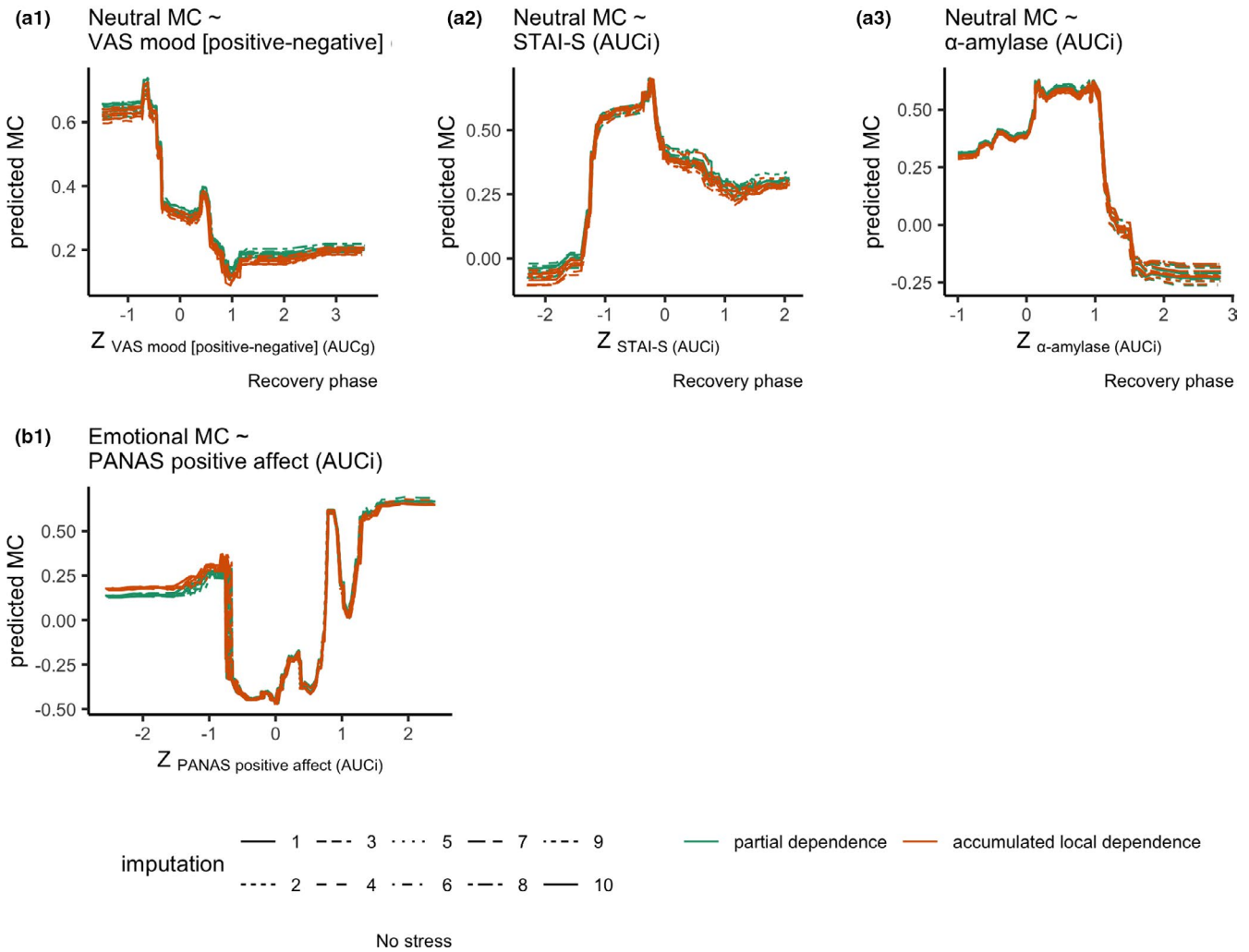
related to other hippocampus-dependent tasks, that is, visuo-spatial abilities (Carbone et al., 2019). There is some evidence that environmental information modulates learning and memory processes in individuals with higher trait agreeableness, conscientiousness or cooperativeness. Firstly, mental toughness, which is positively associated with agreeableness and conscientiousness and reflects a resilient combination of personality traits and coping style to perform under pressure (Lin et al., 2017), has been linked to more effective encoding and more engagement with the learning environment (Lin et al., 2017). The data-driven findings could suggest that this engagement leads to enhanced memory contextualization. Secondly, it has been shown that individuals have a good memory for cooperative people and their related environment (Bell et al., 2010). The data-

driven results could lead to the hypothesis that this ability is particularly present in individuals with relatively high cooperative trait characteristics, who may be more actively looking for collaborative opportunities in the environment.

