



Stress affects the neural ensemble for integrating new information and prior knowledge

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ABSTRACT

Prior knowledge, represented as a schema, facilitates memory encoding. This schema-related learning is assumed to rely on the medial prefrontal cortex (mPFC) that rapidly integrates new information into the schema, whereas schema-incongruent or novel information is encoded by the hippocampus. Stress is a powerful modulator of prefrontal and hippocampal functioning and first studies suggest a stress-induced deficit of schema-related learning. However, the underlying neural mechanism is currently unknown. To investigate the neural basis of a stress-induced schema-related learning impairment, participants first acquired a schema. One day later, they underwent a stress induction or a control procedure before learning schema-related and novel information in the MRI scanner. In line with previous studies, learning schema-related compared to novel information activated the mPFC, angular gyrus, and precuneus. Stress, however, affected the neural ensemble activated during learning. Whereas the control group distinguished between sets of brain regions for related and novel information, stressed individuals engaged the hippocampus even when a relevant schema was present. Additionally, stressed participants displayed aberrant functional connectivity between brain regions involved in schema processing when encoding novel information. The failure to segregate functional connectivity patterns depending on the presence of prior knowledge was linked to impaired performance after stress. Our results show that stress affects the neural ensemble underlying the efficient use of schemas during learning. These findings may have relevant implications for clinical and educational settings.

Introduction

Schemas are associative network structures, which often lack unit detail and are adaptable in the face of new, schema-congruent information (Ghosh and Gilboa, 2014; Gilboa and Marlatte, 2017). Such schemas facilitate memory formation by providing a framework to guide learning (Bartlett, 1932; Kumaran, 2013; van Kesteren et al., 2014). The enhancing effect of schemas on new learning is at the heart of our educational system and has a long standing research tradition in psychology (Bartlett, 1932). Only recently, however, neuroscientists unraveled the neural mechanisms underlying schema-related learning. These studies demonstrated that encoding, consolidating, and retrieving schema-related information critically relies on the medial prefrontal cortex (mPFC), interacting with the angular gyrus and the precuneus (Gilboa and Marlatte, 2017; Spalding et al., 2015; Tse et al., 2007, 2011;

van Kesteren et al., 2010a,b; Wagner et al., 2015). Critically, the mPFC is assumed to detect whether new information is congruent with prior knowledge. If there is relevant prior knowledge, the mPFC integrates this information into the schema (Ghosh et al., 2014; Richards et al., 2014; van Kesteren et al., 2012). In contrast, schema-incongruent or unrelated information is encoded by the hippocampus as new episodic memory (Eichenbaum, 1999; Scoville and Milner, 1957; van Kesteren et al., 2012).

Stressful events are well-known to alter both hippocampal and PFC functioning (Joëls et al., 2006; Schwabe et al., 2012a). For instance, stress and stress mediators, such as corticosteroids and catecholamines, often enhance episodic memory formation (Barsegyan et al., 2010; Cahill et al., 2003; Luethi et al., 2008; Roozendaal et al., 2006; Sandi and Rose, 1994), but impair memory retrieval and prefrontal functions including working memory and goal-directed behavior (Barsegyan et al., 2010;

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Buchanan et al., 2006; de Quervain et al., 1998; de Quervain et al., 2000; Diamond et al., 2006; Roozendaal et al., 2003; Schwabe et al., 2012b; Schwabe and Wolf, 2014; Zoladz et al., 2012). In line with these findings, major stress mediators affect plasticity both in the hippocampus and the PFC (Arnsten, 2009; Diamond et al., 2006; Zoladz et al., 2012). Many previous studies on stress and memory, however, have not considered what an individual brings to a learning situation in terms of prior knowledge. Recent evidence from our lab indicates that stress and the administration of glucocorticoids impair schema-related learning (Kluen et al., 2017). The neural mechanisms underlying the impact of stress on the integration of new information and existing knowledge, however, are unknown. The present experiment therefore aimed at examining the neural mechanisms underlying a stress-induced impairment in schema-related learning.

To this end, participants first learned a hierarchy of six galaxies (Kumaran, 2013, Fig. 1A, ‘phase 1’). One day later, participants underwent a stress induction or a control manipulation before they learned two new hierarchies (‘phase 2’) while neural activity was assessed using functional magnetic resonance imaging (fMRI). Importantly, one of these hierarchies (‘related’) included four galaxies from the original schema, which thus served as a scaffold to learn the new galaxies’ positions in the hierarchy. In contrast, the other (‘novel’) hierarchy consisted of eight completely new galaxies such that there was no schema that could aid new learning (Kumaran, 2013). Based on evidence suggesting that stress may impair mPFC functioning (Arnsten, 2009; Barsegayan et al., 2010; Schwabe et al., 2012b), we hypothesized that stress would reduce schema-related mPFC activity, leading to impaired detection of schema-congruency (van Kesteren et al., 2010a; van Kesteren et al., 2012) and thus to impaired schema-related learning.

Materials and methods

Participants and experimental design

Fifty healthy individuals (25 males, 25 females) completed this experiment (mean age = 25.0 years, SEM = 0.48 years). Individuals with current medication intake, lifetime history of neurological or psychiatric

disorders, or current non-admissibility to the MRI scanner were excluded from participation. Moreover, we excluded smokers and women taking hormonal contraceptives as both can affect the stress response (Kirschbaum et al., 1999; Rohleder and Kirschbaum, 2006). All participants had normal or corrected to normal vision and were screened by an MD prior to MRI scanning for possible MRI contraindications. The protocol was approved by the review board of the German Psychological Society (LS 062014_B), all participants provided written informed consent and received a moderate monetary compensation for participation.

We used a mixed design with the between-subjects factor treatment (stress vs. control manipulation) and the within-subjects factor schema (schema-related vs. novel information) to investigate the effects of stress on the neural mechanisms underlying schema-related learning. Participants were randomly assigned to the experimental groups ($n = 25$ per group).

Experimental procedure

All testing took place in the afternoon and early evening (12:00–20:00).

Day 1. Upon their arrival at the laboratory, participants provided baseline measures of blood pressure (assessed using an Omron blood pressure monitor with arm cuff) and salivary cortisol. To assess the concentrations of cortisol in saliva over time, each participant provided six samples using Salivette® collection devices (Sarstedt). Samples were stored at -18°C . When data acquisition was finished, all samples were thawed and the fraction of free cortisol was measured using a chemiluminescence immunoassay (IBL, Tecan) with a lower detection limit of 0.33 nmol/l. All intra- and inter-assay coefficients of variance were $<10\%$. In addition to these physiological measures, participants completed a German questionnaire assessing subjective mood, wakefulness, and calmness (MDBF; Steyer et al., 1994). Finally, participants performed phase 1 of the learning task during which they acquired a schema (Kumaran, 2013) followed by an explicit memory test (see below and Fig. 1A).

Day 2. One day later, participants came to the MRI scanning facility at the University Medical Center Hamburg-Eppendorf. They completed the

