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Stress disrupts insight-driven mnemonic reconfiguration in the medial temporal lobe

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ABSTRACT

Memories are not stored in isolation. Insight into the relationship of initially unrelated events may trigger a flexible reconfiguration of the mnemonic representation of these events. Such representational changes allow the integration of events into coherent episodes and help to build up-to-date-models of the world around us. This process is, however, frequently impaired in stress-related mental disorders resulting in symptoms such as fragmented memories in PTSD. Here, we combined a real life-like narrative-insight task, in which participants learned how initially separate events are linked, with fMRI-based representational similarity analysis to test if and how acute stress interferes with the insight-driven reconfiguration of memories. Our results showed that stress reduced the activity of medial temporal and prefrontal areas when participants gained insight into the link between events. Moreover, stress abolished the insight-related increase in representational dissimilarity for linked events in the anterior part of the hippocampus as well as its association with measures of subsequent memory that we observed in non-stressed controls. However, memory performance, as assessed in a forced-choice recognition test, was even enhanced in the stress group. Our findings suggest that acute stress impedes the neural integration of events into coherent episodes but promotes long-term memory for these integrated narratives and may thus have implications for understanding memory distortions in stress-related mental disorders.

1. Introduction

When watching a movie, we often experience a *plot twist*, a moment when we realize how earlier, seemingly unrelated scenes are connected. As we gain insight into the relationship between initially unrelated events, we integrate formerly separate memory representations into coherent episodes (Schlichting and Preston, 2017). Inferring which events to integrate and which to keep separate is a fundamental mechanism of memory and requires an intricate interplay of pattern completion and separation processes (Horner and Burgess, 2014; Marr, 1971; Nakazawa et al., 2002a; Norman and O'Reilly, 2003; Rolls and Kesner, 2006). Given its prominent role in both pattern completion and separation processes, it is not surprising that the medial temporal lobe, including the hippocampus, has been identified as a key region for mnemonic integration (Brunec et al., 2020; Collin et al., 2015; Horner et al., 2015; Huffman and Stark, 2014; Marr, 1971; Schapiro et al., 2017; Schlichting et al., 2015). The hippocampus, however, appears not to be functionally homogeneous and previous studies suggested a functional hierarchy along the hippocampal long axis: anterior portions were more related to memory integration, whereas posterior areas were more associated with memory separation, resulting in memory representations with different granularity (Brunec et al., 2020; Collin et al., 2017; Collin et al., 2015; Eichenbaum, 2004; Milivojevic et al., 2015; Morton et al., 2017; Schlichting et al., 2015). Accumulating evidence shows that mnemonic integration processes are altered in stress-related disorders, such as post-traumatic-stress disorder (PTSD), resulting in fragmented memories (Amir et al., 1998; Berntsen et al., 2003). In light of these clinical implications, the key question arises as to which factors modulate the capacity to integrate events into coherent episodes.

Acute stress is known to have a major impact on learning and memory (Joëls et al., 2011; Sandi and Pinelo-Nava, 2007; Schwabe et al.,

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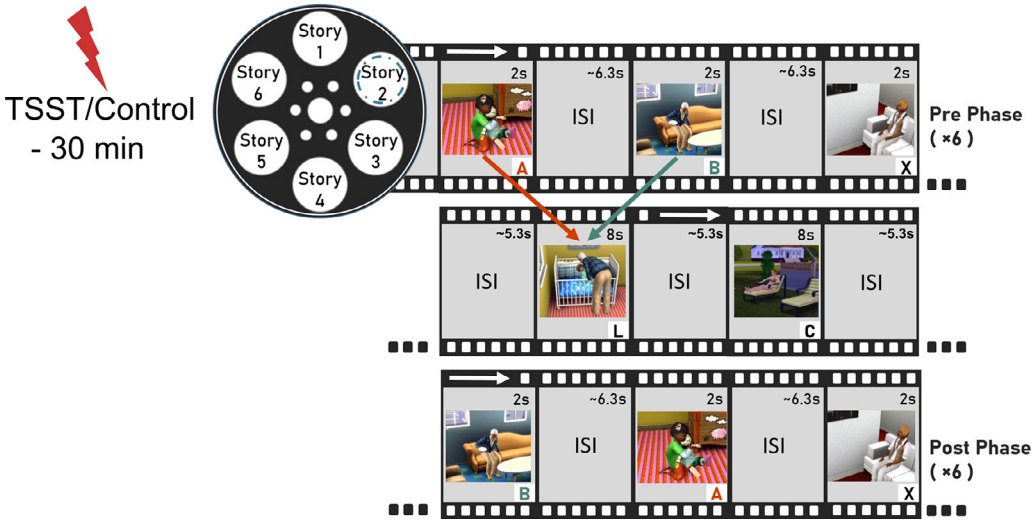

Fig. 1. Narrative-insight task (NIT). The videos (A, B, and X) from each of six story lines could either be integrated (events A and B) into narratives during the linking phase or not (A and X) and were each repeated six times. Between the different phases there was a short break to collect saliva samples.

2012a; Schwabe et al., 2022; Shields et al., 2017). These stress effects are mediated by the action of stress mediators, such as glucocorticoids (mainly cortisol in humans), on prefrontal and medial temporal areas. Converging lines of evidence from cellular to neuroimaging studies show that stress and glucocorticoids may have differential effects on hippocampal neuroplasticity and functioning, depending, for instance, on the timing of the stressor (Diamond et al., 2007; Joëls et al., 2011; Kim and Diamond, 2002). Stress unrelated to learning is generally thought to reduce hippocampal activity and hippocampus-dependent memory processes (Kim and Diamond, 2002; Lupien and Lepage, 2001; Schwabe and Wolf, 2012; Vogel et al., 2018). Beyond the well-known effects of stress and glucocorticoids on hippocampal memory formation and retrieval (de Quervain et al., 1998; Joëls et al., 2011; Schwabe et al., 2012b), stress may bias the engagement of multiple, anatomically and functionally distinct memory systems from 'relational' hippocampus-dependent memory towards rather habit-like forms of memory that depend, for example, on the dorsal striatum (Goodman et al., 2012; Schwabe, 2017; Vogel et al., 2016). Thus, in contrast to hippocampus-dependent memory, dorsal striatum dependent stimulus-stimulus memory is often enhanced after stress (Kim et al., 2001; Schwabe et al., 2007; VanElzakker et al., 2011). The reduced medial temporal lobe involvement after stress might translate into a reduced capacity to integrate separate events into a coherent episode, thus contributing to the mnemonic integration deficit in stress-related disorders. However, whether and how stress may affect this process of dynamic memory integration remains unknown.

In this study, we tested the hypothesis that acute stress interferes with integration processes during insight-driven reconfiguration of memory representations. To this end, we combined fMRI, neuroendocrinology, and representational similarity analysis with a life-like narrative-insight task (Milivojevic et al., 2015; Fig. 1). One week after encoding, we performed a comprehensive behavioral analysis of correctness, detailedness as well as memory representation. The delayed memory test included a standard free recall, a multidimensional arrangement task, and a forced-choice recognition test, and thus provided insights into which memory processes were altered by stress. Because the anterior part of the hippocampus appears to be particularly relevant for mnemonic integration (Collin et al., 2015; Schlichting et al., 2015), we predicted a change in the neural representation of linked events specifically in the anterior part of the hippocampus from pre- to post-insight. As task-unrelated stress is thought to interfere with hippocampal functioning, we hypothesized that acute stress would impair this insight-driven mnemonic reconfiguration in the anterior hippocampus.

2. Methods

2.1. Participants

Fifty-nine right-handed, healthy individuals (30 males, 29 females, age: M = 24.66 years, SD = 4.06 years) with normal or corrected-to-normal vision volunteered to participate in this study. Participants were screened with a standardized interview for exclusion criteria, which encompassed a history of neurological and psychiatric disorders, medication intake and drug abuse, cardiovascular-, thyroid- or kidney-related diseases, body-mass index below 19 and over 26 kg/m^2, any signs for COVID-19 infection or exposure, as well as any contraindications for MRI scanning. We tested only women who did not use hormonal contraceptives and who were not currently menstruating at the first day of the experiment, since these factors are known to influence their endocrine stress response (Kudielka and Kirschbaum, 2005). Two hours prior to the experiment participants were asked to refrain from physical exercise, caffeine and alcohol intake as well as fatty meals. All participants provided informed consent before participation and received a monetary compensation (50€) at the end of the experiment. Procedures were approved by the local ethical review committee (Faculty of Psychology and Human Movement Science, Universität Hamburg, Hamburg, Germany, AZ: 2017_143 Schwabe) and adhered to the Declaration of Helsinki. The sample size is based on an a priori calculation using G*Power, indicating that a sample size of N = 60 is sufficient to detect a medium-sized group × link effect (f = .30) with a power of .80.

We implemented a mixed-design including the within-subject factors link (linked vs. non-linked events) and session (pre- vs. post-link) and the between-subjects factor group (stress/control). Participants were pseudo-randomly assigned to one of the two groups to balance male and female participants per group. The stress group included 30 participants (15 females) and the control group consisted of 29 participants (14 females).

2.2. Procedure

Testing was conducted on two days, one week apart. All experiments took place in the afternoon or early evening (between 12 and 6 p.m.) to account for the diurnal rhythm of the stress hormone cortisol. Before starting the first day of the experiment, participants completed questionnaires assessing trait-anxiety (STAI-T; Laux et al., 1981), depressive symptoms (BDI; Hautzinger et al., 2006), chronic stress (TICS; Schulz and Schlotz, 1999), personality dimensions (BFI-

2; Danner et al., 2016), and chronotypical morningness and eveningness (MEQ; Adan and Almirall, 1991). After verification of eligibility for MRI measurements by a radiologist, participants gave informed consent and completed a state-anxiety questionnaire (STAI-S; Laux et al., 1981) and sleep quality questionnaire (PSQI; Buysse et al., 1989). Thereafter, they performed a training run and a baseline measurement of a working memory task (N-back; Kirchner, 1958) to control for effects due to stress-related impairments in working memory. Next, they completed a training session of the modified narrative-insight task (NIT; Milivojevic et al., 2015), a life-like video-based task that probes the integration of initially distinct events into coherent episodes. Participants then underwent the stress induction or control manipulation and completed the second N-back task and three runs of the modified narrative-insight task in the MRI scanner. One week later, to assess episodic memory integration, participants performed a free recall, a forced-choice recognition test and a multidimensional arena task (MAT; Kriegeskorte and Mur, 2012).

2.2.1. Day 1: Stress manipulation and manipulation check

In order to experimentally manipulate acute stress before the narrative-insight task, which assesses mnemonic integration, participants underwent either the Trier Social Stress Test (TSST; Kirschbaum et al., 1993) or a control manipulation. During the TSST, participants were requested to give a 5-min free speech, after a 3-min preparation period, about their qualification for a job tailored to their interests. Following this, participants had to perform a 5-min mental arithmetic task (counting backwards from 2043 in steps of 17). Both tasks were performed in front of a panel (one man and one woman), dressed in white lab coats. The panel was introduced as experts in behavioral analysis and was instructed to act in a rather cold, non-reinforcing manner, non-responding to questions of the participant. In addition, participants were video-taped during the TSST. In the control condition, participants engaged in two tasks of the same duration. The first task included a free speech about a topic of their choice (e.g. the last book they read). In the second task, participants counted forward (in steps of 15). Importantly, there was no panel present and no video was recorded.

To assess the effectiveness of the stress manipulation, subjective mood ratings, blood pressure, pulse and saliva samples were taken at several time points throughout the experiment. Mood changes were measured via a German mood scale (MDBF; Steyer et al., 1997). MDBF measures were obtained before and after the stress manipulation as well as after participants were removed from the MRI scanner (i.e., -5, +20, +110 min relative to treatment onset). Blood pressure and pulse (arm cuff: Omron Healthcare Europe BV) were measured before, during, and after the stress manipulation as well as after participants were removed from the scanner (i.e., -5, +8, +20, +110 min relative to treatment onset). Saliva samples were collected before and after the experimental treatment, twice in the MRI scanner and after participants were removed from the MRI scanner (i.e., -5, +20, +60, +80, +110 min relative to treatment onset) using Salivette collection devices (Sarstedt, Germany). Saliva samples were stored at -18°C and after completion of data collection, salivary cortisol levels were analyzed using a luminescence assay (IBL, International, Hamburg, Germany).

2.2.2. Day 1: Working memory control task

To control for potential stress effects on working memory, two measurements of working memory performance were obtained before and after the TSST and control manipulation, respectively. The second assessment of working memory took place approximately 20 min after stress induction, before the narrative-insight task began. Working memory was assessed with an N-back task (Kirchner, 1958). In this task, participants were presented with single-digit numbers from 0 to 9 and were asked whether the number on the screen ("target") was the same number as the number presented n-trials before ("cue"). Working memory load was manipulated by using two complexity levels: 3-and 4-back trials. In addition to these two load levels, participants performed a control task (0-back), in which they had to indicate whether the current number was a zero. Responses were given either by pressing the left button ("no") or by pressing the right button ("yes"), if the target number was different or identical to the cue, respectively. The selected response was highlighted. In total, participants were presented with six pseudo-randomized blocks consisting of two blocks from each level (0, 3 and 4 back). All blocks consisted of 20 numbers in random order. Numbers were presented for 500 ms and separated by a delay of 1.5 s. The blocks were separated by 5 s outside the scanner on the baseline assessment and by 13 s inside the scanner on the second assessment. Prior to each block, participants were informed of the type of the upcoming cognitive task (0-, 3-, or 4-back).

2.2.3. Day 1: Narrative-insight task

Approximately 30 min after treatment onset, when cortisol levels were expected to peak (Kirschbaum et al., 1993; Vogel and Schwabe, 2016), participants completed a modified version of the narrative-insight task (NIT; Milivojevic et al., 2015), while functional images were collected in the MRI scanner. In this task, participants were presented with life-like videos from the computer game *The Sims 3* that belonged to multiple different story lines. In total, participants saw 6 different story lines. The videos from each story line could either be integrated (events A and B) into narratives or not (A and X; see Fig. 1). Unbeknownst to the participant, each narrative had 2 possible versions to control for nonspecific stimulus effects and visual similarity. The 2 narrative versions comprised an identical event A, but different events B and linking event (L). Control event X from one version served as event B in the other version. Therefore, all participants saw the same events A, B, and X but 32 participants linked events A and X, while 27 participants linked events A and B.