**3.2.2.1.2 | Honesty-humility.** Two observations suggest that honesty-humility is related to the contextualization of stressful information. Firstly, higher levels of honesty-humility were related to better emotional memory contextualization during the acute phase of the stress response (Figure 5.A3), and secondly, this personality trait has a cubic relation to fear memory contextualization at basal conditions (where memory contextualization seems to benefit most from moderate levels of honesty-humility; Figure 5.C4).



A: recovery phase, B: no stress (basal)

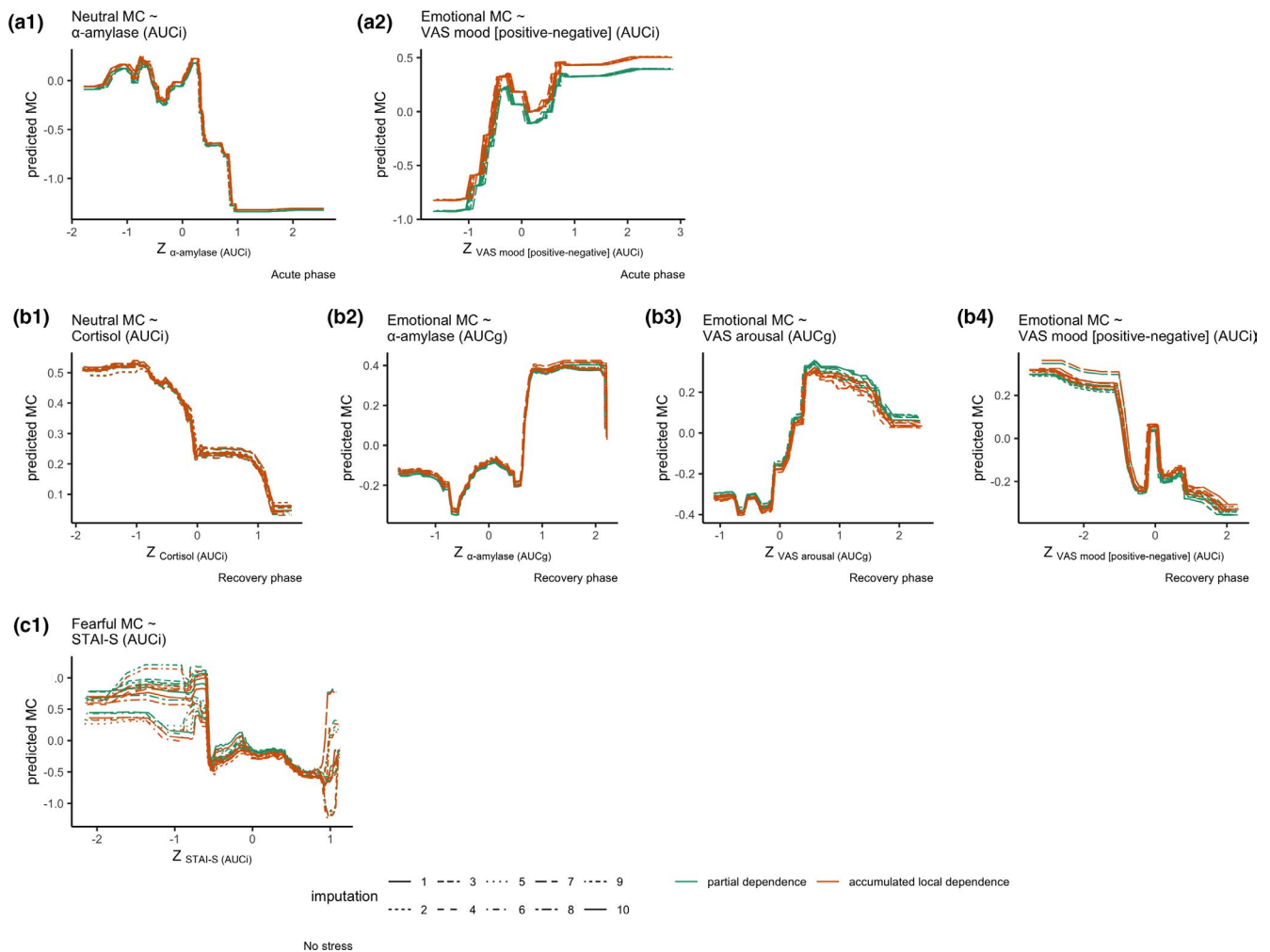


**FIGURE 6** Memory contextualization by significant Boruta selected ‘state during encoding’ variables. Partial dependence (PD; green) and accumulated local effects (ALE; orange) plots show how levels of the x-as variables are expected to change memory contextualization—in each imputed dataset—based on their function in the corresponding Random Forest model. The similarities between the PD and ALE plot suggest that the plots are not biased by highly correlated variables in the Random Forest models. The similarities between the imputations also suggest no bias due to multiple imputation. Salivary  $\alpha$ -amylase (sAA) is indexed as proxy for SAM-axis reactivity. VAS: visual analogue scale, AUCg: area under the curve with respect to ground, AUCi: area under the curve with respect to increase, STAI-S: State-Trait Anxiety Inventory State scale, PANAS: positive and negative affect scale

We could speculate that these relations points towards the involvement of the oxytocin (OT)–arginine vasopressin (AVP) system in contextualization of stressful information. The rationale for the relation between honesty–humility and OT-AVP functioning (under stress) is as follows. Honesty–humility is considered the basic prosocial trait (Thielmann et al., 2020), although prosocial behaviour in high and low trait honesty–humility can be the same under conditions of (self-)uncertainty (Pfattheicher & Böhm, 2018). It has been shown that OT and AVP receptor gene polymorphisms affect prosocial behaviour by modulating threat perception (Poulin et al., 2012). Social context can modulate the effect of OT on prosocial behaviour (Oloff et al., 2013) and honesty (Aydogan et al., 2017). Furthermore,