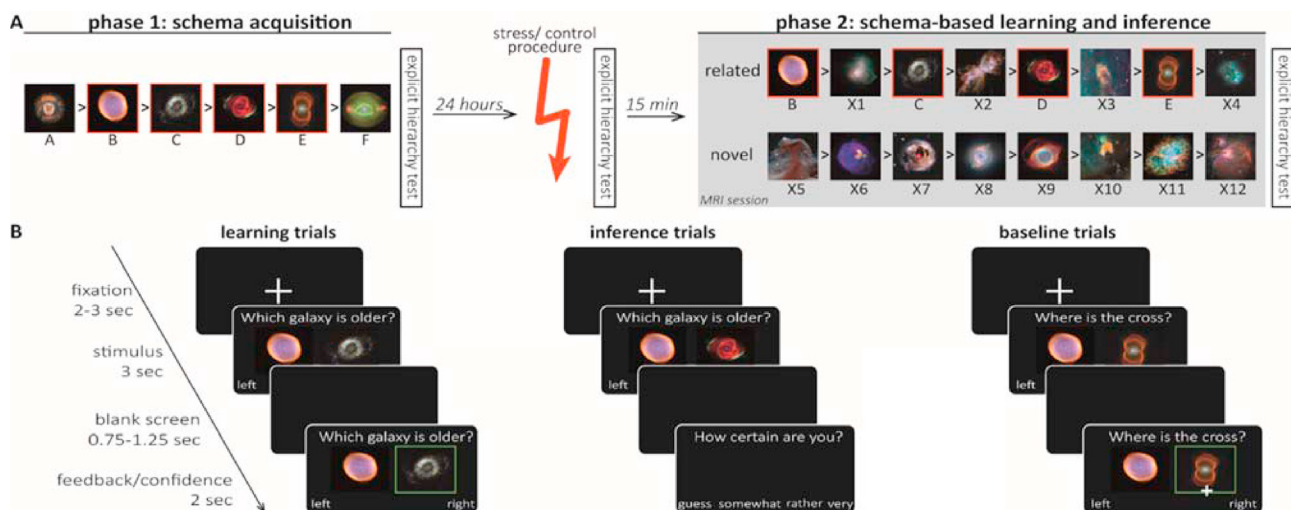


Fig. 1. Experimental setup and learning task. **A** Participants acquired an age hierarchy of six different galaxies by trial and error on day 1 (‘phase 1’, (Kumaran, 2013)), followed by an explicit hierarchy test. A day later, they came to the MRI scanning facility and underwent either a stress or a control manipulation. After another explicit hierarchy recall test, participants learned two new hierarchies of galaxies (‘phase 2’) while their brain activity was measured using functional magnetic resonance imaging (fMRI). Importantly, to acquire one of these hierarchies (‘related’) they could use their knowledge from phase 1 as a schema, as this hierarchy contained items from phase 1. In contrast, for the ‘novel’ hierarchy, the knowledge from phase 1 could not serve as a scaffold guiding new learning as the items were all new. **B** Three trial types were used during both phases. In learning trials, participants saw two neighboring galaxies for 3 s and had to indicate which one is older by button press. They were provided with the correct feedback (2 s) which they could use to learn about the age relationships between the galaxies. In inference trials, participants were presented with non-neighboring galaxies and had to infer the age relationship between these galaxies. Finally, baseline trials served as visuo-motor control trials for the fMRI analyses.

Pittsburgh Sleep Quality Index (German version; Backhaus and Riemann, 1996) and the MDBF, and provided a saliva sample and vital signs assessment. Next, they were brought to a separate room where they underwent either the Trier Social Stress Test (Kirschbaum et al., 1993) or a non-stressful control procedure, depending on group assignment. The TSST is a stress protocol well-known to activate both the autonomic nervous system and the hypothalamus-pituitary-adrenal axis (Kirschbaum et al., 1993). It simulates a 15-min job interview including a public speech about the participant's eligibility for his/her dream job and a mental arithmetic task while being videotaped and evaluated by two serious, non-reinforcing committee members. Participants in the control condition spoke about a topic of their choice followed by a simple arithmetic task (counting forwards in steps of 15), without committee or camera. Directly after the stressor/control manipulation, participants' vital signs were assessed again, followed by a saliva sample, the MDBF, and a rating of the difficulty, stressfulness, and unpleasantness of the experimental treatment. Participants then completed an explicit memory recall test and were brought to the MRI room and prepared for scanning. Approximately 15 min after stressor/control manipulation offset, participants learned schema-related and novel information (phase 2 of the learning task), followed by an anatomical scan and an explicit memory test. Participants left the scanning facility after providing a last saliva sample, vital signs and mood assessment.

Learning task

To investigate schema-related learning, we used a learning task that was modified from Kumaran (Klueen et al., 2017; Kumaran, 2013).

Phase 1: Schema acquisition. In phase 1, participants acquired a (fictive) age hierarchy of six galaxies, $A > B > C > D > E > F$ (Fig. 1A). Three different trial types were presented in 15 blocks: learning, inference and baseline trials (Fig. 1B). In learning trials (5 per block), participants were presented with two neighboring galaxies for 3 s (e.g., B and C) and asked to indicate which one was older by pressing one of two buttons. After a jittered blank screen, feedback was provided for 2 s, highlighting the older galaxy with a green frame. In inference trials (5 per block), two non-neighboring galaxies were presented for 3 s (e.g., B and E) and participants had to infer the older galaxy based on what they had learned during the learning trials. In these inference trials, no feedback was provided, but participants were asked to rate their confidence from 1 ('guess') to 4 ('very sure') after a jittered blank screen. Finally, baseline trials (2 per block) were used as visuo-motor control trials and contained two randomly chosen galaxies for 3 s, one of which was marked with a white cross. Participants had to choose the galaxy with the cross and were provided with the correct feedback after a jittered blank screen. Each block contained two baseline trials and five learning trials that were randomly intermixed, followed by five inference trials.

Phase 2: Schema-related and novel learning. In phase 2, participants learned two new age hierarchies of eight galaxies each in the MRI scanner (Fig. 1A). Importantly, one hierarchy (termed 'related', $B > X1 > C > X2 > D > X3 > E > X4$) included four galaxies from the schema acquired during phase 1, which could thus serve as a scaffold to learn the position of the new galaxies more rapidly. In contrast, the other hierarchy ('novel', $X5 > X6 > X7 > X8 > X9 > X10 > X11 > X12$) included eight completely new galaxies for which the schema could not serve as a scaffold aiding learning during phase 2. Participants were presented with six blocks per hierarchy (12 in total), each comprising two baseline trials randomly intermixed with seven learning trials, followed by six inference trials, which contained only new galaxies and no galaxies from phase 1. Trial timing and setup was identical to phase 1. The assignments of galaxies to hierarchy position and the related vs. novel hierarchy, and whether phase 2 started with a related or novel block, were counter-balanced. Of special interest for the current study were the learning trials as they indexed schema-related learning during phase 2, whereas inference trials mainly targeted inferential reasoning.

Explicit hierarchy test. After phase 1, the stress/control manipulation,

and phase 2, participants were asked to explicitly recall the hierarchical order of the presented galaxies. All galaxies presented up to that time point were shown and participants were asked to indicate the correct order (separately for 'novel' and 'related' after phase 2). In line with previous studies (Kumaran, 2013; Kumaran et al., 2012), we evaluated performance by the summed deviation of the true position from the position indicated by the participant per galaxy (hereafter referred to as 'errors'). Higher values thus represent more errors in explicit hierarchy knowledge.

Statistical analysis of behavioral and physiological data

To test whether the TSST successfully induced stress, data on mood, vital signs, and salivary cortisol were analyzed using mixed-design ANOVAs with the between-subjects factor treatment and the within-subjects factor time after stress/control manipulation onset. T-tests were used to investigate post-hoc group differences in these measures, to test for group differences in stress measures and explicit knowledge on day 1, and to analyze group differences in the ratings of the stress/control manipulation.

Task performance during learning and inference trials was averaged per block and subjected to mixed-design ANOVAs per phase with the between-subjects factor treatment and the within-subjects factors schema (novel vs. related) and block. For explicit memory after phase 2, a similar ANOVA was used with the factors treatment and schema. All analyses were performed in SPSS Statistics 22 (IBM). All P-values are two-tailed and Greenhouse-Geisser correction was applied when necessary.

MRI acquisition and analyses

MRI measurements were acquired using a 3T Skyra scanner (Siemens) equipped with a 32-channel head coil. A sequence sensitive to the blood-oxygenation level dependent (BOLD) response with the following parameters was used to measure brain activity during task performance: 27 transversal slices, slice thickness = 3 mm, distance factor 20%, repetition time (TR) = 2.00s, echo time (TE) = 30 ms, effective voxel size = $3.0 \times 3.0 \times 3.0$ mm. Additionally, we acquired magnetic (B0) field maps to unwarp the functional images and a high-resolution T1-weighted anatomical image (TR = 2.5s, TE = 2.12 ms, 256 slices, voxel size = $0.8 \times 0.8 \times 0.9$ mm). All fMRI data were preprocessed and analyzed in SPM12 (Wellcome Trust Center for Neuroimaging, London) using general linear modeling (GLM). One participant (male, control group) was excluded due to excessive head motion (>4 mm). The first three functional images were discarded to allow for T1 equilibration. Remaining functional images were spatially realigned and unwrapped, coregistered to the structural image, and normalized to MNI space. Finally, the functional images were spatially smoothed using the default 8 mm FWHM Gaussian kernel.