Each story was presented in three phases: pre-insight phase, linking phase, and post-insight phase (Fig. 1). In the *pre-insight phase*, participants were presented with events A, B, and X for 2 s each, separated by inter-stimulus intervals of 1, 4 or 11 s (ISIs; ~5.3 s on average). Each video was presented six times in a pseudorandom order, such that each video was shown before the next round of presentations began and the same video was not presented on two consecutive trials. After the pre-insight phase, participants had to indicate on a scale from not at all (1) to very much (4) how much they thought the events belonged together. In the subsequent *linking phase*, participants viewed the linking video event (L) intertwined with a control video event (C), each presented for 8s and repeated six times (ISIs of 1, 4 or 11 s; ~5.3 s on average). The linking video (L) showed the main characters from videos A and B interacting with each other, whereas the control video (C) showed only an unknown character engaged in an unrelated activity (e.g. a man walking his dog). After the linking phase, participants completed several ratings regarding the understanding of the link and adherence to instructions on a scale ranging from not at all (1) to very much (4). In the final *post-insight phase*, participants again saw events A, B and X presented for 2 s each, repeated six times and separated by inter-stimulus intervals of 1, 4 or 11 s (ISIs; ~5.3 s on average). This phase was mainly used to assess changes in the neural representation of the events A and B, after learning that they were linked. After the post-phase, participants had to indicate again how much they thought that the events belonged together on a scale from not at all (1) to very much (4). Although the process of linking events is thought to occur in the linking phase, the successful linking of the events A and B is operationalized by the ratings of belonging after the linking phase compared to before the linking phase. Events in the post-insight phase were also presented in a pseudo-random order to reduce potential sequence effects. Participants received visual feedback when they entered an answer by highlighting the selected response. In addition to presenting A, B, and X events in the pre- and post-insight-phases, we also presented target events to which participants responded by pressing a button with the index finger of their right hand. These target events accounted for 11% of trials of the pre- and post-insight phases and consisted of a 2 s animated video of a girl on a pink scooter. These target trials were recorded to ensure that participants remained attentive throughout the experiment.

2.2.4. Day 2: Free recall

To measure the detailedness of memory one week after encoding, participants were instructed to recall the events presented on day 1 in as much detail as possible. During free recall, they were voice recorded for a maximum of 15 min. To assess the level of detailedness of the integrated episodes, audio recordings from free recall were scored according to how many details of the different video events (A, B, X, L, and C) were remembered from day one. The rating scheme was such, that it allowed for separate coding of details remembered for the A, B, and X events as well as for the events from the linking phase (L and C). The raters were instructed to assign details only to events where it was clear that they belonged exclusively to that event, so that there was no confusion of details between different events. Two raters rated the first half of the data and the other two raters rated the second half. All raters were blinded with regard to experimental conditions. To assess inter-rater reliability, all raters rated the first 5 participants and on average these ratings correlated highly with each other (*mean correlation* = .83, *SD* = .06). To obtain a better estimate of inter-subjectivity, the ratings were averaged. The details for the different event types (A, B, and X) were summed across stories to give an overall rating of event detail.

2.2.5. Day 2: Multidimensional arena task

To assess the representational structure of episodic memory, participants were asked to arrange representative images of the video events (A, B and X) of each story according to their relatedness on a two-dimensional circular arena in a multidimensional arena (MA) task (Kriegeskorte and Mur, 2012; Fig. S1). They were asked to bring the pictures that had been linked (A and B) one week earlier closer together than the pictures that had not been linked (A and X, B and X) by dragging and dropping them with the computer mouse within a white circular arena on the computer screen. All trials were self-paced and could be ended by the participant by pressing “Done”. On the first trial, participants had to arrange all images by similarity and were instructed to do so carefully. Subsequent trials consisted of subsets of the first trial selected based on an adaptive procedure aimed at minimizing uncertainty and better approximating the high-dimensional perceptual representational space. This procedure is based on an algorithm optimized to provide optimal evidence for the dissimilarity estimates (Kriegeskorte and Mur, 2012). Distances in this MA task were computed by initially computing the squared on-screen distance (Euclidian distance) between all items in the first trial to produce a roughly estimated representative dissimilarity matrix (RDM) and by iteratively updating this RDM by the weighted average of scaled trial estimates. This MA task took 10 min to complete.

2.2.6. Day 2: Forced-choice recognition test

In addition to the free recall test, we administered a forced-choice recognition test. In this test, participants completed a matching task in a forced-choice format. They were presented with an image of event A at the top of the computer screen and had to indicate whether the image of B or X in the bottom half of the screen belonged to A. Participants were presented with these forced-choice options for each of the stories they had seen a week before. After indicating for a story which event belonged to event A, they had to rate how confident they were in their answer. Confidence was rated on a scale from not at all (1) to very sure (4). This was repeated for each of the six stories. Participants were presented with the forced-choice question and the confidence rating for 5.5s each, separated by inter-stimulus intervals of 1, 4 or 11 sec (ISIs; ~5.3 s on average). Participants received visual feedback when they entered a rating question by highlighting the selected response. The forced-choice recognition test lasted about 2 to 3 min.

2.3. Analysis

2.3.1. Behavioral and physiological data analysis

Mood ratings were analyzed by means of a mixed 2 × 2 ANOVA with the between-subjects factor group (stress/control) and the within-subject factor time (-5/+20/+110 min relative to treatment onset). Blood pressure and pulse were analyzed using a mixed 2 × 2 ANOVA with the between-subjects factor group and the within-subject factor time (-5/+3/+20/+110 min relative to treatment onset). Finally, salivary cortisol levels were analyzed by means of a mixed 2 × 2 ANOVA with the between-subjects factor group and the within-subject factor time (-5/+20/+60/+80/+110 min relative to treatment onset).

To assess the degree of insight-dependent mental reorganization, the ratings for the event duplets of interest (AB and AX) from the pre- and post-insight-phase were entered into a mixed 2 × 2 × 2 ANOVA with the between-subjects factor group and the within-subject factors time (pre/post) and link (link/non-link). To evaluate the long-term representation of the integrated events, performance in the forced-choice recognition test was assessed by computing the proportion of correct answers. These performance measures (in %) were then entered into a Welch two-sample t-test with the between-subjects factor group. In order to check for confidence in the forced-choice recognition test, confidence ratings were averaged over the six stories and entered into a Welch two-sample t-test with the between-subjects factor group (Fig. S2). To analyze the representational structure of memory, Euclidian dissimilarity estimates from the multidimensional arena task were extracted for linked (AB) and for non-linked events (AX), averaged over stories, and, thereafter, entered into a mixed 2 × 2 ANOVA with the between-subjects factor group and the within-subject factor link (link/non-link). Details from free recall were entered into a mixed 2 × 2 ANOVA with the between-subjects factor group and the within-subject factor link (link/non-link).

All analyses were performed in R version 4.0.4 (https://www.r-project.org/). In case of violated sphericity, as indicated by Mauchly’s test, Greenhouse-Geisser corrected degrees of freedom and *p*-values are reported. Before analyses data were checked for outliers. Outliers were defined as mean +/- 2.5 SD. For the analysis of the narrative-insight task (NIT), four outliers were identified and excluded (two from the stress group and two from the control group). For the analysis of the forced-choice recognition test, one outlier was identified and excluded (stress group). For the analysis of the multidimensional arena task, two outliers were identified and excluded (one from the stress group and one from the control group). For the free recall analysis, three outliers were identified and excluded (two from the stress group and one from the control group). For the representational similarity analysis (RSA) of the anterior hippocampus, four outliers were identified and excluded (two in the stress group and two in the control group). For the additional RSA of the posterior hippocampus, one outlier was identified and excluded (stress group).

Imaging data were acquired on a 3T Siemens PRISMA scanner (Siemens, Germany) using a 64-channel head coil. Data was collected on three functional runs, separated by short breaks in which saliva samples were collected. We used a custom 3D echo-planar imaging (EPI) pulse sequence acquiring interleaved slices with the following parameters: TR = 2000 ms; TE = 30 ms; flip angle = 60°; volume resolution = 2 mm^3; slices = 62; approx. 530 volumes per run; field of view (FoV) = 224 mm; acceleration factor PE = 2. Additionally, a structural T1-weighted image was acquired using a MPRAGE-grappa sequence with the following parameters: TR = 2500 ms; TE = 2.06 ms; flip angle = 9°; voxel resolution = 0.8 mm^3; slices = 256; field of view (FoV) = 244 mm; 3D acceleration factor = 1 at the end of the MRI session.

2.3.2. fMRI data preprocessing

Preprocessing and analysis of the fMRI data were performed using custom scripts based on MATLAB (The Mathworks, Inc, Natick, US) and SPM 12 (Wellcome Trust Centre for Neuroimaging, London, UK). To allow for magnetic field (T1) equilibration, the first three functional scans

were discarded. First, functional images were spatially realigned and slice-time corrected. Thereafter, functional images were co-registered to the structural image by co-registering the structural image to the mean EPI. To check for differences in motion between the groups, we ran a control analysis and found that there were no group differences on these movement parameters (all $p_{corr} > .120$). Moreover, we controlled for individual head movement by including the motion regressors in our generalized linear model (GLM). For the multivariate analysis (see below), the images were not preprocessed further. For the univariate analysis (see below), the functional images were normalized to the MNI template and subsequently smoothed using a 6 mm^3 full-width at half maximum (FWHM) Gaussian kernel.

Results of the neural analyses were considered significant at a family-wise error (FWE) corrected threshold of $p < .050$. To test our hypotheses, we performed, in addition to more explorative whole-brain analyses, ROI analyses with a-priori defined ROIs using small-volume correction (SVC; $p < .050$, FWE corrected) with an initial threshold of $p < .001$ uncorrected. Based on previous findings in the mnemonic integration and stress literature (Milivojevic et al., 2015; Schlichting et al., 2015; Schwabe et al., 2012a; Wirz et al., 2018), we focused on the following ROIs: amygdala, hippocampus, parahippocampal cortex, and orbitofrontal cortex. The hippocampus was split into posterior and anterior sub-regions, as these have been found to be differentially implicated in mnemonic integration and separation processes (Collin et al., 2015; Dandolo and Schwabe, 2018; Robin and Moscovitch, 2017). We used hippocampal masks built by dividing a hippocampal mask into three parts with approximately equal lengths along the long axis, using the WFU pick-atlas: pHC from $Y = -40$ to -30, mHC from $Y = -29$ to -19, and aHC from $Y = -18$ to -4 (Collin et al., 2015; Dandolo and Schwabe, 2018). With the exception of the hippocampal sub-regions all other anatomical masks were derived from the Harvard-Oxford cortical and subcortical atlas using a probability threshold of 50%. We corrected for the number of ROIs in the specific analyses by applying Bonferroni correction (p_{corr}). The resulting estimates were extracted using the Mars-Bar Toolbox (Brett et al., 2002) to correlate the neural activity with behavioral outcomes.

2.3.3. Univariate fMRI analysis

For the univariate fMRI analysis, data from all three runs were concatenated to allow estimation of neural responses using all acquired data. The concatenated time series was analyzed using a generalized linear model (GLM) as implemented in SPM12. This model included one regressor per event type (A, B, and X) during each phase (pre- and post-link). Each of these six event regressors of interest modelled 36 trials (six different stories). Each model also included the following task nuisance regressors: regressors for the link video and control video in the link phase, and one regressor for the 24 target events (girl on the pink scooter). All task regressors and the nuisance task regressors of no interest were convolved with the canonical hemodynamic response function, producing a modelled time-course of neural activity. All analyses further contained six concatenated nuisance regressors to control for head movement as well as three run constants. A high-pass filter of 128 s was used to remove low-frequency drifts and serial correlations in the time series were accounted for using an autoregressive AR(1)-model. To analyze the neural basis of the change from pre- to post-insight we computed a contrast comparing post link events to pre link events ($AB_{post} > AB_{pre}$). These contrast images were analyzed on the group level using a two-sample t-test. To rule out that the differences found between this contrast are due to time, we also computed a contrast comparing post non-link events to pre non-link events ($X_{post} > X_{pre}$).

2.3.4. Univariate fMRI adaptation in linking phase

To measure insight-related changes during the linking phase, we set up another model contrasting link and control events. This model was adjusted for effects of lag between the presentation of link and control events due to fMRI adaptation. Functional images from all three runs were concatenated to allow for estimation of neural responses using a GLM. This model included single regressors for all event types (A, B, X, L, C) in each story separately. Essentially, to measure the insight-related response that is adjusted for fMRI adaptation processes, six parametric regressors were included that reflect the time between events during the linking phase. To assess the degree of fMRI adaptation, the regressors were defined as –log (time since last presentation of link [linking event to linking event] or control event [control event to control event]). These lags were calculated as the difference between the onsets of the events of interest (e.g. linking event to linking event or control event to control event) and could take on values of 18s, 21s, 24s, 28s, 31s, or 38s. We used log lags according to a previous paper using the same paradigm (Milivojevic et al., 2015) since other studies suggested that adaptation effects are not automatically linear at longer lags between events (Weiner et al., 2010; Zhou et al., 2018). Each model also included the following nuisance variables: one regressor for the 24 target events, six concatenated nuisance regressors to control for head movement as well as three run constants. All task regressors and the regressor for target events were convolved with the canonical hemodynamic response function, producing a modelled time-course of neural activity. A high-pass filter of 128 s was used to remove low-frequency drifts and serial correlations in the time series were accounted for using an autoregressive AR(1)-model. For each subject contrast images collapsed across the six stories were calculated (Link > Control) and were then taken to the second-level group analysis. On the second level, analyses were performed using two-sample t-tests.