it can also be hypothesized that OT-AVP functioning affects memory contextualization under stress because OT and AVP influence the stress response and likely modulate cognitive processes in a (social) context-dependent manner following an inverted U-shape (Erdozain & Peñagarikano, 2020; Joëls & Baram, 2009; Oloff et al., 2013). For example, AVP stimulates the HPA-axis (Joëls & Baram, 2009) and OT dampens the activated HPA-axis (Oloff et al., 2013). In addition, medium—but not high—levels of exogenous OT improved memory specificity (Oloff et al., 2013); and the AVP receptor is implicated in social context-dependent learning (Caldwell et al., 2017). One could argue that we measured aspects of social cognition, as facial stimuli were used. It is possible that OT-AVP variability

A: acute phase, B: recovery phase, C: no stress (basal)



**FIGURE 7** Memory contextualization by significant Boruta selected ‘state during retrieval’ variables. Partial dependence (PD; green) and accumulated local effects (ALE; orange) plots show how levels of the  $x$  as variables are expected to change memory contextualization—in each imputed dataset—based on their function in the corresponding Random Forest model. The similarities between the PD and ALE plot suggest that the plots are not biased by highly correlated variables in the Random Forest models. The similarities between the imputations also suggest no bias due to multiple imputation. Salivary  $\alpha$ -amylase (sAA) is indexed as proxy for SAM-axis reactivity and cortisol as proxy for HPA-axis reactivity. AUCi: area under the curve with respect to increase, AUCg: area under the curve with respect to ground, VAS: visual analogue scale, STAI-S: State-Trait Anxiety Inventory State scale

affected both honesty–humility and memory contextualization. Since no direct measures of OT-AVP were included in the dataset, Boruta might have selected honesty–humility as the variable that captured variability in memory contextualization due to individual differences in OT-AVP functionality.