To assess task-related activity and the effects of treatment, we used a model including separate regressors for stimulus and feedback/confidence presentation during baseline, learning, and inference trials, respectively. To dissociate activity for novel and related trials, the regressors for learning and inference were split, resulting in 10 regressors in total, all events modeled as boxcars with a duration of the events' presentation on screen (baseline, baseline feedback, novel learning, related learning, novel inference, related inference, feedback novel learning, feedback related learning, confidence novel inference, confidence related inference). Additionally, we added a spike regressor for button presses. All regressors were convolved with the canonical hemodynamic response function. Six realignment parameters were added to account for residual motion. Full-factorial designs were used to test for activation differences depending on schema and treatment. Behavioral covariates (average performance in learning and inference trials) were added to the second-level GLMs where indicated (see 3.4) to assess the correlation between neural activation and behavioral performance. Moreover, to correlate brain activity to the cortisol response to treatment,

we calculated the area under the curve with respect to the increase during day 2 (AUCi; Pruessner et al., 2003) and extracted mean parameter estimates for the contrast of interest from the anatomically defined mPFC using MarsBaR (see 3.4). To investigate the effects of treatment on hippocampal and mPFC connectivity during schema-related learning, the 'Psycho-Physiologic Interaction' tool was used as implemented in SPM12 to test for enhanced connectivity during related and novel learning trials as compared to baseline trials, respectively (see 3.5, 3.6). The models contained all task regressors, the interaction term and the time course of the ROI which was anatomically defined using the Harvard-Oxford atlas at a probability of 50%. Again, full-factorial designs were used to test for group differences.

For whole-brain analyses, we used a cluster-defining threshold of $P < .001$ with a cluster-probability of $P < .05$ family-wise error (FWE) corrected for multiple comparisons as suggested by previous research (Eklund et al., 2016). For our regions of interest (ROIs, hippocampus, mPFC, angular gyri, and precuneus), we implemented small volume correction (SVC) using an initial threshold of $P < .005$, uncorrected, which was followed by voxel-wise FWE-correction ($P < .05$) for multiple comparisons within ROIs. The more liberal initial threshold was chosen to enhance sensitivity considering that voxel-wise inference has been shown to be overly conservative (Eklund et al., 2016). The results obtained by SVC are indicated by 'P_{SVC}', all other results are based on whole-brain cluster-inference. Anatomical masks were taken from the Harvard-Oxford atlas using a probability threshold of 50%. For the mPFC, we used the masks for frontal medial cortex and the paracingulate cortex. All images are displayed at $P < .005$, uncorrected, for illustrative purposes.

Results

Successful schema acquisition

On day 1, participants successfully acquired the schema (Fig. 2A). Both during learning trials, in which neighboring galaxies were presented and corrective feedback was provided, and during inference trials, presenting non-neighboring galaxies without feedback (Fig. 2B), task performance increased significantly over blocks (both $F > 20$, $P < .001$, Fig. 2), reaching an average learning and inference performance of 85% in the last task block. Successful schema acquisition was further

supported by the explicit hierarchy test in which participants made on average only 3 mistakes (range 0–18) and 58% of participants made no error at all (Fig. 2C). Furthermore, participants performed significantly better in inference trials in which the hierarchical distance between galaxies was long than in those in which the distance was short ($F(1,48) = 26.32$, $P < 0.001$), indicating that participants had indeed created an associative structure characteristic for a schema. Most importantly, stress and control groups did not differ in schema acquisition on day 1, neither in learning or inference trial performance, nor in the explicit hierarchy test (all main effects and interactions: $P > .25$). Moreover, groups did not differ in any measure of stress on day 1 (all $P > .15$, Table 1) or in self-reported sleep duration and quality in the night after the learning session (both $P > .50$).

Successful stress induction prior to schema-related vs. novel learning

As expected, the TSST induced pronounced subjective, autonomic, and endocrine stress responses. The TSST was rated as more difficult, stressful, and unpleasant (all $t > 4$, $P < .001$, Table 2) and decreased positive mood and calmness (time $\times$ treatment: both $F > 7$, $P \leq .001$) compared to the control manipulation. Whereas groups did not differ before the treatment (all $P > .15$, Table 2), the stress group felt less positive and calm prior to the learning task (both $P \leq .01$). Moreover, the TSST activated the autonomic nervous system as indicated by a pronounced increase in diastolic and systolic blood pressure (time $\times$ treatment: both $F > 8$, $P = .001$, Fig. 3A and B). Groups did not differ prior to treatment (all $P > .60$), but the stress group displayed higher blood pressure after treatment, i.e., before the learning session (both $P < .05$). Finally, the stressor also markedly increased salivary cortisol levels (time $\times$ treatment: $F(2.6,125.5) = 10.75$, $P < .001$, Fig. 3C): Whereas groups did not differ before treatment ($P = .507$), salivary cortisol levels were elevated from stressor offset onwards (stress vs. control directly after treatment: $P = .074$; immediately before learning, after learning, and at the end of day 2: all $P < .001$).

Pre-existing schema enhances learning of related learning material

The stress induced by the TSST did not affect explicit recall of the schema learned on day 1 ($t(48) = 0.00$, $P = 1.000$, Fig. 4C) and recall performance for this previously learned schema was overall very good

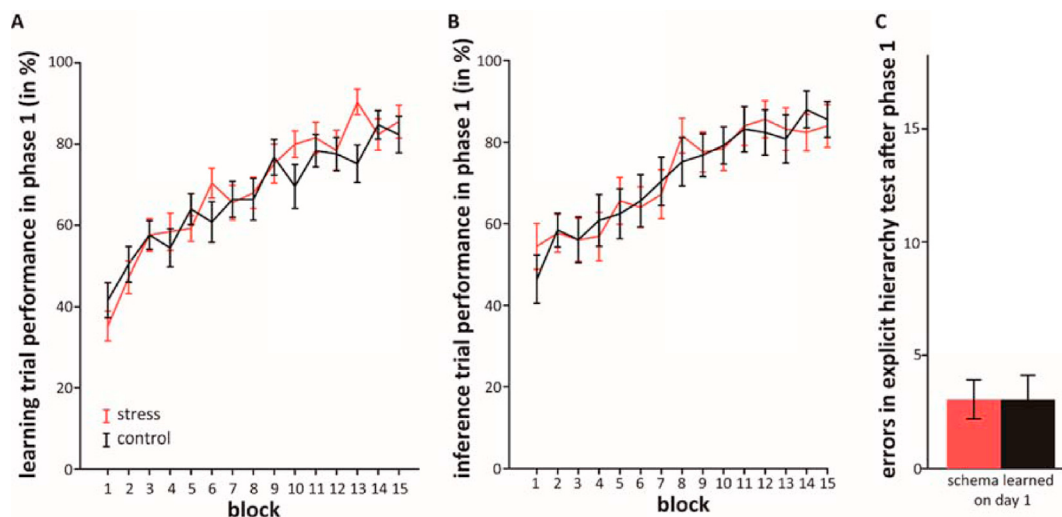


Fig. 2. Task performance and explicit knowledge on day 1. **A** Learning trial performance increased over blocks during phase 1 and was not affected by stress. **B** Similarly, inference trial performance increased during phase 1, but was unaffected by stress. **C** After phase 1, participants were able to explicitly recall the hierarchy learned during phase 1 as indicated by few errors (defined as the sum of all deviations of the hierarchy position indicated by the participant and its true position for all galaxies). The maximum possible amount of errors was 18. Color coding of the groups is the same for all panels, there was no effect of treatment. Data represent means $\pm$ s.e.m.

Table 1
Physiological, endocrine, and subjective measures of stress in both groups on day 1.