2.3.5. Multivariate analysis

In order to assess changes in neural patterns induced by insight into the narrative structure of events, we conducted a Representational Similarity Analysis (RSA, Kriegeskorte et al., 2008) using the rsatoolbox (Nili et al., 2014). We focused on the hippocampal long axis, since its subcomponents have been differentially associated with memory integration as well as segregation – two processes that are critical to episodic memory integration (Brunec et al., 2018; Collin et al., 2017; Dandolo and Schwabe, 2018; Milivojevic et al., 2015; Robin and Moscovitch, 2017; Schlichting et al., 2015). On the first level, functional images from all three runs were concatenated to allow for estimation of neural responses using a GLM. Only un-normalized and un-smoothed images entered the GLM. This model included single regressors for each of the event types and each phase (A_{pre}, B_{pre}, X_{pre}, L, C, A_{post}, B_{post}, X_{post}) in each of the 6 story lines separately. Thus, each event-regressor modeled 6 trials. Each model also included the following additional nuisance regressors: one regressor for the 24 target events, six concatenated nuisance regressors to control for head movement as well as three run constants. All task regressors and the regressor for target events were convolved with the canonical hemodynamic response function, producing a modelled time-course of neural activity. Voxel-wise beta estimates resulting from the regressors of interest (A_{pre}, B_{pre}, X_{pre}, A_{post}, B_{post}, X_{post}) were further transformed into *t*-statistics to account for noise induced unreliability (Walther et al., 2016). In a second analysis step, we back-transformed the ROIs from MNI space to subject-space for each participant individually. The computation of Representational Dissimilarity Matrices (RDMs) for each ROI and each subject was, thus, performed in native space of each participant. The resulting *t*-images from the regressors of interest were used to create vectors of activity pattern for each event, separately for each ROI. These activity patterns were used to calculate the dissimilarity between two trials by correlation distances (1-*r*, Pearson's rank order correlation). Thereafter, the dissimilarities for each combination were entered into a 36×36 Representational Dissimilarity Matrix (RDM). The dissimilarities for linked (AB_{pre}, AB_{post}) and non-linked events (AX_{pre}, AX_{post}) pre- and post-insight were extracted for each story and averaged over stories for each participant. These averaged dissimilarities were then entered into a mixed $2 \times 2 \times 2$ ANOVA in R version 4.0.4 (https://www.r-project.org/) with the between-subjects factor group (stress vs. control) and the within-subject factors time (pre

Table 1
Subjective mood ratings.

	Stress			Control		
	-5	+20	+110	-5	+20	+110
MDBF	*M* (*SD*)	*M* (*SD*)	*M* (*SD*)	*M* (*SD*)	*M* (*SD*)	*M* (*SD*)
Positive mood	33.40 (4.77)	27.57*** (6.61)	31.40* (5.59)	32.89 (5.34)	33.75 (5.27)	34.21 (4.66)
Calmness	31.07 (5.90)	26.10** (6.53)	31.53 (5.66)	30.14 (5.86)	31.21 (5.95)	33.71 (3.65)
Wakefulness	29.67 (5.47)	28.67 (5.60)	**24.07** (6.82)	31.00 (5.48)	30.89 (5.80)	**25.04** (6.72)

The subjective mood scale MDBF with its sub-scales valence, arousal, and wakefulness was rated on a Likert scale ranging from *not at all* (1) to *very much* (5) five minutes prior to treatment onset, 20 min after treatment onset, and 110 min after treatment onset. Data represents means (SD); significant between-subjects effects are indicated by: $^{*}p < .05$, $^{**}p < .01$, $^{***}p < .001$; significant within-subjects effects are highlighted in bold.

vs. post) and link (link vs. non-Link). We corrected for the number of ROIs by applying Bonferroni correction (p_{corr}).

2.3.6. Correlations with cortisol

To relate our behavioral, univariate and multivariate results to cortisol measures, we calculated the *area under the curve with respect to increase* (AUC_I), as this measure has been shown to operationalize a critical aspect of cortisol release: AUC_I is related to the sensitivity of the system and shows changes over time (Pruessner et al., 2003).

2.3.7. Regression analysis

To directly assess the relation between neural dissimilarity measures and perceived dissimilarity in the multidimensional arena task, we calculated a linear regression model and compared it to a quadratic regression model using the likelihood ratio test for the stress and control groups separately. To further probe whether potential group differences were significant, we built a basic model that did not include interaction effects with group and an interaction model that included these interaction effects. We determined which model better fit the data by testing these two models against each other implementing the likelihood ratio test. These analyses were performed in R version 4.0.4 (https://www.r-project.org/).

3. Results

3.1. Successful stress induction

Approximately 30 min before participants completed the narrative-insight task (Fig. 1) in the MRI scanner, they underwent either a psychosocial stressor (Trier Social Stress Test, TSST; $n = 30$) or a non-stressful control manipulation ($n = 29$). Significant changes in subjective mood as well as in blood pressure and salivary cortisol confirmed the successful stress induction by the TSST. Negative mood increased significantly in response to the TSST but not after the control manipulation (*time* × *group* interaction: $F_{(1.96,\ 111.78)} = 14.75$, $p < .001$, $\eta_G = .059$). Post-hoc t-tests showed significantly higher negative mood ratings in the stress group compared to the control group after the experimental manipulation ($t_{(55.23)} = 3.82$, $p < .001$, $d = .99$), as well as at the end of the experiment ($t_{(55.55)} = 2.09$, $p = .041$, $d = .54$), whereas there was no difference at baseline ($t_{(56.07)} = -.04$, $p = .682$, $d = -.11$). There was also a significant increase in restlessness in the stress condition but not in the control condition (*time* × *group* interaction: $F_{(1.99,\ 113.63)} = 9.81$, $p < .001$, $\eta_G = .045$). Post-hoc comparisons revealed significantly higher restlessness ratings after the experimental manipulation in the stress group (vs. control; $t_{(56.81)} = 3.02$, $p = .004$, $d = .78$) and a similar trend at the end of the experiment (vs. control; $t_{(49.30)} = 1.78$, $p = .081$, $d = .46$), while groups did not differ at baseline ($t_{(56.99)} = -.63$, $p = .528$, $d = -.17$). Furthermore, there was an increase in tiredness across the experiment, irrespective of the experimental group ($F_{(1.50,\ 85.22)} = 56.03$, $p < .001$, $\eta_G = .172$; Table 1).

Systolic blood pressure increased significantly in stressed participants but not in the control group (*time* × *group* interaction: $F_{(2.41,\ 132.45)} = 22.66$, $p < .001$, $\eta_G = .057$; see Fig. 2). Post-hoc t-tests showed significantly higher systolic blood pressure in the stress group compared to the control group during the experimental manipulation ($t_{(52.32)} = -4.06$, $p < .001$, $d = 1.07$). There was no significant difference at the other time points of measurement (in minutes relative to treatment onset: -5 min (baseline): $t_{(56.90)} = -.02$, $p = .984$, $d = .01$; +20 min: $t_{(55.85)} = -1.49$, $p = .141$, $d = .39$; +110 min: $t_{(55.44)} = -.97$, $p = .339$, $d = .25$). Likewise, diastolic blood pressure increased in response to the TSST but not to the control manipulation (*time* × *group* interaction: $F_{(2.46,\ 135.44)} = 29.15$, $p < .001$, $\eta_G = .088$; see Fig. 2). Post-hoc t-tests indicated significantly higher diastolic blood pressure in the stress group compared to the control group during the experimental manipulation ($t_{(48.54)} = -4.70$, $p < .001$, $d = 1.23$; all other time points of measurement in minutes relative o treatment onset: -5 min (baseline): $t_{(56.99)} = 1.07$, $p = .291$, $d = -.28$; +20 min: $t_{(55.83)} = -1.17$, $p = .246$, $d = -.31$; +110 min: $t_{(56.84)} = .19$, $p = .848$, $d = -.06$). Furthermore, participants' pulse increased significantly in the stress but not the control group (*time* × *group* interaction: $F_{(2.17,\ 119.09)} = 13.19$, $p < .001$, $\eta_G = .049$; see Fig. 2). Post-hoc t-tests showed again significantly higher pulse in stressed participants compared to controls during the experimental manipulation ($t_{(45.56)} = -3.64$, $p < .001$, $d = .95$; all other time points of measurement in minutes relative to treatment onset: -5 min: $t_{(56.68)} = .10$, $p = .923$, $d = -.03$; +20 min: $t_{(55.98)} = -.66$, $p = .513$, $d = .17$; +110 min: $t_{(56.62)} = -.76$, $p = .452$, $d = .20$).

Finally, salivary cortisol increased significantly in stressed participants but not in controls (*time* × *group* interaction: $F_{(2.64,\ 150.54)} = 9.88$, $p < .001$, $\eta_G = .050$; see Fig. 2). While groups did not differ in baseline cortisol concentrations ($t_{(46.12)} = -.73$, $p = .470$, $d = .18$), stressed participants had significantly higher salivary cortisol concentrations compared to controls after the experimental manipulation, with peak levels at the start of the narrative-insight task ($t_{(35.34)} = -4.35$, $p < .001$, $d = 1.12$), which remained elevated throughout the task (+60 min: $t_{(55.84)} = -3.20$, $p = .002$, $d = .83$; +80 min: $t_{(54.88)} = -2.45$, $p = .018$, $d = .64$; end of the experiment: $t_{(56.98)} = -1.70$, $p = .096$, $d = .44$).

3.2. Superior memory for linked vs. non-linked events

In order to examine stress effects on mnemonic integration, we used a modified narrative-insight task (Fig. 1). In this task, participants first repeatedly watched three videos showing specific episodes (pre-insight phase). Thereafter, a new (linking) event (L) was presented that linked two of the previously seen events (A and B) but left the third event non-linked (control event X; linking phase). Finally, the now linked or non-linked events were presented again to examine insight-driven representational changes (post-insight phase; Fig. 4). In all of these phases, we included target stimuli to which participants should respond, thus controlling for their attention during the task. Participants responded to 94.92% ($SD = 14.04\%$) of the target presentations, without any differences between groups ($t_{(38.117)} = -.81$, $p = .423$, $d = -.21$), indicating that stress did not affect attention during the task.

In the narrative-insight task, all participants gained – as expected – insight into the relationship of the initially separate events, as

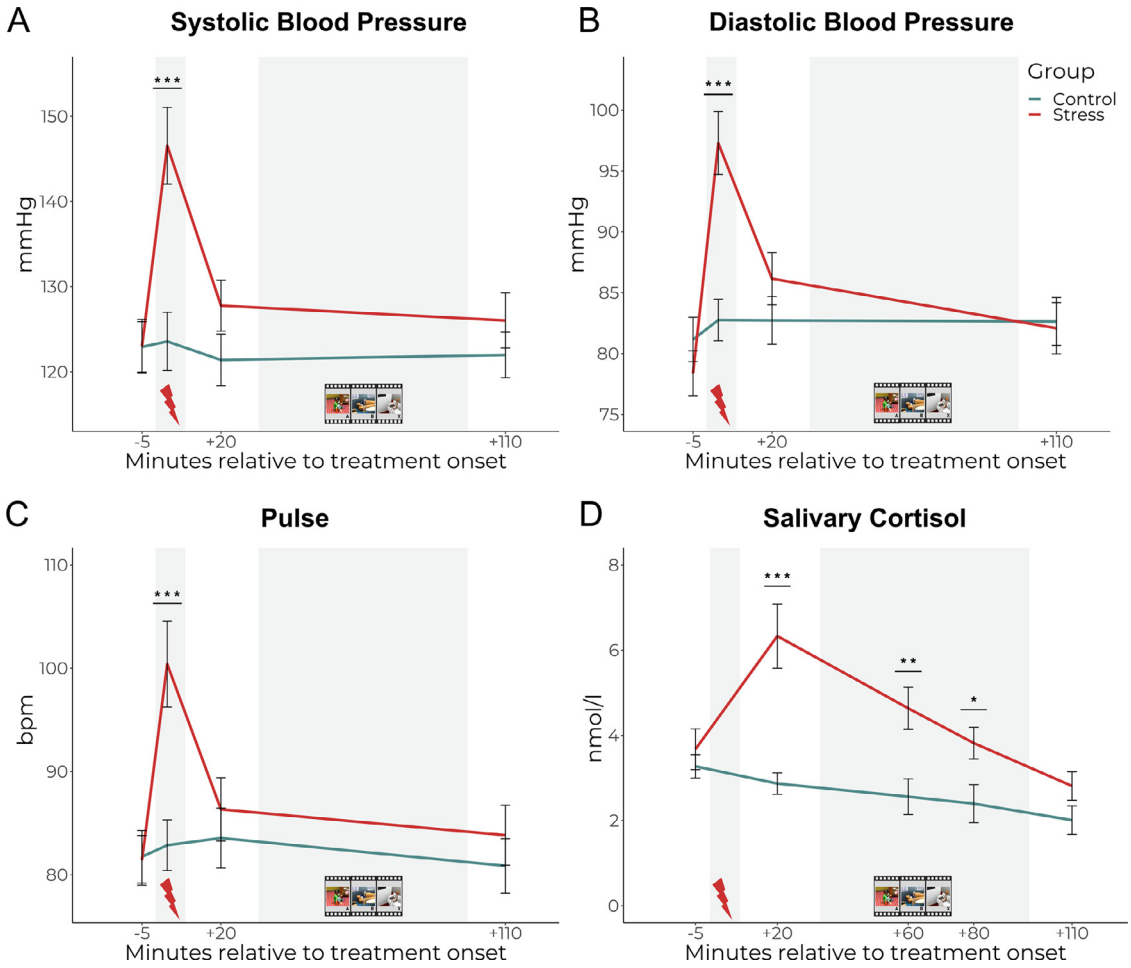

Fig. 2. Physiological stress responses. (A) Significant increases in systolic (mmHG) and (B) diastolic blood pressure (mmHG) and (C) pulse (bpm). (D) as well as in concentrations of salivary cortisol (nmol/l) confirmed the successful stress induction by the Trier Social Stress Test (TSST). Grey shades indicate periods of the TSST and control procedure, respectively, (red flash) and the narrative insight task (film roll). Data represents means (+/- SE); $^{*}p < .05$, $^{**}p < .01$, $^{***}p < .001$.

reflected in significantly increased assessments of belonging after the linking phase for linked than non-linked events (*time* × *link* interaction: $F_{(1, 53)} = 745.21$, $p < .001$, $\eta_G = .626$, Fig. 4). Importantly, groups did not differ in these assessments of belonging, indicating that stress did not affect the basic insight into the relationship of events. In addition to the initial linking of events on day 1, which required connection and integration of the initially unrelated events, we also examined memory for this insight, one week later. The findings of day 1 were also reflected in the multidimensional arena task one week after encoding of the events. In this task, in which participants placed events that belong together closer to each other, participants performed very well (multidimensional arena task: *mean distance for linked events* = .02, *SD* = .01; *mean distance for non-linked events* = .05, *SD* = .02; Fig. 4). Again, there were no significant differences between stressed and control participants (multidimensional arena task: *link:* $F_{(1, 50)} = 89.35$, $p < .001$, $\eta_G = .324$), thus indicating that both groups remembered the basic association between events. In line with this view, those in both groups who rated the linked events as more closely related after insight also arranged the linked events more closely in the multidimensional arena task one week later ($r = -.49$, $t_{(50)} = -3.96$, $p < .001$). In addition, those in both groups who distinguished more between linked and non-linked events after insight (link - nonlink) arranged the linked events closer together in the multidimensional arena task ($r = -.30$, $t_{(46)} = -2.14$, $p = .038$). However, we found that the increase in cortisol over time (AUC_I) in the stress group was associated with closer distances for non-linked events (A and X), whereas this was not the case in the control group (stress: $r = -.43$, $t_{(23)} = -2.26$, $p = .034$; control: $r = .08$, $t_{(24)} = .41$, $p = .683$; stress vs. control: $z = -1.91$, $p = .028$; Fig. 3).