**3.2.2.1.3 | Age.** Age was positively related to neutral memory contextualization during the recovery phase in our sample (Figure 5.B1). This age effect could complement observations in children where there is some evidence for more fear generalization, suggesting less fear memory contextualization, in children below the age of 10 (Lonsdorf & Merz, 2017). It has been shown that younger adults’—compared to older adults’—memory specificity benefits

more from attending to stimulus differences (which might rely on similar processes as memory contextualization; Carr et al., 2015). The observation that the positive relation seems to flatten with increasing age in our (relatively young) sample could be a precursor for the reduced contextual dependency of neutral memories that has been previously shown in older adults (60–80 years; Strunk et al., 2017), potentially due to an age-related reduction in hippocampal neurogenesis (Alam et al., 2018).

### 3.2.2.2 | State at encoding: Mood

The data-driven analysis revealed mood during encoding as an important predictor of memory contextualization, outside the acute phase of the stress response. More specifically,

at basal conditions both positive and negative mood correlated with the degree of emotional memory contextualization (Figure 6.B1). During the recovery phase, neutral memory contextualization was reduced in individuals with a more negative mood (Figure 6.A1).

Together these results points towards a role for mood, in addition to physiological or perceived arousal, during encoding. More specifically, outside the acute phase (i.e. without an acute stress response and during the recovery phase of the stress response), mood seemed to improve the contextualization of mood-congruent stimuli. It has been shown before that mood facilitates retrieval of emotional memories when the valence of the current mood state is consistent with the valence of the emotional memory being retrieved, also called mood congruent memory facilitation (Haas & Canli, 2008). This mood congruent memory bias is not only linked to processes during retrieval (Haas & Canli, 2008) but also to processes during encoding, like the use of semantic knowledge (Kiefer et al., 2007) and differential PFC activity (Fitzgerald et al., 2011). The data-driven results suggest that memory contextualization might also contribute to the mood congruent memory bias.

### 3.2.2.3 | State at retrieval: Mood and arousal

In our theory-driven approach, we only focused on state/arousal during encoding. The data-driven approach reveals that context-dependent retrieval is also affected by state mood and arousal. Firstly, perceived arousal, that is, state anxiety, related to reduced context-dependent retrieval of fearful information that was encoded in the absence of acute stress (Figure 7.C1). Secondly, physiological arousal (measured by sAA) related to reduced context-dependent retrieval of neutral information that was encoded during the acute phase of the stress response (Figure 7.A1). On the other hand, moderate-high levels of physiological (Figure 7.B2) and psychological arousal (Figure 7.B3) were related to improved context-dependent retrieval of emotional material, learned during the recovery phase. Furthermore, higher cortisol levels were associated with less context-dependent retrieval of neutral material encoded during the recovery phase of the stress response (Figure 7.B1). Finally, negative mood was positively and negatively related to the context-dependent retrieval of emotional material that was learned during the acute (Figure 7.A2) and recovery phase (Figure 7.B4), respectively.

To summarize the findings above, arousal during retrieval might reduce context-dependent recollection of (a) fearful information encoded without stress and (b) neutral information encoded directly after stress, while it might facilitate the retrieval of emotional material encoded during the recovery phase of the stress response. While noradrenaline, released during arousal, usually promotes memory encoding at the