Variable	Stress group		Control group		Statistics	
	M	SEM	M	SEM	t	P
Systolic blood pressure (mmHg)	118.36	3.05	119.14	2.93	-.18	.854
Diastolic blood pressure (mmHg)	81.92	2.04	82.34	1.55	-.16	.870
Heart rate (bpm)	81.16	2.84	80.92	2.29	.07	.948
Salivary cortisol (nmol/l)	5.51	0.96	4.51	0.56	.89	.379
Subjective mood	35.56	0.69	34.88	0.74	.67	.506
Wakefulness	30.64	0.93	31.24	1.25	-.39	.702
Restlessness	33.96	0.84	31.92	1.14	1.44	.156

(only 3 mistakes on average, range 0–18). Thus, possible treatment effects on schema-congruent learning on day 2 cannot be explained by a simple stress-induced retrieval deficit.

As expected, the presence of a relevant schema boosted performance in learning trials, indicated by better acquisition of the related hierarchy compared to the novel hierarchy (schema: $F(1,48) = 41.20$, $P < .001$; block: $F(3.8, 181.2) = 25.23$, $P < .001$, schema $\times$ block:

$F(4.2,202.6) = 2.83$, $P = .023$; Fig. 4A). Inference performance, in contrast, was comparable for both hierarchies (all $P > .15$, Fig. 4B), suggesting that inference was not modulated by the presence of a schema. The idea that learning and inference trials tracked different processes is supported by our fMRI results (Fig. 5) showing increased activation in memory-related areas during learning trials as compared to inference trials (hippocampus, mPFC, and angular gyrus), but no enhanced activation in the hippocampus, mPFC, angular gyrus, or precuneus in inference trials as compared to learning trials (no significant voxel even at $P < .005$, uncorrected). As we were mainly interested in learning and less in inference processes, we focused our further analyses mainly on learning trials. In line with the schema-related learning enhancement, participants made fewer errors in the explicit memory test at the end of day 2 for the congruent hierarchy than for the incongruent hierarchy ($F(1,48) = 5.05$, $P = .029$, Fig. 4C). However, at the group level we found no effect of treatment (all main effects or interactions: $P > .20$), also not when excluding the three participants of the stress group that were classified as cortisol-nonresponders based on a cortisol response to the stressor of less than 1.5 nmol/l (Miller et al., 2013). We also explored whether gender interacted with treatment or schema to affect performance. Although men outperformed women in the explicit knowledge test ($F(1,46) = 9.14$, $p = .004$) and inference trials ($F(1,46) = 6.93$,

Table 2
Subjective measures of stress in both groups over the course of day 2.

Variable	Stress group			Control group		
	Before stress induction	After stress induction	End of day 2	Before control procedure	After control procedure	End of day 2
<i>Mood questionnaire</i>						
Subjective mood	35.16 (0.77)	29.60* (1.31)	32.44 (1.00)	34.60 (1.04)	34.16 (1.09)	33.80 (0.80)
Wakefulness	30.04 (0.98)	29.88 (0.94)	26.08 (1.06)	31.92 (1.23)	31.44 (1.11)	25.68 (1.16)
Calmness	33.84 (0.81)	27.52** (1.17)	32.08 (0.98)	32.12 (1.21)	32.36 (1.22)	33.84 (0.78)
<i>Ratings of stressor/control procedure</i>						
Difficult	–	69.20*** (4.00)	–	–	32.80 (5.49)	–
Unpleasant	–	64.00*** (4.08)	–	–	30.00 (5.80)	–
Stressful	–	66.40*** (4.51)	–	–	26.40 (4.47)	–

Note: Data represent mean (standard error). Higher values in subjective mood represent elevated mood. *** $P < .001$ compared to control group, ** $P < .01$ compared to control group, * $P < .05$ compared to control group.

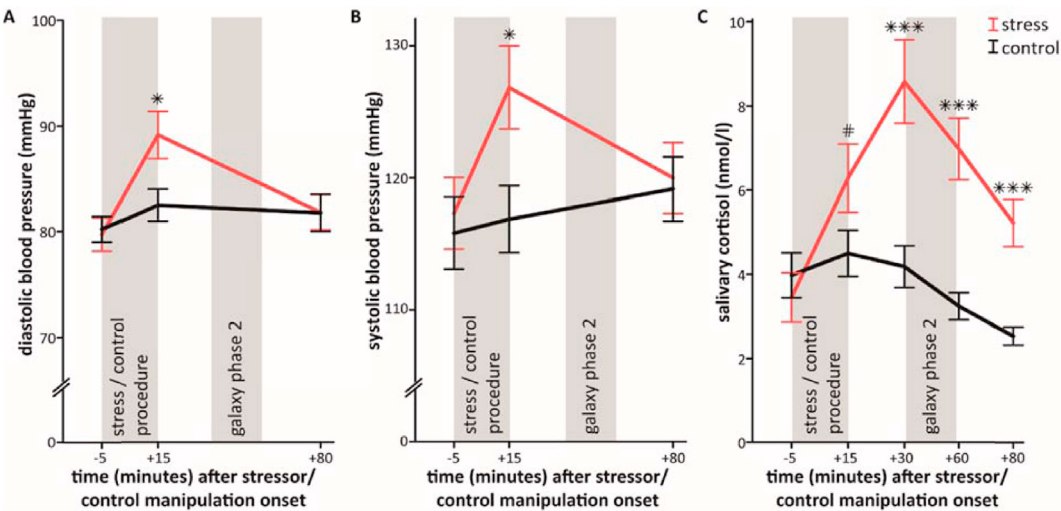


Fig. 3. Successful stress induction indicated by physiological parameters. **A** Participants in the stress group showed increased diastolic and **B** systolic blood pressure after treatment compared to participants in the control group. **C** The stress procedure increased salivary cortisol levels compared to the control procedure. Data represent means $\pm$ s.e.m. * $P < .001$, * $P < 0.05$.

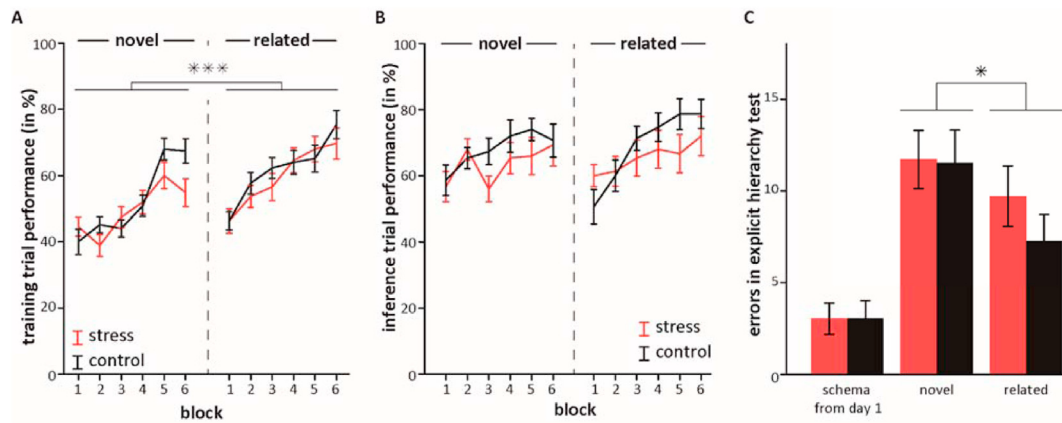


Fig. 4. Task performance and explicit hierarchy knowledge on day 2. **A** Learning trial performance was better for the related compared to the novel structure, indicating that the presence of a schema facilitated learning of schema-related information. **B** Inference trial performance increased across blocks but was not facilitated by the presence of prior knowledge. **C** Stress did not affect explicit retrieval of the hierarchy learned on day 1 (schema) as assessed directly after the stress/control manipulation. Supporting enhanced learning if a relevant schema is available, participants made fewer errors in the explicit hierarchy test for the related hierarchy compared to the novel hierarchy. Data represent means $\pm$ s.e.m. *** $P < .001$, * $P < .05$.

$p = .011$; learning trials: $p > .10$), these effects were independent of treatment or schema (all $p > .10$).