Strikingly, whether events were linked or not during encoding had a significant impact on the memory for these events, as assessed one week after encoding in the free recall test: participants recalled linked events (averaged A and B) in significantly more detail than non-linked events (X; *item:* $F_{(1, 53)} = 48.27$, $p < .001$, $\eta_G = .243$; Figs. 4D and S5). This enhanced memory for linked vs. non-linked events was observed in both groups (stress: $t_{(26)} = 4.79$, $p < .001$, $d_{repeated\ measures} = -.86$; control: $t_{(27)} = 5.05$, $p < .001$, $d_{repeated\ measures} = -.79$; *group* × *item:* $F_{(1, 53)} = .32$, $p = .575$, $\eta_G = .002$). Although the stress group seemed to recall more details on a descriptive level, there was no significant effect of group in the free recall test (*group:* $F_{(1, 53)} = 1.96$, $p = .167$, $\eta_G = .023$). We also found that those in both groups who recalled more details for linked events also arranged the linked events closer together in the multidimensional arena task ($r = -.32$, $t_{(49)} = -2.39$, $p = .021$).

In addition to the free recall test, we administered also a forced-choice recognition test, which involves lower memory search demands. Overall, performance in the forced-choice recognition test was very high (*M* = 79.95%; *SD* = 22.17%). Interestingly, stressed participants performed better than controls in this task (forced-choice recognition test: $t_{(46.79)} = -2.17$, $p = .035$, $d = -.58$). Moreover, we found a positive relationship between post-insight link ratings and delayed forced-choice recognition test performance across both groups ($r = .48$, $t_{(55)} = 4.01$, $p < .001$), suggesting that those participants who gained better insight into which events were linked on day 1 also performed better in the

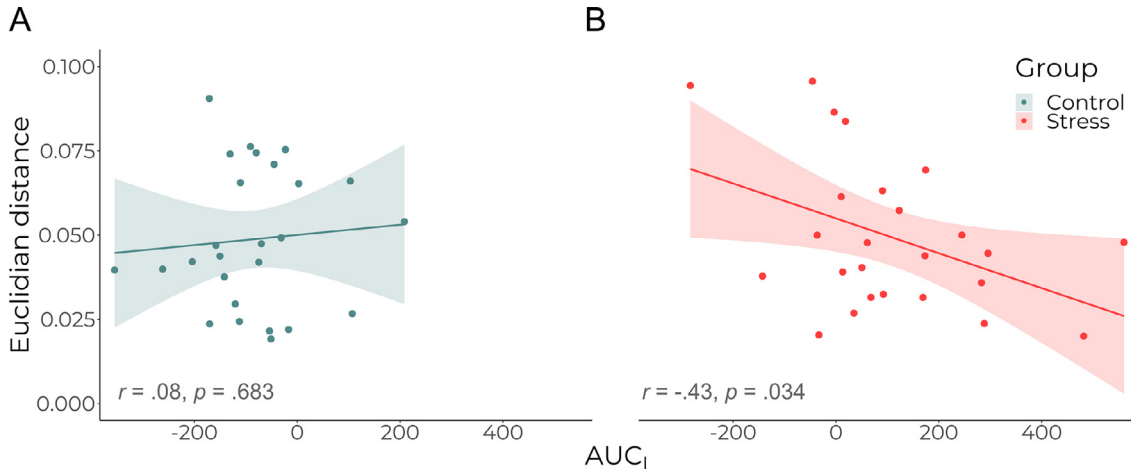

Fig. 3. Association between cortisol and multidimensional arena task. (A) Non-significant correlation between the increase in cortisol release over time (AUC_I) and Euclidian distance for non-linked events (A and X) in the multidimensional arena task in controls. (B) Significant correlation between the increase in cortisol release over time (AUC_I) and Euclidian distance for non-linked events (A and X) in the multidimensional arena task.

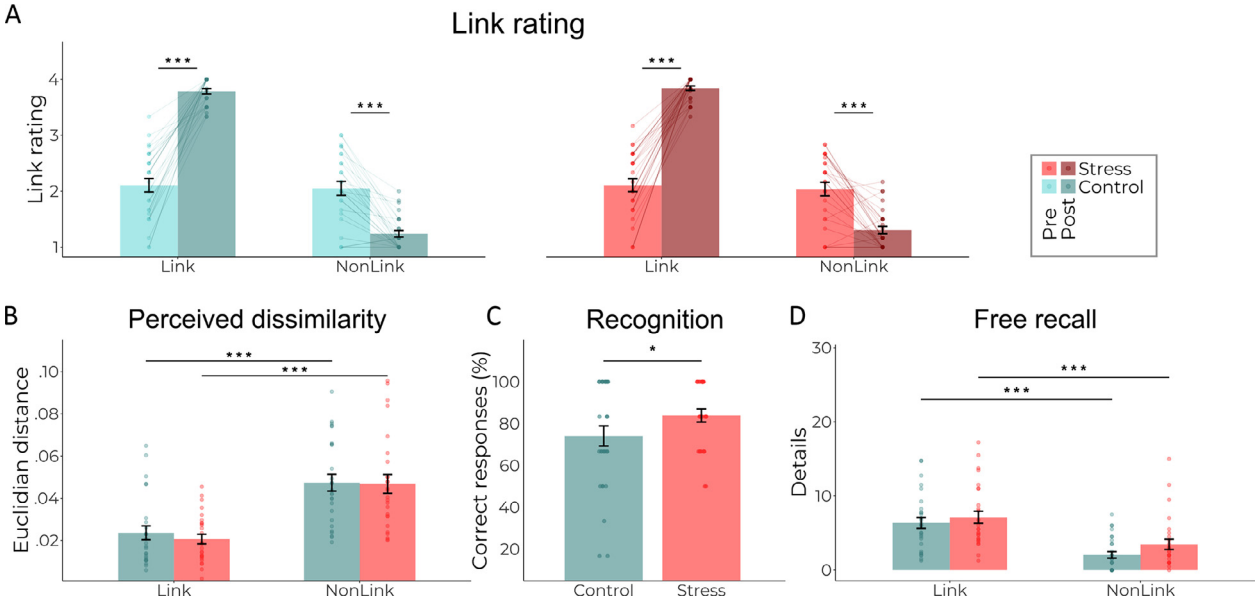

Fig. 4. Behavioral measures of insight and memory performance. (A) Significant increases in ratings of belonging for linked events and significant decreases in ratings of belonging for non-linked events in the control group (left) and in the stress group (right). (B) Significant differences between linked and non-linked events in the multidimensional arena task (Euclidian distance) for the control and stress group. (C) High performance (correct responses (%)) in the forced-choice recognition test for both groups. (D) Significant differences between linked (A and B) and non-linked events (X) events in the free recall for the stress and control group. Data represents means (+/- SE); $^{*}p < .05$, $^{***}p < .001$.

forced-choice recognition test. We further obtained that those in both groups who differentiated better between linked and non-linked events post-insight also performed better in the forced-choice recognition test (r = .32, $t_{(51)}$ = 2.44, p = .018). Participants in both groups who arranged the linked events closer together in the multidimensional arena task also performed better on the forced-choice recognition test (r = -.59, $t_{(49)}$ = -5.17, p < .001).

3.3. Stress lowers medial temporal lobe activity during linking of events

To shed light on the insight-related neural processes underlying episodic integration, we measured BOLD-activity using fMRI during the linking phase, when participants learned about the relationship of the initially unrelated events A and B through a linking video (L), which was interleaved with an unrelated control video (C). We compared the neural activity of the linking event (L) with control events (C; Link > Control; Fig. 5) and accounted for fMRI adaptation processes by including parametric regressors that reflect the time between events during the linking phase. We used log lags since previous studies suggested that adaptation effects are not automatically linear at longer lags between events (Weiner et al., 2010; Zhou et al., 2018). This analysis revealed that stress (vs. control) lowered linking-related activity in the left hippocampus (SVC peak level: x = -28, y = -10, z = -20; $t_{(1,57)}$ = 4.49, p_{corr}(FWE) = .012, k = 23) extending into the left amygdala (SVC peak level: x = -26, y = -8, z = -20; $t_{(1,57)}$ = 4.25, p_{corr}(FWE) = .012, k = 13). In an exploratory analysis, we found a correlation suggesting that participants in the stress group with higher amygdala activity during linking also recalled more details for non-linked events (r = .37, t(26) = 2.05, p = .051). As this correlation did not reach statistical significance, this association should be interpreted with caution though.

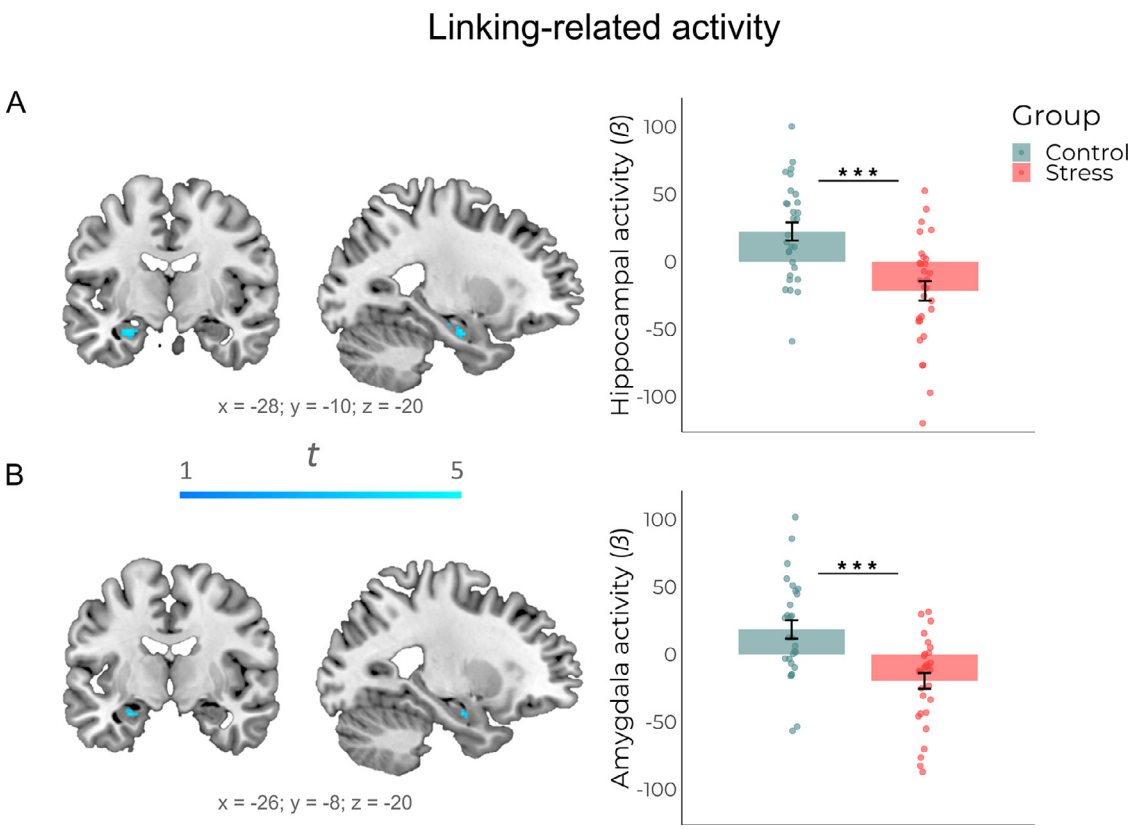

Fig. 5. Neural activity during linking phase (stress vs control group). (A) Significant decreases in stressed participants (vs. controls; Link > Control) in left hippocampus (SVC peak level: x = -28, y = -10, z = -20). Only masked ROI is displayed. Coronal and sagittal sections are shown, superimposed on a T1-template image. Depicted next to this is the peak voxel activity of the left hippocampus (HC) for stressed participants and controls during linking. Data represents means (+/- SE); $^{***}p < .001$. (B) Significant decreases in stressed participants (vs. controls; Link > Control) extended into the left amygdala (SVC peak level: x = -26, y = -8, z = -20). Only masked ROI is displayed. Coronal and sagittal sections are shown, superimposed on a T1-template image. Depicted next to this is the peak voxel activity of the left amygdala (AMY) for stressed participants and controls during linking. Data represents means (+/- SE); $^{***}p < .001$ and left amygdala when accounted for fMRI adaptation processes.