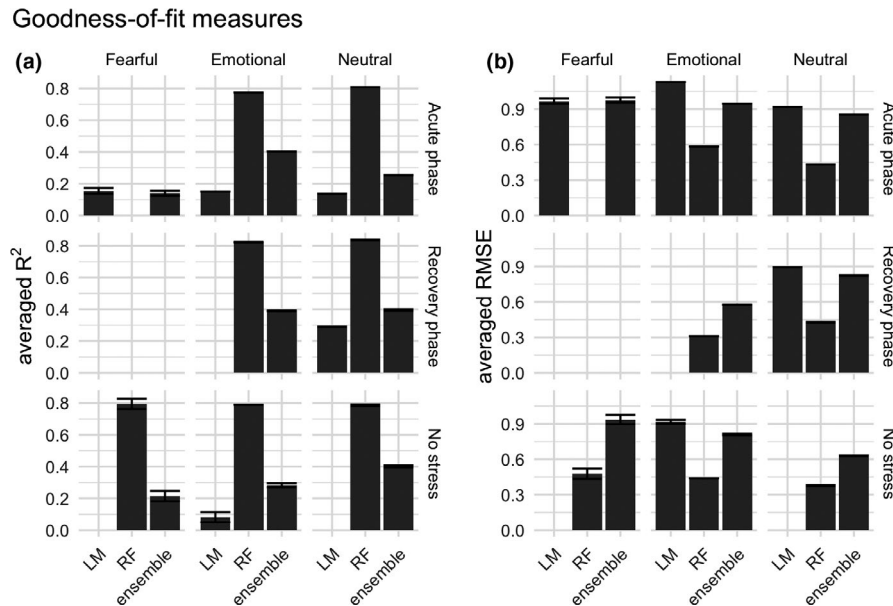
cost of stressor-irrelevant memory retrieval, it can also enhance retrieval when the arousal originates from the retrieval situation (Quaedflieg & Schwabe, 2018). For example, noradrenaline improves retrieval of negative faces under stress (Schönfeld et al., 2014).

The context-dependent retrieval of neutral material that is encoded during the recovery phase of the stress response seems to be hampered by a higher cortisol concentration. Interestingly, although the cortisol levels during retrieval were not evoked by a stressor but represent basal cortisol levels, the observed direction aligns with results from the theory-driven approach, where higher cortisol levels—following acute stress—reduced context-dependent encoding of neutral information. It has also been shown that higher cortisol levels, either exogenous or following an endogenous stress response, reduce memory retrieval (Gagnon & Wagner, 2016; Quaedflieg & Schwabe, 2018), perhaps the same applies for higher ‘basal levels’ and context-dependent memory retrieval.

Negative mood—during retrieval—seems to facilitate context-dependent retrieval of emotional-material encoded during the acute of the stress response, while reducing context-dependent retrieval of emotional-material encoded during the recovery of the stress response. This observation—like the data-driven findings on mood during encoding—fit nicely with the concept of mood congruent memory bias (Haas & Canli, 2008), and provide additional support for the idea that memory contextualization plays a role in this phenomenon.

## 3.3 | Performance evaluation of theory-driven and data-driven models

The goodness-of-fit measures (Figure 8; A:  $R^2$  and B: RMSE) indicate that the Random Forest models performed better than linear regression or ensemble models (Figure 8). This is to be expected because Random Forest modelling incorporates non-linear relationships and hidden variable interactions automatically (Smith et al., 2013). Although Random Forest models explained the data more accurately, the methodology is not optimal for biological interpretation of the identified relationships (Elragal & Klischewski, 2017; McCue & McCoy, 2017). What is particularly interesting is that the polynomial interpretations of the Random Forest variables (linear, quadratic or cubic, as derived from the PD and ALE plots in Figures 5–7) improved the predictive value of the theoretical model (Figure 8). This underlines that the hypothesized relations, formulated as research questions and hypotheses below (in section “Summary data-driven approach”), might improve the ability to explain individual memory contextualization in future studies, above and beyond the current theoretical model.



**FIGURE 8** Model performance of theoretical, data-driven and integrated ensemble models. The theoretical (Linear Model; LM), data-driven (Random Forest; RF) and ensemble models are indicated on the X-axis, per stress response phase and information valence type. The goodness-of-fit measures—averaged over the ten imputed datasets—are indicated on the Y-axis (A: R<sup>2</sup>; B: Root Mean Square Error (RMSE)). The error bars indicate the standard deviation between imputations. Better model fit—that is how well the model explains the data—is indicated by lower RMSE values and/or higher R<sup>2</sup> values. The formula for the calculation of R<sup>2</sup> is provided in Equation (3) on p. 5 of the Supporting Information