Stress affects neural activity underlying schema-related learning

Across groups, learning of schema-related information compared to novel information activated a set of brain regions known to be implicated in schema processing in humans and rodents (Gilboa and Marlatte, 2017; Spalding et al., 2015; Tse et al., 2011; van Buuren et al., 2014; van Kesteren et al., 2010b; van Kesteren et al., 2012; Wagner et al., 2015). Specifically, we found activation in the angular gyri, the precuneus (all $P_{FWE} < .05$, Fig. 6A), and the mPFC ($P_{SVC} = .017$, $k = 44$, $T = 3.98$). On the group level, schema-related neural activity was not affected by treatment (all $P > .10$). However, given its important role in learning new

schema-related information (Gilboa and Marlatte, 2017; Sommer, 2017; Wagner et al., 2015), the mPFC activation was of special interest to us. This structure is assumed to detect the congruency between new information and recently learned (i.e., 24h ago) prior knowledge and to integrate the new information into the schema (van Kesteren et al., 2012). Interestingly, this mPFC activation to schema-related information was only present (as a trend) in the control group ($P_{SVC} = .051$, $k = 20$, $T = 3.53$), whereas we found no significantly activated voxel for related > novel learning in the mPFC in the stress group (even not at a lenient threshold of $P < .005$, uncorrected; extracted parameters from the underlying anatomical region, frontal medial cortex, shown in Fig. 6B). Although these group differences were only trend-level significant ($t(47) = -1.726$, $p = .091$), the activation for related > novel learning in the mPFC was negatively correlated with the individual cortisol response

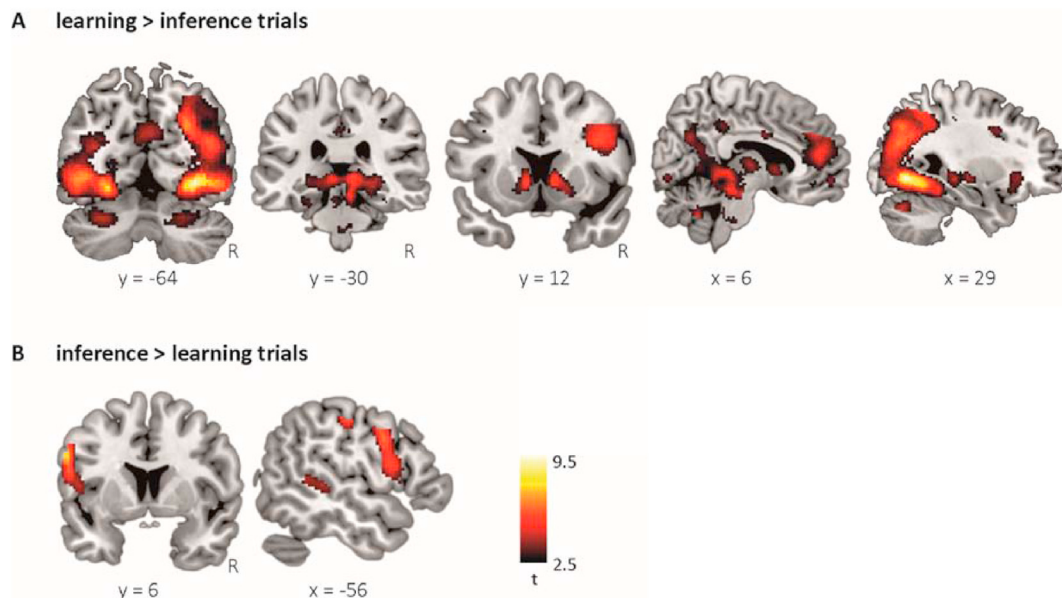


Fig. 5. Learning trials and inference trials resulted in different patterns of neural activation. **A** Brain regions more responsive to learning as compared to inference trials included widespread occipital brain regions, ventral striatum, right inferior frontal cortex (all $P_{FWE} < 0.05$), the hippocampus (right: $P_{SVC} = 0.006$, $k = 78$, $T = 4.23$; left: $P_{SVC} = 0.055$, $k = 25$, $T = 3.38$), the medial prefrontal cortex (mPFC, $P_{SVC} = 0.048$, $k = 30$, $T = 3.42$) and, at trend level, the right angular gyrus ($P_{SVC} = 0.063$, $k = 41$, $T = 3.32$). **B** In contrast, brain regions more activated by inference trials included the left inferior frontal cortex, the left superior temporal gyrus, and the left pre- and postcentral gyri (all $P_{FWE} < 0.05$). Importantly, there was no activated voxel in the hippocampus, mPFC, angular gyri, or precuneus in this contrast at $P < 0.005$, uncorrected. This supports that learning trials tracked the learning of schema-related and novel information whereas inference trials rather targeted inferential reasoning. Images are displayed at $P < 0.005$, uncorrected, for illustration purposes.

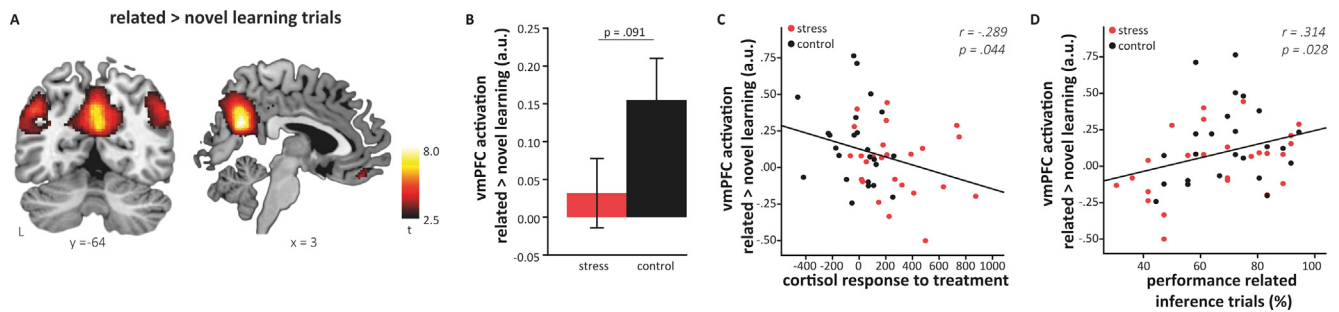


Fig. 6. Brain regions supporting schema-related learning are affected by individual differences in stress levels. **A** Across groups, brain regions responding more to related than novel learning trials were the medial prefrontal cortex (mPFC, $P_{SVC} = .017$, $k = 44$, $T = 3.98$), the precuneus, and both angular gyri (all $P_{FWE} < .05$). **B** Extracting the parameter estimates for this contrast from the mPFC using an anatomical mask showed that this schema-related mPFC activation tended to be less pronounced in the stress group than in the control group ($t(47) = -1.726$, $p = .091$). **C** Moreover, across groups this mPFC activation during learning of schema-related information was negatively correlated with the cortisol response to treatment as assessed using the area under the curve with respect to the increase. **D** Finally, mPFC activation during schema-related learning was positively correlated with performance in related inference trials, supporting the crucial role of the mPFC in integrating new information into an existing schema. Images are displayed at $P < 0.005$, uncorrected, for illustration purposes.

to the treatment ($r = -.289$, $P = .044$, anatomical mask, Fig. 6C). Although this finding should be interpreted with caution considering that the correlation was not significant in the stress group alone ($r = -.203$, $P = .332$, control group alone: $r = -.192$, $P = .368$), it suggests that individuals with a higher cortisol response to treatment might show less schema-related mPFC activation, possibly indicating reduced congruency detection and impaired integration of related information into the schema. In support of the hypothesis that mPFC activation is associated with successful schema-congruent learning, this mPFC activation was also positively correlated with performance in inference trials of the related hierarchy ($r = .314$, $P = .028$, Fig. 6D). According to a model of schema-related neural processing, the detection of congruency by the mPFC should lead to a suppression of memory encoding and neural activity in medial temporal lobe regions such as the hippocampus (van Kesteren et al., 2012). This model would suggest an enhanced activity in the hippocampus for related information if stress would affect mPFC functioning, as the hippocampus would be less inhibited, which would in turn be associated with less schema-related learning. Indeed, within the stress group, we found that hippocampal activity during related learning trials as compared to baseline trials was negatively associated with performance in related trials ($P_{SVC} = .028$, $k = 48$, $T = 3.68$, Fig. 7), suggesting impaired schema-related learning when stressed participants engaged the hippocampus. The association between hippocampal activity (anatomically defined) and related learning performance was not significant across groups ($r = -.174$, $p = .233$) or in the control group

($r = .016$, $p = .939$). It is to be noted, however, that the correlations did not significantly differ between groups ($p = .110$).