3.4. Stress hinders insight-related increase in medial temporal lobe activity

To assess neural changes associated with insight induced during the linking phase, we compared BOLD-activity changes for events that were linked (A and B) from the pre- with the post-insight-phase (AB_{post} > AB_{pre}). Our initial whole-brain analysis revealed a decrease in neural activity from pre- to post-insight in stressed participants (vs. controls) in the right putamen (whole-brain cluster-level: x = 18, y = 14, z = -8; $t_{(1,57)}$ = 4.95, p_{corr}(FWE) = .005, k = 215; Fig. S4 in supplementary material). Focusing on our regions of interest, we found decreases from pre- to post-insight in neural activity in stressed participants (vs. controls) in the right orbitofrontal cortex (OFC: SVC peak level: x = 34, y = 28, z = -8; $t_{(1,57)}$ = 4.25, p_{corr}(FWE) = .036, k = 4; Fig. 6), and in the bilateral parahippocampal cortices (left PHC: SVC peak level: x = -24, y = 0, z = -30; $t_{(1,57)}$ = 4.30, p_{corr}(FWE) = .012, k = 22; Fig. 6; right PHC: SVC peak level: x = 20, y = -16, z = -28; $t_{(1,57)}$ = 4.67, p_{corr}(FWE) = .004, k = 19). We performed an exploratory analysis to relate this result to the behavioral level and found that across both groups, those who had a greater increase from pre to post insight for linked events in the right parahippocampus tended to remember fewer details for the non-linked event (r = -.26, t(54) = -1.96, p = .055); yet this results needs to be interpreted with caution as the correlation did not reach statistical significance. To rule out that these differences for linked events were only due to the passage of time, we also compared activity changes for non-linked events from the pre- with the post-insight-phase and found no differences between the groups (left OFC: SVC peak level: x = -16, y = 22, z = -24; $t_{(1,57)}$ = 3.68, p_{corr}(FWE) = .120, k = 3; left PHC: SVC peak level: x = -26, y = -2, z = -32; $t_{(1,57)}$ = 3.45, p_{corr}(FWE) = .133, k = 1), thus suggesting that the above activity changes were specific to the insight into the link between initially unrelated events. Interestingly, we found that the change in the right orbitofrontal cortex from pre- to post-insight was negatively associated with the cortisol increase (AUC_I) over both groups (r = -.37, $t_{(55)}$ = -3.00, p = .004).

3.5. Stress disrupts insight-related change in event representations

Finally, to examine the representational change induced by insight into the relationship of initially unrelated events, we compared multivariate voxel patterns pre- and post-insight by performing a ROI-based representational similarity analysis (RSA). We focused primarily on the longitudinal long axis of the hippocampus, since hippocampal sub-regions have been differentially implicated in integration and segregation of events in general (Cohn-Sheehy et al., 2021b; Dandolo and Schwabe, 2018; Lohnas et al., 2018; Schlichting et al., 2015) and mnemonic integration across initially unrelated events in particular (Collin et al., 2015; Milivojevic et al., 2015). In this analysis, representational dissimilarity matrices (RDMs) were computed for the anterior and the posterior portion of the hippocampal long axis. Thereafter, we extracted the neural dissimilarities averaged over stories for linked and non-linked events pre- and post-insight from these RDMs for each participant (Fig. 7B) and compared them in a mixed analysis of variance. Interestingly, we found that while control partici-

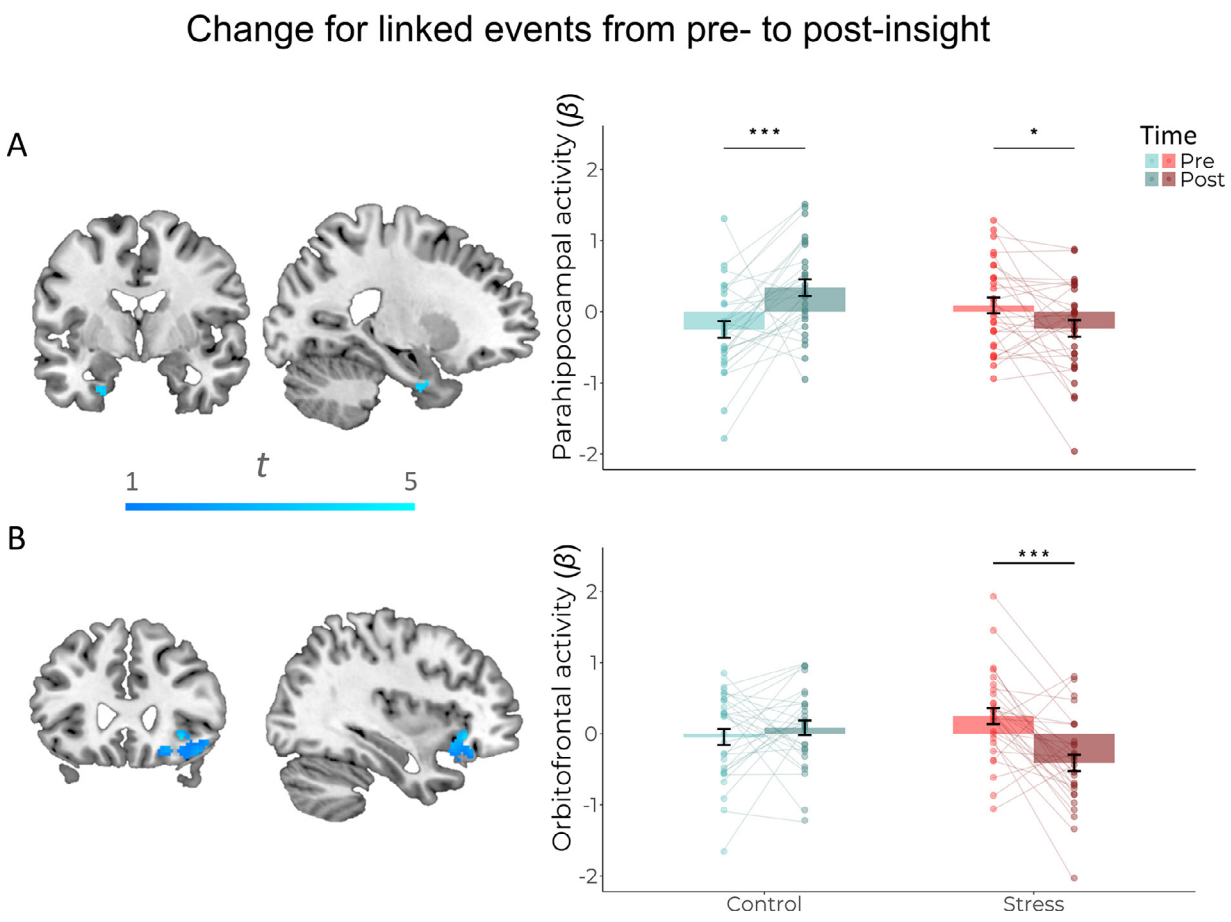

Fig. 6. Change in neural activity from pre- to post-insight. (A) Significant decreases in stressed participants (vs. controls; Linkpost > Linkpre) from pre to post insight in left parahippocampus (SVC peak level: x = -24; y = 0; z = -30). Only masked ROI is displayed. Coronal and sagittal sections are shown, superimposed on a T1-template image. (B) Peak voxel activity of the left parahippocampal cortex (PHC) for stressed participants and controls pre- and post-insight. Data represents means (+/- SE); $^{*}p < .05$, $^{***}p < .001$. (C) Significant decreases in stressed participants (vs. controls; Linkpost > Linkpre) in orbitofrontal cortex (SVC peak level: x = 34; y = 28; z = -8). Only masked ROI is displayed. Coronal and sagittal sections are shown, superimposed on a T1-template image. (D) Peak voxel activity of the right orbitofrontal cortex (OFC) for stressed participants and controls pre- and post-insight. Data represents means (+/- SE); $^{***}p < .001$.

pants exhibited a significant increase in representational dissimilarity for linked events from pre to post insight in the right anterior hippocampus, stress abolished this insight-related change in anterior hippocampal representations (*group* × *time* × *link* interaction: $F_{(1, 53)} = 6.20$, $p_{corr} = .032$, $\eta_G = .017$; Fig. 7C). For the posterior hippocampus, there was no such change (*group* x *time* × *link* interaction: $F_{(1, 56)} = 1.03$, $p_{corr} = .626$, $\eta_G = .002$; Fig. S3), in line with previous studies suggesting that the anterior but not the posterior part of the hippocampus is involved in mnemonic integration (Collin et al., 2015; Dandolo and Schwabe, 2018; De Shetler and Rissman, 2017; Duncan and Schlichting, 2018; Morton et al., 2017; Robin and Moscovitch, 2017). We performed a follow-up analysis of the interaction in the anterior hippocampus and found that controls showed a significant increase in representational dissimilarity from pre to post specifically for linked events ($t_{(26)} = -2.13$, $p = .043$, $d_{repeated\ measures} = .41$; Fig. 7C) but no increase in representational dissimilarity from pre to post for non-linked events ($t_{(26)} = .05$, $p = .620$, $d_{repeated\ measures} = -.10$; *time* × *link* interaction: $F_{(1, 26)} = 4.51$, $p = .043$, $\eta_G = .027$). After stress, the change in representational dissimilarity for linked events was eliminated (*time* × *link* interaction: $F_{(1, 27)} = 2.09$, $p = .160$, $\eta_G = .011$). The representational dissimilarity for linked events in the right anterior hippocampus post-insight was negatively related to the increase in cortisol release over time (AUC_I) across both groups, which was not the case for the representational dissimilarity pre-insight in the right anterior hippocampus (pre: $r = .06$, $t_{(53)} = .42$, $p = .678$; post: $r = -.31$, $t_{(53)} = -2.34$, $p = .023$; pre vs. post: $z = 1.90$, $p = .029$).

To further elucidate the behavioral relevance of the neural representational changes and their abolishment by stress, we first tested for a potential linear relationship between representational dissimilarity in the right anterior hippocampus post-insight for linked events and distances between linked events in the multidimensional arena task. In this analysis, however, we observed no significant effect ($R^2 = -.02$, $F_{(1, 24)} = .44$, $p = .514$). Since recent studies indicated that there might be a non-linear, quadratic relationship between memory processes and changes in representational similarity (Wammes et al., 2022), we tested also for a potential quadratic relationship and indeed obtained not only a better model fit for the quadratic compared to the linear relationship ($\chi^2_{(1)} = 15.21$, $p < .001$) but also a significant quadratic association between representational dissimilarity in the right anterior hippocampus post-insight for linked events and linked events in the multidimensional arena task in controls ($R^2 = .41$, $F_{(2, 23)} = 9.52$, $p < .001$; Fig. 6D). Importantly, this association was abolished by acute stress: neither the linear ($R^2 = -.02$, $F_{(1, 23)} = .54$, $p = .472$), nor the quadratic model ($R^2 = .06$, $F_{(2, 22)} = 1.78$, $p = .192$; linear vs. quadratic model: $\chi^2_{(1)} = 3.18$, $p = .075$; Fig. 6D) provided a significant fit in stressed participants. The significant interaction effect dissimilarity^2 × group in the interaction model, which showed a better fit compared to the basic model ($\chi^2_{(2)} = 10.83$, $p = .004$), indicated that the groups differed significantly from each other regarding

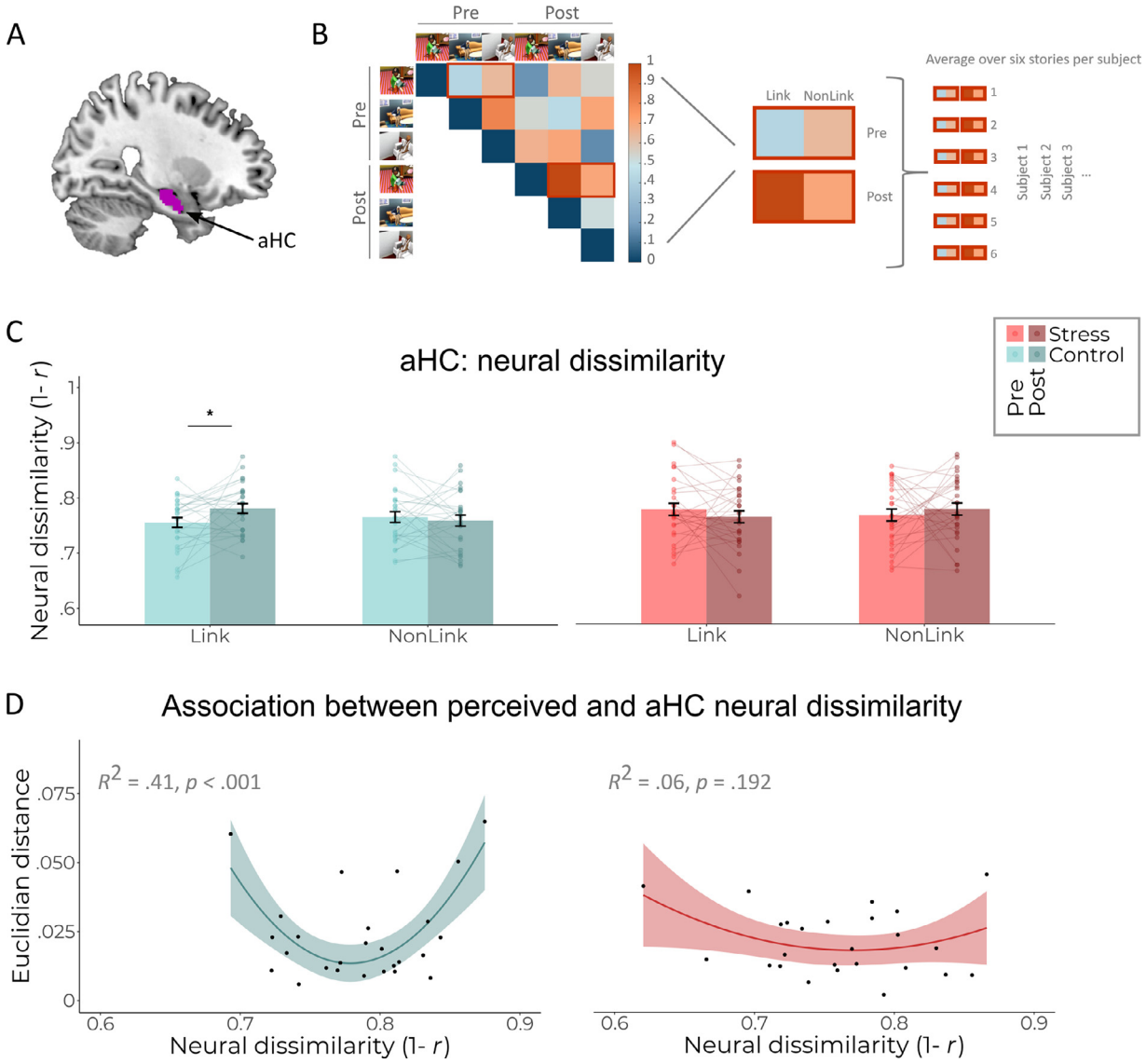

Fig. 7. Conceptual RSA and results for anterior hippocampus (aHC). (A) Masked right anterior hippocampus. (B) Conceptual neural dissimilarity matrix from right anterior hippocampus. Dissimilarities for linked and non-linked events were extracted and averaged across six stories for each participant resulting in average dissimilarities for link and non-link pre- and post-insight. (C) Significant difference between pre- and post-insight for linked events in the right anterior hippocampus in controls as well as non-significant differences in the stress group. Data represents means (+/- SE); $^{*}p < .05$. (D) Significant quadratic regression between neural dissimilarity post-insight in right aHC and perceived dissimilarity from MA-task (in Euclidian distance) for control group and non-significant quadratic regression for stress group. Each point represents one participants. Fitted quadratic regression line with shaded 95% confidence interval.

the fit of the quadratic model (Table 2). We further found confirmation of the behavioral relevance of neural dissimilarities post-insight, as higher dissimilarities were related to greater distances between non-linked events in the multidimensional arena task ($r = .31$, $t_{(51)} = 2.29$, $p = .026$). Furthermore, those who had higher post-insight neural dissimilarities for linked events also differentiated better between linked and non-linked events in the multidimensional arena task ($r = -.30$, $t_{(49)} = -2.23$, $p = .031$).

