COGNITIVE NEUROSCIENCE

Post-retrieval stress impairs subsequent memory depending on hippocampal memory trace reinstatement during reactivation

Hendrik Heinbockel[1], Anthony D. Wagner[2], Lars Schwabe[1]*

Upon retrieval, memories can become susceptible to meaningful events, such as stress. Post-retrieval memory changes may be attributed to an alteration of the original memory trace during reactivation-dependent reconsolidation or, alternatively, to the modification of retrieval-related memory traces that impact future remembering. Hence, how post-retrieval memory changes emerge in the human brain is unknown. In a 3-day functional magnetic resonance imaging study, we show that post-retrieval stress impairs subsequent memory depending on the strength of neural reinstatement of the original memory trace during reactivation, driven by the hippocampus and its cross-talk with neocortical representation areas. Comparison of neural patterns during immediate and final memory testing further revealed that successful retrieval was linked to pattern-dissimilarity in controls, suggesting the use of a different trace, whereas stressed participants relied on the original memory representation. These representation changes were again dependent on neocortical reinstatement during reactivation. Our findings show disruptive stress effects on the consolidation of retrieval-related memory traces that support future remembering.

INTRODUCTION

Memories are highly dynamic entities and can be changed even long after initial consolidation (*1*). One potential mechanism underlying the dynamics of memory is reconsolidation. More specifically, it is hypothesized that consolidated and seemingly stable memories can re-enter a transient state of instability when their neural signature is reactivated, requiring another period of stabilization called reconsolidation (*2*). Critically, post-reactivation memories are argued to be labile again and can be weakened, strengthened, or updated (*3*, *4*). While reconsolidation theory posits that post-retrieval manipulations alter the original memory trace, an alternative account emphasizes that new memories are formed during retrieval, which may then compete with the original memory trace during later attempts to remember (*5*). In general, the impact of event retrievals on subsequent memory, whether based on reconsolidation or interference processes, is fundamental for updating knowledge in light of new information and thus has crucial implications for educational, legal, or clinical contexts (*3*, *4*, *6*). In clinical settings, post-retrieval changes in memory might represent a unique window of opportunity to modify unwanted memories. In line with this notion, some initial evidence suggests that post-reactivation manipulations can attenuate symptoms in disorders such as addiction, posttraumatic stress disorder (PTSD), or anxiety disorders (*7*–*10*), whereas others (*11*–*14*) report failed attempts to implement reconsolidation-based interventions. Given the fundamental relevance and far-reaching implications of post-retrieval memory processes, understanding the involved brain mechanisms is essential.

Over the past two decades, animal studies provided important insights into the mechanisms of reconsolidation-based memory modifications. These studies elucidated the molecular mechanisms underlying reconsolidation (*15*), demonstrated that reconsolidation is protein synthesis-dependent (*16*, *17*), and showed that it involves the recruitment of brain areas relevant for initial memory formation, such as the amygdala in fear memory or the hippocampus in contextual memory (*18*, *19*). A recent study in transgenic mice indicated that effective post-reactivation manipulations involve the reactivation of a discrete subset of neurons within the engram (*20*), suggesting that the original memory trace contributes to memory changes during reconsolidation. Comparable evidence from humans is missing and, in particular, it remains unclear what happens to the original memory trace in humans after retrieval. In general, there are relatively few studies that used functional neuroimaging to shed light on the mechanisms of post-retrieval memory changes in the human brain. Although functional magnetic resonance imaging (fMRI) is not able to capture event-specific engrams at the level of individual neurons, extant fMRI studies in humans suggest that, in line with the rodent studies, effective post-retrieval manipulations are accompanied by neural activity changes in brain areas that were also recruited during the retrieval itself, including the hippocampus (*21*–*24*). However, a deeper understanding of the neural mechanisms of post-retrieval memory updating in humans is hampered by a lack of studies that assessed memory representations across all memory stages, i.e., initial encoding, memory trace reactivation (during memory retrieval), and delayed recall of the reactivated memory.