## 4 | DISCUSSION

The aim of the current study was to explore which individual differences contribute to memory contextualization after acute stress. We first developed a theoretical model of individual differences in memory contextualization following acute stress based on previous studies, which stated that memory contextualization is determined by responsiveness of the SAM-axis and HPA-axis; and that, in turn, reactivity of these systems is shaped by trait anxiety and cumulative exposure to life adversity. Such a theory-driven approach facilitates biological interpretability, yet prohibits the unbiased discovery of complex hidden relations, fostering new hypotheses (Elragal & Klischewski, 2017). To achieve the latter, we next performed a data-driven approach. As a final step, the explorative theory-driven and data-driven analyses were integrated and compared.

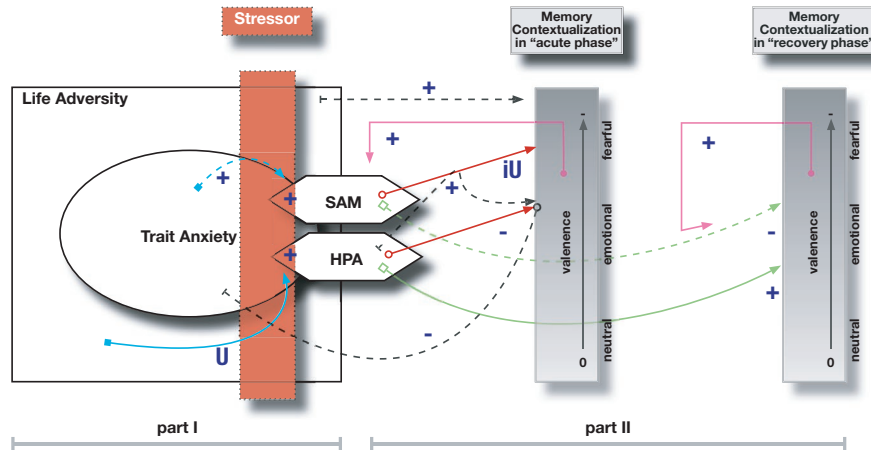
### 4.1 | Summary theory-driven approach

Trait anxiety and life adversity significantly affected the influence of SAM-axis and HPA-axis (re)activity on memory contextualization, the directions depending on stressor-encoding delay and information valence. We found evidence for most of the hypothesized relations (Figure 9. Solid arrows) and some unpredicted connections (Figure 9. Black dashed arrows). However, in contrast to our hypothesis no interaction between life adversity and trait anxiety was observed. In summary, information processing

in the memory contextualization task during the *acute phase* of the stress response indicates reduced contextualization of neutral material via cortisol in all subjects. Individuals with high life adversity (i.e. 1SD above the mean) showed better memory contextualization of emotional details during this acute phase. Directly after stress, sAA and cortisol promoted fear memory contextualization in individuals with, respectively, low life adversity and low trait anxiety. The data suggest that during the *recovery phase*, neutral information was better contextualized (a) via the delayed effects of cortisol in individuals that experienced low levels of life adversity and (b) via the (reduction in) delayed effects of sAA in individuals that experienced more life adversity. It should be noted, in general, that causal relationships based on regression analyses should be made with extreme care.

### 4.2 | Summary data-driven approach

The data-driven approach follows the theoretically motivated inference that life adversity influences memory contextualization of (neutral and) negatively valenced material following acute stress, while the delayed effects of arousal modulate neutral memory contextualization. In addition, the newly identified characteristics lead us to speculate about additional traits and mechanisms during encoding and retrieval that might contribute to individual differences in memory contextualization. The findings give rise to six new potential insights that could be taken into account when optimizing the initial, theoretical model:



**FIGURE 9** Schematic overview of the observed relations in the framework of the hypothesized Theoretical Model. Solid lines indicate hypothesized relations that were confirmed by the statistical analysis. Dashed black lines indicate relations non-hypothesized relations, dashed coloured lines indicate unconfirmed hypothesis. Positive (+), negative (-), U-shaped (U) and inverted U-shaped (iU) directions are indicated and colour codes follow Figure 1. Blue: influence of trait anxiety and life adversity on SAM- and HPA-axis reactivity (following acute stress). Red & Green: effects of SAM- and HPA-axis reactivity during acute (red) and recovery (green) phase. Pink: SAM-axis activation by negative valence. Grey gradient: information valence (light = neutral, dark = negative)