Stressed individuals show enhanced hippocampal connectivity with brain regions involved in schema-related learning

In order to investigate how this stronger involvement of the hippocampus during related learning trials may be detrimental to learning in stressed individuals, we assessed functional connectivity of the left hippocampus (anatomically defined) during related learning trials as compared to baseline trials, providing an index that is independent of any changes in novel trials, using a psychophysiological interaction (PPI) analysis. Across groups, we found enhanced schema-related hippocampal connectivity with the left angular gyrus, precuneus, left inferior temporal gyrus (all $P_{FWE} < .05$, Fig. 8A), mPFC ($P_{SVC} = .027$, $k = 93$, $T = 3.49$), right angular gyrus ($P_{SVC} = .031$, $k = 111$, $T = 3.64$), and right hippocampus ($P_{SVC} = .014$, $k = 69$, $T = 3.95$). In contrast, we found no enhanced hippocampal connectivity during baseline trials (no significant voxel even at $P < .005$, uncorrected). More importantly, stress enhanced connectivity between the hippocampus and the set of brain regions involved in schema processing during related learning trials, i.e., the angular gyri (left: $P_{FWE} < .05$, right: $P_{SVC} = .048$, $k = 68$, $T = 3.46$, Fig. 9), and the mPFC ($P_{SVC} = .044$, $k = 86$, $T = 3.89$), as compared to the control group. When examining both groups separately, there was no significantly enhanced connectivity during related learning trials between the

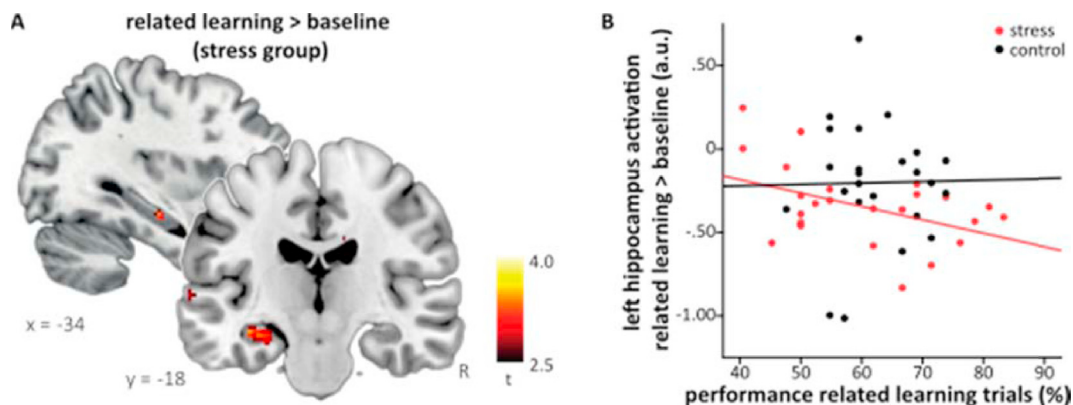


Fig. 7. Hippocampal activity during schema-related learning is detrimental to performance in the stress group. **A** In the stress group, we found a negative association between hippocampal activation during schema-related learning (as compared to baseline trials) and performance in related learning trials, suggesting that an enhanced hippocampal involvement during the related condition is disadvantageous for performance. **B** Scatterplot showing the correlation between activation of the anatomical left hippocampus (related learning > baseline) and related learning trial performance in the stress group but not the control group. Images are displayed at $P < .005$, uncorrected, for illustration purposes.

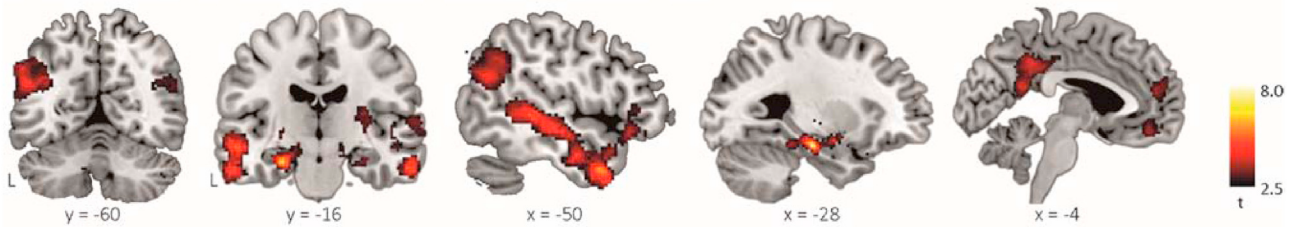
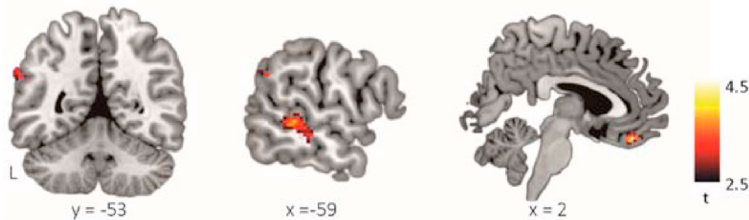
A hippocampal connectivity (related learning > baseline trials)**B vmPFC connectivity (novel learning > baseline trials)**

Fig. 8. Functional connectivity of the hippocampus and medial prefrontal cortex (mPFC) during schema-related and novel learning across groups. **A** Using a psychophysiological interaction (PPI) analysis, we found enhanced schema-related hippocampal connectivity with the left angular gyrus, precuneus, left inferior temporal gyrus (all $P_{FWE} < .05$, Fig. 8A), mPFC ($P_{SVC} = .027$, $k = 93$, $T = 3.49$), right angular gyrus ($P_{SVC} = .031$, $k = 111$, $T = 3.64$), and right hippocampus ($P_{SVC} = .014$, $k = 69$, $T = 3.95$). **B** Using another PPI analysis focusing on novel (versus baseline) trials, we found increased coupling of the mPFC with the left angular gyrus ($P_{SVC} = .047$, $k = 8$, $T = 3.24$, Fig. 8B) and the mPFC itself ($P_{SVC} = .003$, $k = 68$, $T = 4.53$). Images are displayed at $P < 0.005$, uncorrected, for illustration purposes.

hippocampus and these regions in the control group (no significant voxel even at $P < .005$, uncorrected), suggesting that the control group successfully isolated the hippocampus during schema-related learning from these structures. In the stress group, however, we found pronounced connectivity between the hippocampus and the angular gyri ($P_{FWE} < .05$), the mPFC ($P_{SVC} = .006$, $k = 220$, $T = 4.24$), and middle temporal cortices ($P_{FWE} < .05$) during related learning trials, suggesting that the hippocampus was inserted into this group of brain regions involved in schema-related learning. This might imply a lack of separation between memory networks for schema-related information and novel information, which may be associated with impaired congruency detection and less integration of related information into an existing schema.

Stressed individuals recruit brain regions involved in schema-related learning when learning novel information

As we observed a lack of segregation between functional connectivity patterns in the stress group during related learning trials, we reasoned that stressed individuals may have difficulties in separating brain regions suitable for learning of information for which prior knowledge exists (related) vs. learning of novel information. If this is the case, stress may also affect the brain regions recruited during the processing of novel information. To test this idea, we used a similar PPI model, now seeding on the mPFC during novel learning trials as compared to baseline trials. In general, novel learning increased mPFC coupling with the left angular gyrus ($P_{SVC} = .047$, $k = 8$, $T = 3.24$, Fig. 8B) and the mPFC itself ($P_{SVC} = .003$, $k = 68$, $T = 4.53$) whereas no brain region showed increased mPFC coupling during baseline trials. More importantly, however, we found in the stress group during novel learning trials enhanced mPFC connectivity with brain regions involved in schema-related learning, i.e. the mPFC itself ($P_{SVC} = .002$, $k = 132$, $T = 4.68$) and, at trend level, the angular gyri (left: $P_{SVC} = .051$, $k = 31$, $T = 3.21$; right: $P_{SVC} = .081$, $k = 11$, $T = 3.28$, Fig. 10A). In contrast, we found no enhanced connectivity of the mPFC with any region involved in schema processing during novel learning in the control group (no significant voxel at $P < .005$, uncorrected). Although the group differences did not reach statistical significance (all $P_{SVC} > .15$), this might suggest that

stressed individuals recruited the cluster of brain regions involved in schema processing when faced with novel information for which no prior knowledge existed. Interestingly, a stronger connectivity between the mPFC and the angular gyrus during novel learning trials was associated with impaired performance in these trials across both groups ($P_{SVC} = .007$, $k = 77$, $T = 4.27$, Fig. 10B) and in the stress group alone ($P_{SVC} = .017$, $k = 130$, $T = 3.95$). This indicates that stronger connectivity between brain regions involved in schema-related learning during novel learning trials in the stress group (and a potential lack of segregation) was detrimental to performance.