3.6. Control variables

To rule out the possibility that the stress and control groups differed in terms of trait-anxiety (STAI-T), state-anxiety (STAI-S), sleep quality (PSQI), chronic stress (TICS), depressive symptoms (BDI), personality dimensions (BFI-2), and chronotype (MEQ), participants completed corresponding questionnaires before the experiment. There were no differences between the groups on any of these measures (all $p > .10$; see Table 3; for MEQ: Fisher´s exact test, $p = .358$).

Furthermore, there was no difference between participants in their working memory capacity, as measured by an N-back task, neither at baseline nor before the task (see Table 4). Thus, it is unlikely that stress effects during the narrative insight task (or in the retention test 1 week later) were influenced by mere group differences in working memory.

4. Discussion

Integrating initially unrelated events into coherent episodes in light of new information is a fundamental memory process. This process may, however, be impaired in stress-related disorders, such as PTSD (Balderston et al., 2017; Berntsen et al., 2003; Lange et al., 2017). Therefore, we tested here the hypothesis that acute stress interferes with the insight-driven reconfiguration of memory. Our results show that, compared to a control manipulation, acute stress reduced medial tempo-

Table 2
Regression models for the prediction of distances for linked events in the multidimensional arena task.

Model	Variable	B	95% CI	β	t	p	R^2 *adjusted*
Basic	Constant	.99	[.41, 1.56]	-.32	-2.02	.049*	.15
	Dissimilarity	-2.53	[-4.02, -1.03]	.11	.79	.434	
	Dissimilarity^2	1.65	[.67, 2.63]	.33	3.40	.001**	
	Group	-.00	[-.01, .00]	-.14	-1.03	.310	
IA	Constant	2.89	[1.59, 4.18]	-.46	-2.99	.005**	.29
	Dissimilarity	-7.38	[-10.70, -4.06]	-.07	-.52	.608	
	Dissimilarity^2	4.74	[2.62, 6.85]	.57	4.76	<.001***	
	Group	-2.34	[-3.78, -.90]	.15	.99	.329	
	Dissimilarity × Group	6.00	[2.29, 9.72]	.09	.68	.502	
	Dissimilarity^2 × Group	-3.85	[-6.23, -1.46]	-.39	-3.24	.002**	

Note. Basic: basic model without interaction terms; IA: interaction model including the group interaction effects; CI = confidence interval for B; β coefficients are standardized. $^*p < .05$, $^{**}p < .01$, $^{***}p < .001$.

Table 3
Control variables.

	Stress		Control		
Measure	M	SD	M	SD	p
STAI-T	37.47	9.26	35.90	8.87	.509
STAI-S	36.90	6.90	35.72	7.35	.534
PSQI	6.07	3.25	5.44	2.10	.402
TICS	25.77	8.57	25.21	9.05	.808
BDI	7.13	7.93	4.79	4.44	.167
BFI-2 E	42.50	6.51	40.76	6.69	.315
BFI-2 N	31.03	7.59	28.62	9.23	.278
BFI-2 O	44.03	5.75	43.17	9.00	.665
BFI-2 C	39.83	7.80	43.31	7.95	.096
BFI-2 A	45.87	4.42	47.07	6.78	.400

Note. The questionnaires (STAI-T, BDI, BFI-2 all dimensions) were completed via an online-link before participants came in for day 1 and STAI-S and PSQI were completed at the beginning of the experiment. No significant difference between the groups were observed on these measures. Data represents means (+/- SD).

Table 4
N-back task.

	Stress		Control		
N-back	M	SD	M	SD	p
Pre					
3-back Acc	79.75%	11.91%	79.40%	10.93%	.906
3-back RT	780.57 ms	164.01 ms	729.20 ms	164.91 ms	.235
4-back Acc	78.33%	9.20%	77.24%	11.52%	.690
4-back RT	765.27 ms	144.87 ms	722.75 ms	206.18 ms	.365
Post					
3-back Acc	80.58%	13.17%	80.00%	15.40%	.877
3-back RT	782.96 ms	182.44 ms	795.93 ms	211.56 ms	.802
4-back Acc	76.25%	12.71%	76.81%	15.25%	.879
4-back RT	779.51 ms	162.71 ms	797.09 ms	194.50 ms	.708

Note. Participants completed the N-back task before stress induction at baseline and after stress induction before they completed the narrative-insight task in the scanner. Groups did not differ on N-back measures pre- or post-stress or –control manipulation. Data represents means (+/- SD).

ral activity when learning about the link between initially unrelated events as well as the increase in medial temporal activity from pre- to post-insight for linked events. Moreover, stress abolished the change in the neural representation of linked events in the anterior hippocampus that we observed in a non-stressed control group. These stress-induced changes in the neural implementation of the integration across initially unrelated events were directly linked to subsequent mnemonic measures of insight. Control analyses showed that these effects of acute stress could not be explained by group differences in chronic stress, anxiety, depressive mood or working memory capacity.

Across groups, our behavioral data revealed a memory benefit for linked compared to non-linked events, suggesting that narrative coherence may promote memory longevity. This finding is in line with the notion that the brain stores episodic memories as coherent narratives (Tulving, 1983) and with recent findings suggesting that integrated episodes can be recalled more easily (Cohn-Sheehy et al., 2021a; Wang et al., 2015). This memory advantage of integrated episodes over non-linked events might be due to a pattern completion process, which allows cueing of an entire episode with a single element (Gardner-Medwin, 1976; Horner and Burgess, 2014; Nakazawa et al., 2002b; Rolls, 2013). Although events A and B were not repeated during the linking phase, the linking events may have induced a reactivation of these events, which may further have contributed to the differences in detail recall for linked and non-linked events. Notably, the basic insight into the relationship between linked and non-linked events was not affected by stress, most likely because the task was designed to result in high insight performance. In line with this view, performance in the insight task was near-ceiling for both groups.

While performance in the multidimensional arrangement test was comparable between groups, the stress group outperformed the control group in the forced-choice recognition test. A similar, but non-significant trend was observed in the free recall test; the lack of significance in the free recall test may be due to factors such as task sensitivity or differences in task difficulty. Compared to free recall, the forced-choice recognition test is cognitively less demanding as it requires only a limited search process. In accordance with previous work, that has shown that stress prior encoding led to improved recognition performance for high-arousal pairings (Goldfarb et al., 2019) and congruent pairings of faces and scenes one day after encoding (Sep et al., 2019), we show that stress prior encoding one week later led to improved recognition performance of events that were linked through a narrative compared to non-linked events. This memory boost in stressed participants may have been due to delayed cortisol effects that have been suggested to boost memory consolidation processes and to potentially counteract initial impairments of memory updating (Schwabe et al., 2022; van Ast et al., 2013).

At the neural level, however, stress led to a significant reduction of insight-related increases of activity in the parahippocampus, orbitofrontal cortex, and putamen. The finding that parahippocampal activity increased after having learned which scenes belong together is generally in line with reports suggesting that the parahippocampus encodes spatial settings, such as scenes (Epstein and Kanwisher, 1998; Faivre et al., 2019), as well as non-spatial associations (Aminoff et al., 2007; Bar et al., 2008). The orbitofrontal cortex and the putamen have

been associated with reward processing and goal orientation (Basu et al., 2021; Porcelli et al., 2012; Rudebeck and Rich, 2018), pointing to a role in monitoring which events were linked into episodes and which were not.

Most strikingly, non-stressed control participants showed an increase from pre- to post-insight in neural dissimilarity in the anterior hippocampus for linked events. This finding is consistent with studies highlighting the anterior hippocampus as key region for mnemonic integration (Collin et al., 2015; Hannula et al., 2013; Schlichting et al., 2015). Because the anterior hippocampus is also critical for representing both (spatial) context (Brunec et al., 2018; Collin et al., 2015; Fritch et al., 2020), novelty (Bunzeck and Düzel, 2006; Cowan et al., 2021; Kaplan et al., 2014), and repulsion between overlapping representations (Chanales et al., 2017, 2021) may explain why we observed an increase in dissimilarity particularly in this region after participants learned that two of the events were linked via another event, resulting in an integrated episode. Critically, however, this insight-driven change in neural representations disappeared in stressed participants. Consistent with this stress effect, the more cortisol increased over time, the smaller the insight-related neural reconfiguration in the right anterior hippocampus. In light of evidence suggesting that stress might impair processes of pattern completion and separation (Balderston et al., 2017; Berntsen et al., 2003; Esterling et al., 1999; Leal et al., 2014), it is tempting to speculate that acute stress disrupted these processes which are likely mechanisms allowing representational dissimilarity to change (Muller and Kubie, 1987).

Interestingly, we observed an increase in dissimilarity in the anterior hippocampus, but not an increase in similarity, as observed in some earlier studies (Collin et al., 2015; Dimsdale-Zucker et al., 2018; Hannula et al., 2013; Schlichting et al., 2015) or an increase in similarity for linked events and a decrease in similarity for non-linked events, as observed in the posterior hippocampus in previous work (Milivojevic et al., 2015). Importantly, our design differs from previous work (Milivojevic et al., 2015) that used the narrative-insight task in terms of video length: the events during the pre- and post-phase were presented for 2 sec while events in the linking phase were presented for 8 sec for technical reasons. In addition, our design differs from this previous work in that we used a control event (C) during the linking phase to which the linking event (L) was compared to obtain only the linking-related activity. It has also been suggested that hippocampal similarity may increase when events share item as well as context associations but not when events shared either context (scene) or item (people) information (Libby et al., 2019), which may have been the case in the present study. This was, however, also the case in a previous study using the same paradigm in which increased similarity for linked events was found in the anterior hippocampus (Collin et al., 2015). Further evidence suggests that memory representations that have been moderately co-activated, result in increased dissimilarity (Wammes et al., 2022). Increases in dissimilarity between related memories might be interpreted as a pattern separation mechanism allowing inferences across events (Molitor et al., 2021). Indeed, increased dissimilarity has been associated with better memory performance in several previous studies (Chanales et al., 2017; Dandolo and Schwabe, 2018; Favila et al., 2016; Hulbert and Norman, 2015; Koolschijn et al., 2019). In line with these findings, we also found a link between neural dissimilarity post-insight and memory performance (in the multidimensional arena task) in controls. Here, medium dissimilarity values were related to the smallest distance between linked events, whereas low and high dissimilarities resulted in worse performance. Although Wammes et al. (2022) found that the co-activation of memories is non-monotonically related to a resulting increase or decrease in dissimilarity, our results even suggest that the resulting representational dissimilarity is related to a behavioral outcome in a quadratic manner. Wammes et al. (2022) show that low levels of co-activation resulted in no change regarding the dissimilarity between memories and that high levels of co-activation led to decreased dissimilarity. Moderate levels of co-activation, however, – where one memory is strongly activated and the unique parts of the other memory are moderately active – resulted in increased dissimilarity and, thus, less competition between these memories, which might have been the case in the present study. Again, the link between hippocampal reconfiguration and subsequent memory was abolished by acute stress.

Beyond the insight-driven reconfiguration of memory representations, acute stress did also affect the neural processes involved in the linking of initially unrelated events itself. During the linking phase, stress particularly reduced medial temporal lobe activity, in line with the proposed stress-induced shift of multiple memory systems at the expense of a 'cognitive', medial temporal lobe-based system (Goodman et al., 2012; Kim et al., 2001; Schwabe, 2017; Schwabe and Wolf, 2012; Vogel et al., 2016; Wirz et al., 2017). Linking two previously unrelated events together requires a neural substrate that can integrate these memories into a novel unified mnemonic representation, and the hippocampus has been found to be specifically relevant to this function (Bowman and Zeithamova, 2018; Griffiths and Fuentemilla, 2020; Schlichting et al., 2015). Here, it should be noted that linking previously separate events into a coherent narrative requires several sub-processes, such as the successful retrieval of the previously encoded events, the inference of their link, and their mnemonic integration, all of which are relevant and likely dependent on the hippocampus but can hardly be dissociated during the linking process. In addition to the hippocampus, we observed increased amygdala activity in controls during link vs. control events, which was directly associated with insight manifestations one week later. Given the well-documented role of the amygdala in both positive and negative affect (LeDoux, 2007; Phelps and LeDoux, 2005; Weymar and Schwabe, 2016), it is tempting to speculate that the insight into the link between previously unrelated events comes with an (presumably positive) affective response, which may facilitate the subsequent memory of the gained insight. Indeed, there is abundant evidence that emotion-related amygdala activation may modulate mnemonic processing in other brain areas, such as the hippocampus, to promote memory consolidation (Roozendaal et al., 2009; Roozendaal and McGaugh, 2011).

In sum, our findings show that acute stress comes with significant changes in the neural integration of initially separated events into coherent episodes. Specifically, stress reduced medial temporal activity when learning about the links between events and hindered an increase in medial temporal activity from pre- to post-insight. Moreover, stress abolished the insight-driven representational reconfiguration in the anterior hippocampus, which was directly linked to the subsequent memory of the linked events. Although stress reduced the neural changes associated with insight, it enhanced long-term memory, most likely due to the facilitating effect of glucocorticoids on memory consolidation. Together, the present findings shed light on how acute stress impacts mnemonic integration across separate events and may aid our understanding of disintegrated, fragmented memories in stress-related disorders, such as PTSD (Amir et al., 1998; Bisby et al., 2020; Esterling et al., 1999).