After retrieval, reactivated memories are sensitive to various manipulations, ranging from new learning experiences (*22*, *25*–*27*) to pharmacological interventions (*21*, *28*) or electroconvulsive shock (*29*). Of particular relevance for memory in the context of eyewitness testimony or mental disorders are the effects of acute stress on memory updating. It is now well established that acute stress exerts a major impact on memory (*30*–*32*). Although research has focused mostly on stress effects on memory formation and retrieval, it has been repeatedly shown that stress may influence subsequent remembering also when experienced after retrieval (*33*–*39*). Stressful events are often unpredictable and associated with a prediction error (*40*–*42*), which is thought to trigger reconsolidation processes (*43*–*45*). Moreover, stress mediators, such as glucocorticoids or noradrenaline, may act directly on brain areas critically implicated in memory reconsolidation, including the hippocampus (*46*–*49*). Post-retrieval

[1]Department of Cognitive Psychology, Universität Hamburg, 20146 Hamburg, Germany. [2]Department of Psychology, Wu Tsai Neurosciences Institute, Building 420, Stanford, CA 94305, USA.
*Corresponding author. Email: lars.schwabe@uni-hamburg.de

stress is generally assumed to impair subsequent memory [(*35*, *37*, *38*, *50*, *51*); but see (*52*, *53*) for an opposite effect], which may have implications for understanding memory distortions in stress-related disorders and for potential treatment approaches for these disorders. Despite the relevance of post-retrieval stress effects, the neural mechanisms underlying these effects in humans are completely unknown. In particular, it remains unclear to what extent these effects depend on the neural reactivation of the memory trace.

The present study aimed to elucidate the mechanisms underlying post-retrieval memory changes in humans in general and the mechanisms involved in post-retrieval effects of stress in particular. To this end, we used a 3-day paradigm, in which 80 healthy participants first learned a series of word-picture pairs, followed by an immediate four-alternative-forced-choice (4AFC) cued recall test. Twenty-four hours later, participants performed a memory cueing task in which half of the learned word-picture pairs were cued during a 2AFC cued recall test, whereas the other half were not cued [for a similar design; see (*54*)]. Only cued and correct associations are posited to undergo reconsolidation (*54*), and interference accounts highlight the critical relevance of context memory reinstatement (*5*). Note that we use the term "retrieval" to refer to the conscious recall of learned items and "reactivation" to refer to the neural level of memory. Immediately after the memory cueing task, participants underwent a standardized stressor [Trier Social Stress Test, TSST; (*55*)] or a non-stressful control procedure. Another 24 hours later, participants completed a final 4AFC cued recall memory test, probing the influence of post-retrieval stress on future remembering. Critically, brain activity was measured using fMRI during all stages of the memory paradigm.

Given that the majority of previous studies suggest a detrimental effect of post-retrieval stress on subsequent memory (*35*, *38*, *50*), we hypothesized that stress after retrieval would impair subsequent memory, especially for associations that were strongly reactivated. Given that associative memories rely on the hippocampus and its interaction with neocortical representation areas, such as the posterior cingulate cortex (PCC), which is assumed to represent memory traces formed during retrieval (*56*, *57*), and ventral temporal cortex [VTC; (*56*, *58*, *59*)], which represents the specific stimulus categories (scenes and objects) encountered during encoding (*60*, *61*), we predicted that these areas and the connectivity between them would be critically implicated in memory reactivation and the effects of post-retrieval stress on subsequent memory. Building on recent findings in rodents (*62*), we further expected that the impairing effects of post-retrieval stress would critically depend on the reinstatement of the neural event representation during retrieval. To probe this reactivation, we leveraged multivariate pattern analysis (MVPA) across experimental days. Specifically, we used, on the one hand, the reactivation of category-based (scene versus object) information and, on the other hand, the event-specific representational similarity between encoding and retrieval as indicators of event-level memory reactivation (i.e., cortical reinstatement). Last, and most critically, we analyzed the impact of neural reactivation and stress on the subsequent availability and use of the original memory representation by comparing the memory representations during successful recall on the immediate (day 1) and final (day 3) memory tests.