1. Non-anxious traits improve neutral and emotional memory contextualization in the absence of acute stress.
2. The OT-AVP system affects memory contextualization of stressful information.
3. Neutral memory contextualization is affected by age.
4. The mood congruent memory bias is partly based on memory contextualization and context-dependent retrieval.
5. Arousal affects context-dependent retrieval of stressful information.
6. Basal cortisol levels during retrieval reduce context-dependent retrieval of neutral information.

#### 4.3 | Best of both worlds: Integrate theory- and data-driven analyses

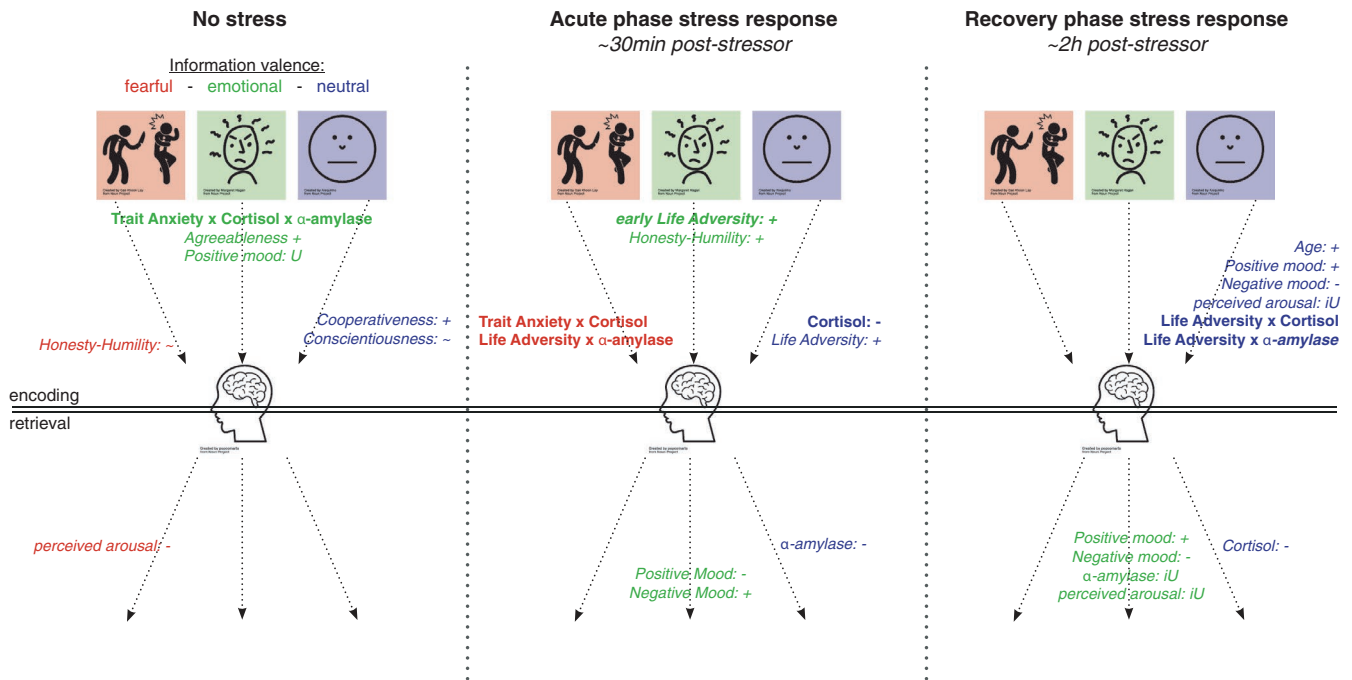
The theory-driven analyses supported most of the hypothesized effects of trait anxiety and life adversity via SAM-axis and HPA-axis activation on memory contextualization. As expected, the influence of these characteristics depends on situational aspects like information valence and stressor-encoding delay. The unbiased data-driven approach underlined the importance of life adversity during the acute phase and SAM-axis functioning during the delayed phase, and offered leads for new hypotheses about non-anxious personality traits, age, mood and states during retrieval. Model performance evaluations suggest that future efforts to incorporate the postulated hypotheses into the theoretical model might improve its ability to explain memory contextualization at the level of the individual.