Data and code availability

Code and data reported in this manuscript are available from the first author's GitHub repository under https://github.com/an-ma-grob/EpInt_Stress. The RSA analyses were performed using the rsatoolbox (Nili et al., 2014), which can be found under https://git.fmrib.ox.ac.uk/hnili/rsa.

Ethics

Human subjects: University of Hamburg approved the study. All participants gave informed consent to participate in this study.

Declaration of Competing Interest

The authors declare no competing interests

Credit authorship contribution statement

Anna-Maria Grob: Methodology, Formal analysis, Validation, Investigation, Data curation, Writing – original draft, Visualization, Project administration. **Branka Milivojevic:** Methodology, Formal analysis, Validation, Writing – review & editing. **Arjen Alink:** Methodology, Resources, Writing – review & editing. **Christian F. Doeller:** Conceptualization, Methodology, Validation, Resources, Writing – review & editing, Funding acquisition. **Lars Schwabe:** Conceptualization, Methodology, Validation, Writing – original draft, Supervision, Project administration, Funding acquisition.

Data availability

Code and data reported in this manuscript are available from the first author's GitHub repository under https://github.com/anma-grob/EpInt_Stress.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.neuroimage.2022.119804.

References

Adan, A., Almirall, H., 1991. Horne & Östberg morningness-eveningness questionnaire: a reduced scale. Pers. Individ. Differ. 12 (3), 241–253. doi:10.1016/0191-8869(91)90110-W.

Aminoff, E., Gronau, N., Bar, M., 2007. The parahippocampal cortex mediates spatial and nonspatial associations. Cereb. Cortex 17 (7), 1493–1503. doi:10.1093/cercor/bhl078.

Amir, N., Stafford, J., Freshman, M.S., Foa, E.B., 1998. Relationship between trauma narratives and trauma pathology. J. Trauma Stress 11 (2), 385–392. doi:10.1023/A:1024415523495.

Balderston, N.L., Mathur, A., Adu-Brimpong, J., Hale, E.A., Ernst, M., Grillon, C., 2017. Effect of anxiety on behavioural pattern separation in humans. Cogn. Emot. 31 (2), 238–248. doi:10.1080/02699931.2015.1096235.

Bar, M., Aminoff, E., Schacter, D.L., 2008. Scenes Unseen: the parahippocampal cortex intrinsically subserves contextual associations, not scenes or places per se. J. Neurosci. 28 (34), 8539–8544. doi:10.1523/JNEUROSCI.0987-08.2008.

Basu, R., Gebauer, R., Herfurth, T., Kolb, S., Golipour, Z., Tchumatchenko, T., Ito, H.T., 2021. The orbitofrontal cortex maps future navigational goals. Nature 599 (7885), 7885. doi:10.1038/s41586-021-04042-9, Article.

Berntsen, D., Willert, M., Rubin, D.C., 2003. Splintered memories or vivid landmarks? Qualities and organization of traumatic memories with and without PTSD. Appl. Cogn. Psychol. 17 (6), 675–693. doi:10.1002/acp.894.

Bisby, J.A., Burgess, N., Brewin, C.R., 2020. Reduced memory coherence for negative events and its relationship to posttraumatic stress disorder. Curr. Dir. Psychol. Sci. 29 (3), 267–272. doi:10.1177/0963721420917691.

Bowman, C.R., Zeithamova, D., 2018. Abstract memory representations in the ventromedial prefrontal cortex and hippocampus support concept generalization. J. Neurosci. 38 (10), 2605–2614. doi:10.1523/JNEUROSCI.2811-17.2018.

Brett, M., Anton, J.L., Valabregue, R., Poline, J.B., 2002. Region of interest analysis using an SPM toolbox. In: Proceedings of the 8th International Conference on Functional Mapping of the Human Brain, 16, p. 497.

Brunec, I.K., Bellana, B., Ozubko, J.D., Man, V., Robin, J., Liu, Z.X., Grady, C., Rosenbaum, R.S., Winocur, G., Barense, M.D., Moscovitch, M., 2018. Multiple scales of representation along the hippocampal anteroposterior axis in humans. Curr. Biol. 28 (13), 2129–2135. doi:10.1016/j.cub.2018.05.016, e6.

Brunec, I.K., Robin, J., Olsen, R.K., Moscovitch, M., Barense, M.D., 2020. Integration and differentiation of hippocampal memory traces. Neurosci. Biobehav. Rev. 118, 196–208. doi:10.1016/j.neubiorev.2020.07.024.

Bunzeck, N., Düzel, E., 2006. Absolute coding of stimulus novelty in the human substantia Nigra/VTA. Neuron 51 (3), 369–379. doi:10.1016/j.neuron.2006.06.021.

Buysse, D., Reynolds, C., Monk, T., Berman, S., Kupfer, D., 1989. The pittsburgh sleep quality index—a new instrument for psychiatric practice and research. Psychiatry Res. 28 (2), 193–213. doi:10.1016/0165-1781(89)90047-4.

Chanales, A.J.H., Oza, A., Favila, S.E., Kuhl, B.A., 2017. Overlap among spatial memories triggers repulsion of hippocampal representations. Curr. Biol. 27 (15), 2307–2317. doi:10.1016/j.cub.2017.06.057, e5.

Chanales, A.J.H., Tremblay-McGaw, A.G., Drascher, M.L., Kuhl, B.A., 2021. Adaptive repulsion of long-term memory representations is triggered by event similarity. Psychol. Sci. 32 (5), 705–720. doi:10.1177/0956797620972490.

Cohn-Sheehy, B.I., Delarazan, A.I., Crivelli-Decker, J.E., Reagh, Z.M., Mundada, N.S., Yonelinas, A.P., Zacks, J.M., Ranganath, C., 2021a. Narratives bridge the divide between distant events in episodic memory. Mem. Cognit. doi:10.3758/s13421-021-01178-x.

Cohn-Sheehy, B.I., Delarazan, A.I., Reagh, Z.M., Crivelli-Decker, J.E., Kim, K., Barnett, A.J., Zacks, J.M., Ranganath, C., 2021b. The hippocampus constructs narrative memories across distant events. Curr. Biol. 31 (22), 4935–4945. doi:10.1016/j.cub.2021.09.013, e7.

Collin, S.H.P., Milivojevic, B., Doeller, C.F., 2015. Memory hierarchies map onto the hippocampal long axis in humans. Nat. Neurosci. 18 (11), 1562–1564. doi:10.1038/nn.4138.

Collin, S.H.P., Milivojevic, B., Doeller, C.F., 2017. Hippocampal hierarchical networks for space, time, and memory. Curr. Opin. Behav. Sci. 17, 71–76. doi:10.1016/j.cobeha.2017.06.007.

Cowan, E.T., Fain, M., O'Shea, I., Ellman, L.M., Murty, V.P, 2021. VTA and anterior hippocampus target dissociable neocortical networks for post-novelty enhancements. J. Neurosci. 41 (38), 8040–8050. doi:10.1523/JNEUROSCI.0316-21.2021.

Dandolo, L.C., Schwabe, L., 2018. Time-dependent memory transformation along the hippocampal anterior–posterior axis. Nat. Commun. 9 (1), 1205. doi:10.1038/s41467-018-03661-7.

Danner, D., Rammstedt, B., Bluemke, M., Treiber, L., Berres, S.,Soto, C., & John, O. P. (2016).Die deutsche Version des Big Five Inventory 2 (BFI-2). Zusammenstellung sozialwissenschaftlicher Items und Skalen [German version of the Big Five Inventory 2 (BFI-2)]. Mannheim, Germany: GESIS. https://doi.org/10.6102/zis247

de-Quervain, D.J.F., Roozendaal, B., McGaugh, J.L., 1998. Stress and glucocorticoids impair retrieval of long-term spatial memory. Nature 394 (6695), 787–790. doi:10.1038/29542.

De Shetler, N.G., Rissman, J., 2017. Dissociable profiles of generalization/discrimination in the human hippocampus during associative retrieval. Hippocampus 27 (2), 115–121. doi:10.1002/hipo.22684.

Diamond, D.M., Campbell, A.M., Park, C.R., Halonen, J., Zoladz, P.R., 2007. The temporal dynamics model of emotional memory processing: a synthesis on the neurobiological basis of stress-induced amnesia, flashbulb and traumatic memories, and the yerkes-dodson law. Neural Plast. 2007, e60803. doi:10.1155/2007/60803.

Dimsdale-Zucker, H.R., Ritchey, M., Ekstrom, A.D., Yonelinas, A.P., Ranganath, C., 2018. CA1 and CA3 differentially support spontaneous retrieval of episodic contexts within human hippocampal subfields. Nat. Commun. 9 (1), 294. doi:10.1038/s41467-017-02752-1.

Duncan, K.D., Schlichting, M.L., 2018. Hippocampal representations as a function of time, subregion, and brain state. Neurobiol. Learn. Mem. 153, 40–56. doi:10.1016/j.nlm.2018.03.006.

Eichenbaum, H., 2004. Hippocampus: cognitive processes and neural representations that underlie declarative memory. Neuron 44 (1), 109–120. doi:10.1016/j.neuron.2004.08.028.

Epstein, R., Kanwisher, N., 1998. A cortical representation of the local visual environment. Nature 392 (6676), 598–601. doi:10.1038/33402.

Esterling, B.A., L'Abate, L., Murray, E.J., Pennebaker, J.W., 1999. Empirical foundations for writing in prevention and psychotherapy: mental and physical health outcomes. Clin. Psychol. Rev. 19 (1), 79–96. doi:10.1016/S0272-7358(98)00015-4.

Faivre, N., Dubois, J., Schwartz, N., Mudrik, L., 2019. Imaging object-scene relations processing in visible and invisible natural scenes. Sci. Rep. 9 (1), 1. doi:10.1038/s41598-019-38654-z, Article.

Favila, S.E., Chanales, A.J.H., Kuhl, B.A., 2016. Experience-dependent hippocampal pattern differentiation prevents interference during subsequent learning. Nat. Commun. 7 (1), 1. doi:10.1038/ncomms11066, Article.

Fritch, H.A., MacEvoy, S.P., Thakral, P.P., Jeye, B.M., Ross, R.S., Slotnick, S.D., 2020. The anterior hippocampus is associated with spatial memory encoding. Brain Res. 1732, 146696. doi:10.1016/j.brainres.2020.146696.

Gardner-Medwin, A.R., 1976. The recall of events through the learning of associations between their parts. Proc. R. Soc. Lond. B. Biol. Sci. 194 (1116), 375–402. doi:10.1098/rspb.1976.0084.

Goldfarb, E.V., Tompary, A., Davachi, L., Phelps, E.A., 2019. Acute stress throughout the memory cycle: diverging effects on associative and item memory. J. Exp. Psychol. Gen. 148 (1), 13–29. doi:10.1037/xge0000472.

Goodman, J., Leong, K.C., Packard, M.G., 2012. Emotional modulation of multiple memory systems: Implications for the neurobiology of post-traumatic stress disorder. Rev. Neurosci. 23 (5), 627–643. doi:10.1515/revneuro-2012-0049, –6.