Discussion

The integration of new information into pre-existing knowledge structures is key to efficient learning. Indeed it is well known that information is learned more easily if it can be linked to prior knowledge (Bartlett, 1932). Despite the crucial relevance of this so-called schema-congruent memory for educational settings, factors modulating this fundamental process of learning are largely unexplored. Recently, we reported that acute stress and the administration of glucocorticoids reduce schema-based learning (Kluen et al., 2017). Here, we investigated the underlying neural mechanisms and show that the exposure to acute stress impairs the separation of brain regions supporting the acquisition of schema-related and novel information. We found no stress effects on memory performance on group level, most likely owing to a lack of statistical power as a post-hoc power analysis using the software G*Power (Faul et al., 2009) indicated that a sample size of 94 participants would have been required to detect the previously reported behavioral effect (Kluen et al., 2017) with a power of 95 percent. Nonetheless, the stress-induced changes in neural processing reported here could explain how stress may hamper the use of prior knowledge to support memory performance.

In line with previous studies implicating the mPFC, precuneus, and angular gyrus in schema-congruent learning (Sommer, 2017; Tse et al., 2011; van Buuren et al., 2014; van Kesteren et al., 2010b; Wagner et al., 2015), we found enhanced activity in these regions when comparing the acquisition of schema-related information with learning of novel information. Earlier studies in rodents and humans suggested a key role for

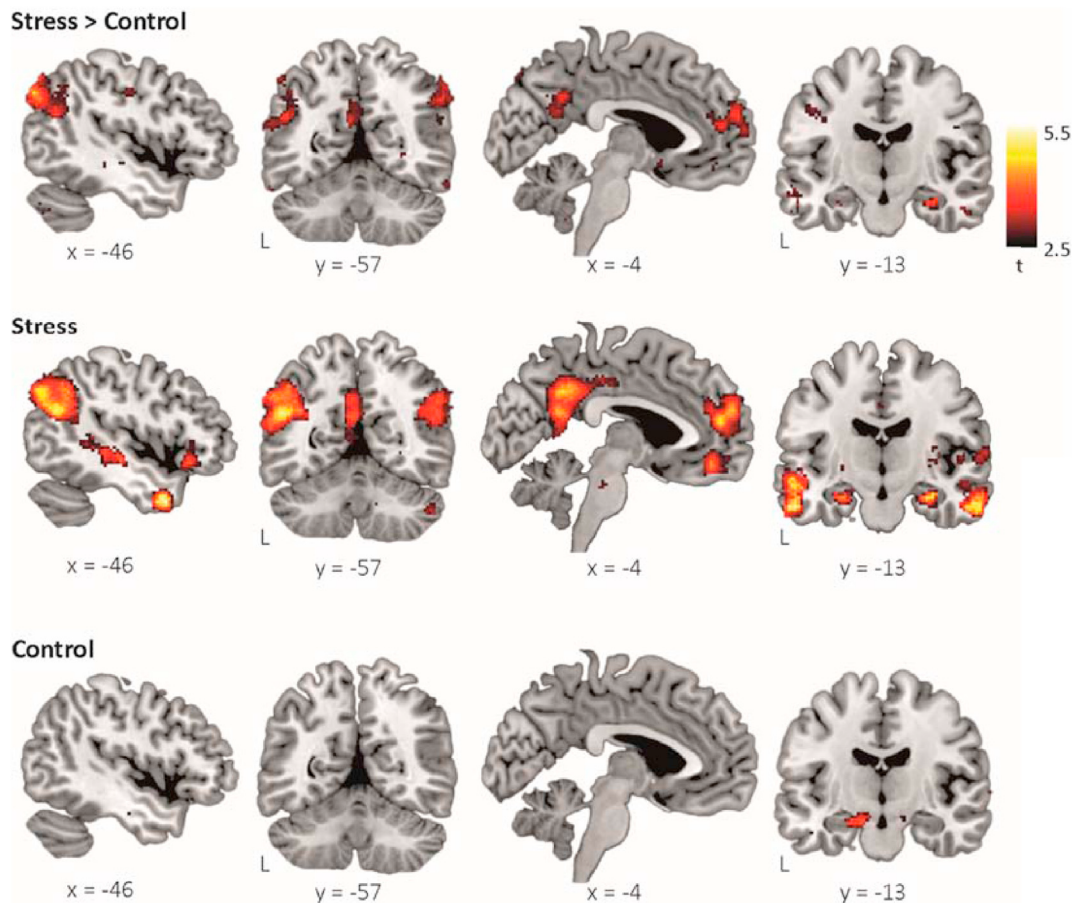


Fig. 9. Stress-induced incorporation of the hippocampus into the cluster of brain regions involved in schema-related learning. **Top:** Main effect of stress on functional connectivity of the left anatomical hippocampus in related learning trials as compared to baseline trials, modeled as psychophysiological interaction (PPI). Stress enhanced connectivity between the hippocampus and the angular gyri (left: $P_{FWE} < .05$, right: $P_{SVC} = .048$, $k = 68$, $T = 3.46$) and the medial prefrontal cortex (mPFC; $P_{SVC} = .044$, $k = 86$, $T = 3.89$). **Middle:** When examining the stress group separately, we found enhanced hippocampal connectivity during related learning trials to both angular gyri ($P_{FWE} < .05$), the mPFC ($P_{SVC} = .006$, $k = 220$, $T = 4.24$), and middle temporal cortices ($P_{FWE} < .05$), suggesting that the stress group inserted the hippocampus into the cluster involved in schema processing. **Bottom:** In contrast, there was no schema-related enhancement of connectivity between the hippocampus and these regions in the control group (no significant voxel at $P < .005$, uncorrected), suggesting that the control group successfully segregated the hippocampus during schema-related learning. Images are displayed at $P < 0.005$, uncorrected, for illustration purposes.