Besides the insights in individual characteristics that contribute to memory contextualization following stress, this study also offers an example of the integration of theory-driven and

data-driven perspectives. It is not (yet) common in neuroscience to combine both methodologies, although they complement each other in the research cycle (Hulsen et al., 2019). Theory-driven strategies excel in studying why certain correlations in the data exist, which is crucial for the practical application of knowledge in the clinic (Mazzocchi, 2015). However, they are constrained to the current knowledge and therefore inherently biased. Data-driven strategies, on the other hand are unbiased and have good predictive value, but the interpretability of the findings is limited (Elragal & Klischewski, 2017). Here, we show how the two approaches can be merged to facilitate two aspects of the research cycle: (a) testing interpretable hypotheses (theory driven) and (b) generating new unbiased hypotheses for future studies (data driven).

#### 4.4 | Importance of individual difference in the study of stress and memory

These findings complement a recent review that highlights the crucial, but (mostly) 'situational', characteristics that need to be taken into account when studying stress and cognition in the laboratory (Shields, 2020). The current study adds the importance of both anxious and non-anxious personality traits, cumulative life adversity exposure and state mood and (perceived) arousal during encoding and retrieval, depending on the stressor-encoding delay and information valence type of interest. A graphical overview of all the individual characteristics that potentially influence memory contextualization is provided in Figure 10, grouped by information valence and stressor-encoding delay. Together, our exploratory analyses illustrate that a healthy population—selected for



**FIGURE 10** Predictors of individual variation in memory contextualization. Schematic representation of the significant terms from the theory-driven analyses (bold) and Boruta selected variables (italic), per stress response phase and information valence (red: fearful, green: emotional; blue: neutral). Predictors that are identified by both approaches are indicated in bold italic. Symbols indicate: Linear relations (+: positive; -: negative), quadratic relations (U: U-shaped; iU: inverted U-shape), cubic relations (~) and interaction (x) effects

absence of psychopathology—is not necessarily a homogeneous group. By measuring the discussed characteristics that contribute to individual variation, future studies are enabled to clarify the nature of the within-group variance. This might be of particular importance when patient characteristics are compared to a healthy control group, as variance caused by these individual characteristics could be wrongfully attributed to disease status.

## 4.5 | Limitations

It must be noted that this study is explorative in nature, and has some associated limitations. The theory-driven analyses were not corrected for multiple comparisons and the data-driven analyses were not validated with separate training, test and validation datasets. Although we have taken measures to limit potential bias, future studies should validate our findings in a separate cohort.

## ACKNOWLEDGEMENTS

We thank Valeria Bonapersona, Fenne Smits, Tim Varkevisser and other colleagues for their valuable input on the statistical analyses and discussions about the interpretation of the results. We also thank all participants for their contribution to this study.

## CONFLICT OF INTEREST

None.

## AUTHORS CONTRIBUTIONS

MS, EG and MJ designed the study. MS collected and analysed the data, and wrote the original draft of the manuscript. MS, EG and MJ edited and reviewed the manuscript.

## FUNDING INFORMATION

This research was supported by the Dutch Ministry of Defence. Milou Sep is supported by a personal grant, which is part of Graduate Program project #022.003.003 from The Netherlands Organization of Scientific Research.

## PEER REVIEW


The peer review history for this article is available at <https://publons.com/publon/10.1111/ejn.15067>.


## DATA AVAILABILITY STATEMENT

The data and code will be available via Open Science Framework (<https://osf.io/6kf34/>).

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### SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

**How to cite this article:** Sep MSC, Joëls M, Geuze E. Individual differences in the encoding of contextual details following acute stress: An explorative study. *Eur J Neurosci*. 2020;00:1–25. <https://doi.org/10.1111/ejn.15067>