Griffiths, B.J., Fuentemilla, L., 2020. Event conjunction: how the hippocampus integrates episodic memories across event boundaries. Hippocampus 30 (2), 162–171. doi:10.1002/hipo.23161.
Hannula, D.E., Libby, L.A., Yonelinas, A.P., Ranganath, C., 2013. Medial temporal lobe contributions to cued retrieval of items and contexts. Neuropsychologia 51 (12), 2322–2332. doi:10.1016/j.neuropsychologia.2013.02.011.
Hautzinger, M., Keller, F., Kühner, C., 2006. *Beck Depressions-Inventar (BDI-II). Revision*. Frankfurt/Main: Harcourt Test Services.
Horner, A.J., Bisby, J.A., Bush, D., Lin, W.J., Burgess, N., 2015. Evidence for holistic episodic recollection via hippocampal pattern completion. Nat. Commun. 6 (1), 1–11. doi:10.1038/ncomms8462.
Horner, A.J., Burgess, N., 2014. Pattern Completion in Multielement Event Engrams. Curr. Biol. 24 (9), 988–992. doi:10.1016/j.cub.2014.03.012.
Huffman, D.J., Stark, C.E.L., 2014. Multivariate pattern analysis of the human medial temporal lobe revealed representationally categorical cortex and representationally agnostic hippocampus. Hippocampus 24 (11), 1394–1403. doi:10.1002/hipo.22321.
Hulbert, J.C., Norman, K.A., 2015. Neural differentiation tracks improved recall of competing memories following interleaved study and retrieval practice. Cereb. Cortex 25 (10), 3994–4008.
Joëls, M., Fernandez, G., Roozendaal, B., 2011. Stress and emotional memory: a matter of timing. Trends Cogn. Sci. 15 (6), 280–288. doi:10.1016/j.tics.2011.04.004.
Kaplan, R., Horner, A.J., Bandettini, P.A., Doeller, C.F., Burgess, N., 2014. Human hippocampal processing of environmental novelty during spatial navigation. Hippocampus 24 (7), 740–750. doi:10.1002/hipo.22264.
Kim, J.J., Diamond, D.M., 2002. The stressed hippocampus, synaptic plasticity and lost memories. Nat. Rev. Neurosci. 3 (6), 453–462. doi:10.1038/nrn849.
Kim, J.J., Lee, H.J., Han, J.S., Packard, M.G., 2001. Amygdala is critical for stress-induced modulation of hippocampal long-term potentiation and learning. J. Neurosci. 21 (14), 5222–5228. doi:10.1523/JNEUROSCI.21-14-05222.2001.
Kirchner, W.K., 1958. Age differences in short-term retention of rapidly changing information. J. Exp. Psychol. 55 (4), 352–358. doi:10.1037/h0043688.
Kirschbaum, C., Pirke, K.M., Hellhammer, D.H., 1993. The 'Trier Social Stress Test' – a tool for investigating psychobiological stress responses in a laboratory setting. Neuropsychobiology 28 (1), 76–81. doi:10.1159/000119004, –2.
Koolschijn, R.S., Emir, U.E., Pantelides, A.C., Nili, H., Behrens, T.E.J., Barron, H.C., 2019. The hippocampus and neocortical inhibitory engrams protect against memory interference. Neuron 101 (3), 528–541. doi:10.1016/j.neuron.2018.11.042, e6.
Kriegeskorte, N., Mur, M., 2012. Inverse MDS: inferring dissimilarity structure from multiple item arrangements. Front. Psychol. 3. doi:10.3389/fpsyg.2012.00245.
Kriegeskorte, N., Mur, M., Bandettini, P.A., 2008. Representational similarity analysis—connecting the branches of systems neuroscience. Front. Syst. Neurosci. 2. doi:10.3389/neuro.06.004.2008.
Kudielka, B.M., Kirschbaum, C., 2005. Sex differences in HPA axis responses to stress: a review. Biol. Psychol. 69 (1), 113–132. doi:10.1016/j.biopsycho.2004.11.009.
Lange, I., Goossens, L., Michielse, S., Bakker, J., Lissek, S., Papalini, S., Verhagen, S., Leibold, N., Marcelis, M., Wichers, M., Lieverse, R., van Os, J., van Amelsvoort, T., Schruers, K., 2017. Behavioral pattern separation and its link to the neural mechanisms of fear generalization. Soc. Cogn. Affect. Neurosci. 12 (11), 1720–1729. doi:10.1093/scan/nsx104.
Laux, L., Glanzmann, P., Schaffner, P., Spielberger, C.D., Laux, L., Glanzmann, P., Schaffner, P., Spielberger, C.D., 1981. State-trait anxiety inventory—manual of the German version. Beltz.
Leal, S.L., Tighe, S.K., Jones, C.K., Yassa, M.A., 2014. Pattern separation of emotional information in hippocampal dentate and CA3. Hippocampus 24 (9), 1146–1155. doi:10.1002/hipo.22298.
LeDoux, J., 2007. The amygdala. Curr. Biol. 17 (20), R868–R874.
Libby, L.A., Reagh, Z.M., Bouffard, N.R., Ragland, J.D., Ranganath, C., 2019. The hippocampus generalizes across memories that share item and context information. J. Cogn. Neurosci. 31 (1), 24–35. doi:10.1162/jocn_a_01345.
Lohnas, L.J., Duncan, K., Doyle, W.K., Thesen, T., Devinsky, O., Davachi, L., 2018. Time-resolved neural reinstatement and pattern separation during memory decisions in human hippocampus. Proc. Natl Acad. Sci. 115 (31), E7418–E7427. doi:10.1073/pnas.1717088115.
Lupien, S.J., Lepage, M., 2001. Stress, memory, and the hippocampus: can't live with it, can't live without it. Behav. Brain Res. 127 (1), 137–158. doi:10.1016/S0166-4328(01)00361-8.
Marr, D., 1971. A theory of archicortical function. Proc. R. Soc. Lond. B Biol. Sci. 262, 23–81.
Milivojevic, B., Vicente-Grabovetsky, A., Doeller, C.F., 2015. Insight reconfigures hippocampal-prefrontal memories. Curr. Biol. 25 (7), 821–830. doi:10.1016/j.cub.2015.01.033.
Molitor, R.J., Sherrill, K.R., Morton, N.W., Miller, A.A., Preston, A.R., 2021. Memory reactivation during learning simultaneously promotes dentate Gyrus/CA $_{2,3}$ pattern differentiation and CA $_{1}$ memory integration. J. Neurosci. 41 (4), 726–738. doi:10.1523/JNEUROSCI.0394-20.2020.
Morton, N.W., Sherrill, K.R., Preston, A.R., 2017. Memory integration constructs maps of space, time, and concepts. Curr. Opin. Behav. Sci. 17, 161–168. doi:10.1016/j.cobeha.2017.08.007.
Muller, R.U., Kubie, J.L., 1987. The effects of changes in the environment on the spatial firing of hippocampal complex-spike cells. J. Neurosci. 7 (7), 1951–1968. doi:10.1523/JNEUROSCI.07-07-01951.1987.
Nakazawa, K., Quirk, M.C., Chitwood, R.A., Watanabe, M., Yeckel, M.F., Sun, L.D., Kato, A., Carr, C.A., Johnston, D., Wilson, M.A., Tonegawa, S., 2002a. Requirement for hippocampal CA3 NMDA receptors in associative memory recall. Science doi:10.1126/science.1071795.
Nakazawa, K., Quirk, M.C., Chitwood, R.A., Watanabe, M., Yeckel, M.F., Sun, L.D., Kato, A., Carr, C.A., Johnston, D., Wilson, M.A., Tonegawa, S., 2002b. Requirement for hippocampal CA3 NMDA receptors in associative memory recall. Science 297 (5579), 211–218. doi:10.1126/science.1071795, (New York, N.Y.).
Nili, H., Wingfield, C., Walther, A., Su, L., Marslen-Wilson, W., Kriegeskorte, N., 2014. A toolbox for representational similarity analysis. PLoS Comput. Biol. 10 (4), e1003553. doi:10.1371/journal.pcbi.1003553.
Norman, K.A., O'Reilly, R.C, 2003. Modeling hippocampal and neocortical contributions to recognition memory: A complementary-learning-systems approach. Psychol. Rev. 110 (4), 611–646. doi:10.1037/0033-295X.110.4.611.
Phelps, E.A., LeDoux, J.E., 2005. Contributions of the amygdala to emotion processing: from animal models to human behavior. Neuron 48 (2), 175–187. doi:10.1016/j.neuron.2005.09.025.
Porcelli, A.J., Lewis, A.H., Delgado, M.R., 2012. Acute stress influences neural circuits of reward processing. Front. Neurosci. 6, 157.
Pruessner, J.C., Kirschbaum, C., Meinlschmid, G., Hellhammer, D.H., 2003. Two formulas for computation of the area under the curve represent measures of total hormone concentration versus time-dependent change. Psychoneuroendocrinology 28 (7), 916–931. doi:10.1016/S0306-4530(02)00108-7.
Robin, J., Moscovitch, M., 2017. Details, gist and schema: hippocampal–neocortical interactions underlying recent and remote episodic and spatial memory. Curr. Opin. Behav. Sci. 17, 114–123. doi:10.1016/j.cobeha.2017.07.016.
Rolls, E., 2013. The mechanisms for pattern completion and pattern separation in the hippocampus. Front. Syst. Neurosci. 7. https://www.frontiersin.org/article/10.3389/fnsys.2013.00074.
Rolls, E.T., Kesner, R.P., 2006. A computational theory of hippocampal function, and empirical tests of the theory. Prog. Neurobiol. 79 (1), 1–48. doi:10.1016/j.pneurobio.2006.04.005.
Roozendaal, B., McEwen, B.S., Chattarji, S., 2009. Stress, memory and the amygdala. Nat. Rev. Neurosci. 10 (6), 423–433. doi:10.1038/nrn2651.
Roozendaal, B., McGaugh, J.L., 2011. Memory modulation. Behav. Neurosci. 125 (6), 797–824. doi:10.1037/a0026187.
Rudebeck, P.H., Rich, E.L., 2018. Orbitofrontal cortex. Curr. Biol. 28 (18), R1083–R1088. doi:10.1016/j.cub.2018.07.018.
Sandi, C., Pinelo-Nava, M.T., 2007. Stress and memory: behavioral effects and neurobiological mechanisms. Neural Plast. 2007, e78970. doi:10.1155/2007/78970.
Schapiro, A.C., Turk-Browne, N.B., Botvinick, M.M., Norman, K.A., 2017. Complementary learning systems within the hippocampus: a neural network modelling approach to reconciling episodic memory with statistical learning. Philos. Trans. R. Soc. B Biol. Sci. 372 (1711), 20160049. doi:10.1098/rstb.2016.0049.
Schlichting, M.L., Mumford, J.A., Preston, A.R., 2015. Learning-related representational changes reveal dissociable integration and separation signatures in the hippocampus and prefrontal cortex. Nat. Commun. 6 (1), 1–10. doi:10.1038/ncomms9151.
Schlichting, M.L., Preston, A.R, 2017. The hippocampus and memory integration: building knowledge to navigate future decisions. In: Hannula, D.E., Duff, M.C. (Eds.), The Hippocampus from Cells to Systems: Structure, Connectivity, and Functional Contributions to Memory and Flexible Cognition. Springer International Publishing, pp. 405–437. doi:10.1007/978-3-319-50406-3_13.
Schulz, P., Schlotz, W., 1999. Trierer Inventar zur Erfassung von chronischem Sre (TICS): Skalenkonstruktion, teststatistische Überprüfung und Validierung der Skala Arbeitsüberlastung, [The Trier Inventory for the Assessment of Chronic Stress (TICS), Scale construction, statistical testing, and validation of the scale work overload]. Diagnostica 45 (1), 8–19. doi:10.1026//0012-1924.45.1.8.
Schwabe, L., 2017. Memory under stress: from single systems to network changes. Eur. J. Neurosci. 45 (4), 478–489. doi:10.1111/ejn.13478.
Schwabe, L., Hermans, E.J., Joëls, M., Roozendaal, B., 2022. Mechanisms of memory under stress. Neuron doi:10.1016/j.neuron.2022.02.020.
Schwabe, L., Joëls, M., Roozendaal, B., Wolf, O.T., Oitzl, M.S., 2012a. Stress effects on memory: an update and integration. Neurosci. Biobehav. Rev. 36 (7), 1740–1749. doi:10.1016/j.neubiorev.2011.07.002.
Schwabe, L., Oitzl, M.S., Philippsen, C., Richter, S., Bohringer, A., Wippich, W., Schachinger, H., 2007. Stress modulates the use of spatial versus stimulus-response learning strategies in humans. Learn. Mem. 14 (1), 109–116. doi:10.1101/lm.435807, –2.
Schwabe, L., Tegenthoff, M., Höffken, O., Wolf, O.T., 2012b. Simultaneous glucocorticoid and noradrenergic activity disrupts the neural basis of goal-directed action in the human brain. J. Neurosci. 32 (30), 10146–10155. doi:10.1523/JNEUROSCI.1304-12.2012.
Schwabe, L., Wolf, O.T., 2012. Stress modulates the engagement of multiple memory systems in classification learning. J. Neurosci. 32 (32), 11042–11049. doi:10.1523/JNEUROSCI.1484-12.2012.
Sep, M.S.C., van Ast, V.A., Gorter, R., Joëls, M., Geuze, E., 2019. Time-dependent effects of psychosocial stress on the contextualization of neutral memories. Psychoneuroendocrinology 108, 140–149. doi:10.1016/j.psyneuen.2019.06.021.
Shields, G.S., Sazma, M.A., McCullough, A.M., Yonelinas, A.P., 2017. The effects of acute stress on episodic memory: a meta-analysis and integrative review. Psychol. Bull. 143 (6), 636.
Steyer, R., Schwenkmezger, P., Notz, P., Eid, M., 1997. Der Mehrdimensionale Befindlichkeitsfragebogen. Hogrefe.
Tulving, E., 1983. Elements of episodic memory. Oxford University Press.
van Ast, V.A., Cornelisse, S., Meeter, M., Joëls, M., Kindt, M., 2013. Time-dependent effects of cortisol on the contextualization of emotional memories. Biol. Psychiatry 74 (11), 809–816. doi:10.1016/j.biopsych.2013.06.022.
VanElzakker, M., Zoladz, P., Thompson, V., Park, C., Halonen, J., Spencer, R., Diamond, D., 2011. Influence of pre-training predator stress on the expression of c-fos mRNA in the hippocampus, amygdala, and striatum fol-

lowing long-term spatial memory retrieval. Front. Behav. Neurosci. 5. https://www.frontiersin.org/articles/10.3389/fnbeh.2011.00030.

Vogel, S., Fernández, G., Joëls, M., Schwabe, L., 2016. Cognitive adaptation under stress: a case for the mineralocorticoid receptor. Trends Cogn. Sci. 20 (3), 192–203. doi:10.1016/j.tics.2015.12.003.

Vogel, S., Kluen, L.M., Fernández, G., Schwabe, L., 2018. Stress leads to aberrant hippocampal involvement when processing schema-related information. Learn. Mem. 25 (1), 21–30. doi:10.1101/lm.046003.117.

Vogel, S., Schwabe, L., 2016. Stress in the zoo: Tracking the impact of stress on memory formation over time. Psychoneuroendocrinology 71, 64–72. doi:10.1016/j.psyneuen.2016.04.027.

Walther, A., Nili, H., Ejaz, N., Alink, A., Kriegeskorte, N., Diedrichsen, J., 2016. Reliability of dissimilarity measures for multi-voxel pattern analysis. Neuroimage 137, 188–200. doi:10.1016/j.neuroimage.2015.12.012.

Wammes, J., Norman, K.A., Turk-Browne, N., 2022. Increasing stimulus similarity drives nonmonotonic representational change in hippocampus. ELife 11, e68344. doi:10.7554/eLife.68344.

Wang, Q., Bui, V.K., Song, Q., 2015. Narrative organisation at encoding facilitated children's long-term episodic memory. Memory 23 (4), 602–611. doi:10.1080/09658211.2014.914229.

Weiner, K.S., Sayres, R., Vinberg, J., Grill-Spector, K., 2010. fMRI-adaptation and category selectivity in human ventral temporal cortex: regional differences across time scales. J. Neurophysiol. 103 (6), 3349–3365. doi:10.1152/jn.01108.2009.

Weymar, M., Schwabe, L., 2016. Amygdala and emotion: the bright side of It. Front. Neurosci. 10. https://www.frontiersin.org/article/10.3389/fnins.2016.00224.

Wirz, L., Bogdanov, M., Schwabe, L., 2018. Habits under stress: mechanistic insights across different types of learning. Curr. Opin. Behav. Sci. 20, 9–16. doi:10.1016/j.cobeha.2017.08.009.

Wirz, L., Wacker, J., Felten, A., Reuter, M., Schwabe, L., 2017. A deletion variant of the α2b-adrenoceptor modulates the stress-induced shift from "Cognitive" to "Habit" memory. J. Neurosci. 37 (8), 2149–2160. doi:10.1523/JNEUROSCI.3507-16.2017.

Zhou, J., Benson, N.C., Kay, K.N., Winawer, J., 2018. Compressive temporal summation in human visual cortex. J. Neurosci. 38 (3), 691–709. doi:10.1523/JNEUROSCI.1724-17.2017.