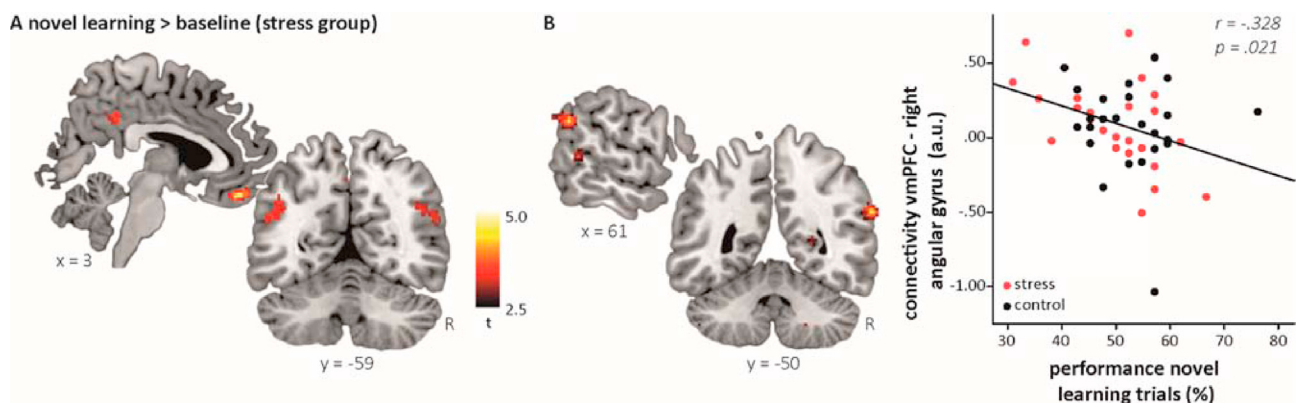


Fig. 10. Stress induced connectivity between regions involved in schema-related processing during learning of novel items. **A** Functional connectivity of the anatomical medial prefrontal cortex (mPFC) during novel learning as compared to baseline, modeled as psychophysiological interaction (PPI) in the stress group. We found enhanced mPFC connectivity to both angular gyri (left: $P_{SVC} = .051$, $k = 31$, $T = 3.21$; right: $P_{SVC} = .081$, $k = 11$, $T = 3.28$), and the mPFC itself ($P_{SVC} = .002$, $k = 132$, $T = 4.68$) during novel learning. **B** The enhanced connectivity with the angular gyrus during novel learning was negatively correlated with performance in novel learning trials across groups ($P_{SVC} = .007$, $k = 77$, $T = 4.27$) and in the stress group alone ($P_{SVC} = .017$, $k = 130$, $T = 3.95$, data not shown). The scatter plot illustrates the correlation of mPFC-angular gyrus connectivity (anatomically defined) and performance during novel learning trials. Images are displayed at $P < 0.005$, uncorrected, for illustration purposes.

the mPFC in the integration of related information into existing neocortical representation networks (Ghosh et al., 2014; Spalding et al., 2015; Tse et al., 2011; van Buuren et al., 2014; van Kesteren et al., 2010a). For instance, rodent data showed rapid activation in the mPFC when schema-related information was successfully learned (Tse et al., 2011), and patients with mPFC lesions showed less access to prior knowledge, resulting in difficulties to benefit from prior knowledge during learning (Ghosh et al., 2014; Gilboa et al., 2009; Kan et al., 2008). In line with this crucial role of the mPFC in schema-related learning, we found that the mPFC responded more to schema-related than novel items and schema-related activity in the mPFC predicted later performance. In contrast to the mPFC, the hippocampus is particularly important to learn detailed episodic information that is incongruent with prior knowledge or novel (van Kesteren et al., 2012) and should be less involved during learning of schema-related information (Tse et al., 2011; van Kesteren et al., 2014). Accordingly, when investigating brain regions underlying schema-related learning (as compared to baseline trials) in non-stressed controls, we did not find any significant activation in the hippocampus.

However, stress tended to impair schema-related mPFC activity and, within the stress group, increased hippocampal activity for the related hierarchy was associated with impaired schema-related learning. The hippocampus has previously been shown to respond to associative novelty (Köhler et al., 2005), supporting the idea that those individuals who engaged the hippocampus when presented with schema-related galaxy pairs might not have been able to make use of their schema and rather treated the information as if it was novel. Together, these findings suggest that stress might hinder successful schema-related learning by impairing mPFC functioning and aberrant hippocampal processing. Our results further suggest that the stress hormone cortisol may be mediating this stress effect, in line with recent findings showing that hydrocortisone administration is sufficient to hamper schema-related learning (Kluen et al., 2017).

In line with the hypothesis of reduced hippocampal involvement in learning schema-related information (van Kesteren et al., 2010a; van Kesteren et al., 2012), our results suggest that the hippocampus is less functionally connected to brain regions involved in schema processing when control participants are presented with information that relates to their prior knowledge. Supposedly, this information is rapidly integrated into the neocortical network by the mPFC without the need for strong hippocampal involvement (Tse et al., 2007, 2011; van Kesteren et al., 2012). Importantly, our results show that stress led to a strong coupling between the hippocampus, angular gyrus, and mPFC when stressed individuals were presented with schema-related information. As the hippocampus is crucial to encode detailed episodic memories (Eichenbaum, 1999), this episodic encoding might be hindering memory encoding when sufficient prior knowledge is present to encode the information more rapidly in the neocortex (van Kesteren et al., 2012). However, other studies reported enhanced coupling between mPFC and hippocampus to be beneficial when acquiring conceptual knowledge (Kumaran et al., 2012), suggesting that the exact relationship between mPFC-hippocampal interaction and learning may differ depending on, for instance, schema richness or the precise definition of schema-unrelated, novel trials (Gilboa and Marlatte, 2017).

Interestingly, we found stress-induced alterations in brain connectivity not only when participants encoded schema-related information, but also when presented with information for which they had no prior knowledge. In particular, connectivity between the mPFC and the angular gyrus was enhanced when stressed participants encoded novel information (compared to baseline trials) and this enhanced connectivity was detrimental to the successful acquisition of novel items. In contrast, there was no significantly enhanced mPFC connectivity with the angular gyrus during novel learning trials compared to baseline trials in the control group. Together, these findings indicate that stressed participants were less able to select the relevant set of brain regions depending on the presence or absence of relevant prior knowledge, which in turn deteriorated performance. Moreover, our findings show that an activation of

brain regions involved in schema-related learning is not beneficial per se but can even be detrimental to learning if activated in the absence of relevant prior knowledge. However, with more practice or a longer period of consolidation, a new schema for the novel items may be built, which could be accompanied by changes in mPFC and angular gyrus activity and connectivity that are beneficial for performance (Bontempi et al., 1999; Takashima et al., 2006; Wagner et al., 2015).

Another interesting aspect of our results is that, while we often found bilateral activations and connectivity patterns, we sometimes obtained activation in or connectivity with structures in one hemisphere only. Particularly, we found that schema-related activity in the left hippocampus was associated with impaired schema-related learning in the stress group which is in line with previous reports showing that memory related activity in the left hippocampus was negatively related to congruency (or schema-relatedness), and congruency in turn was associated with better memory (van Kesteren et al., 2013). Additionally, schema-related connectivity of the hippocampus was somewhat stronger in the left hemisphere (note, however, that also the seed was in the left hemisphere), which might be related to previous findings suggesting that the left angular gyrus recombines consolidated schema components into one memory representation when learning new, schema-related information (Wagner et al., 2015). However, it is important to note that we did not assess laterality specifically, i.e., whether activation in or connectivity with a given structure was stronger than activity in or connectivity with the corresponding structure in the other hemisphere. Moreover, laterality is known to depend strongly on task characteristics and the baseline used (Harrington et al., 2006) and is therefore usually assessed using multiple tasks (Seghier, 2008). More research is thus needed to clarify potential lateralization processes in schema-related learning.

In contrast to previous findings (Kumaran, 2013), we did not find beneficial effects of a schema on inference performance. One possible explanation for this discrepancy is the difference in the extent of training on day 1. In the study by Kumaran (2013), participants were more extensively trained (120 learning trials and 120 inference trials) whereas the current project encompassed only 75 trials each due to practical limitations. In line with that reasoning, another recent study (Kluen et al., 2017, experiment 1) was not able to replicate the schema-effect on inference performance. Interestingly, the second experiment of this study that tested a larger sample did find the schema-effect on inference performance (Kluen et al., 2017, experiment 2). Thus, it might be that the ameliorating effect of a schema on inference performance depends on very thorough schema training and may need more statistical power to be detected.

Conclusion

Successful integration of new information into prior knowledge depends on the functional integrity of the mPFC, closely interacting with the angular gyrus and the precuneus to encode schema-related information. The present study suggests that individuals with strong cortisol responses to stress display less mPFC activity during encoding of schema-related information and that their performance is deteriorated if they rely on the hippocampus instead. Moreover, we show that stress reduces the separation between brain connectivity patterns for learning related and novel information, respectively, which was associated with impaired memory performance. The present findings go significantly beyond prior studies showing effects of stress on memory encoding, consolidation or retrieval, which did not take into account the individual background of established prior knowledge. The present study may thus be relevant with respect to distorted memory processes in patients with stress-related mental disorders (Ehlers and Clark, 2000) which often involve strong negative schemas (Beck, 2008; Beck and Clark, 1997). Moreover, a better understanding of how stress might impair learning in general (Vogel and Schwabe, 2016) and schema-related learning in particular may have critical implications for educational contexts, in which stress is common

(Valizadeh et al., 2012) and the use of prior knowledge during learning is a key factor for successful performance.

Conflicts of interest

The authors declare no conflict of interest.

Acknowledgments

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