RESULTS

Day 1: Successful memory encoding

In a cued recall task immediately after encoding (Fig. 1), participants were presented with all previously studied (old) words, as well as 152 new words. On each trial, participants were requested to select one out of four response options: "new," "old," "old/scene," and "old/object" (4AFC decision). Participants correctly recognized old words in 74.3% of the trials (responses "old," "old/scene," and "old/object" to old word cues), with a false alarm rate of 19.5% (responses "old," "old/scene," and "old/object" to new word cues; tables S1 and S2). In 51.6% of the trials in which a studied word was presented, participants selected the correct image category associated with the word (e.g. "old/scene" when the associate had been a scene), reflecting associative category hits. In 14.7% of the trials in which a studied word was presented, participants chose the wrong picture category

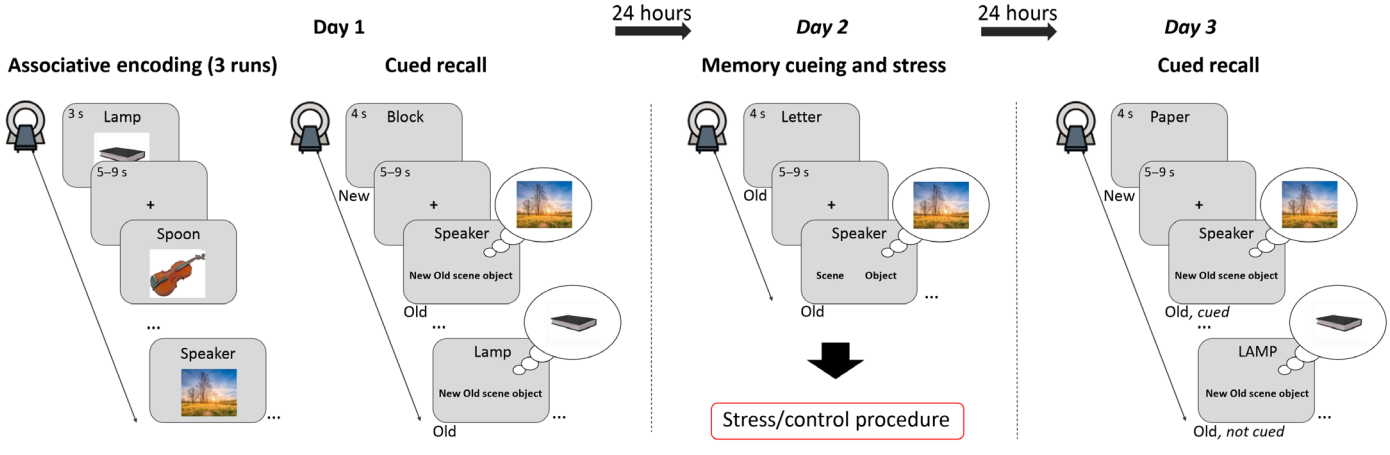

Fig. 1. Experimental task. Stress effects on memory reconsolidation were probed in a 3-day paradigm, with fMRI measurements on all 3 days. On day 1, participants encoded word-picture pairs across three runs and underwent an immediate 4AFC cued recall test including both previously presented and new words. On day 2, 24 hours later, we attempted to reactivate memories for half of the word-picture pairs by presenting the corresponding word and having participants make a 2AFC cued recall decision (i.e., cued pairs); the other half of day 1 pairs was not cued. Following this cued recall task, participants experienced a standardized stress or control manipulation. On day 3, again 24 hours later, participants completed a final 4AFC cued recall test for all encoded word-picture pairs.

(e.g., responding "old/object" when the associate had been a scene), reflecting associative category errors.

A signal detection theory–based memory sensitivity analysis yielded an average associative d' of 1.18 (SE = 0.09). Immediate cued recall performance (associative d') was comparable for later cued and correct pairs (associative hits during memory cueing on day 2) and pairs not cued on day 2 [$F_{(1,78)} = 0.33$, $P = 0.566$, $\eta^2 < 0.001$]; day 1 cued recall performance also did not differ between the stress and control groups (all main and interaction effects, Ps > 0.098; table S3). Moreover, groups did not differ in subjective mood, autonomic arousal, or salivary cortisol before the immediate cued recall test on day 1 (all Ps > 0.141; table S4). Last, whole-brain univariate fMRI analyses of associative retrieval success effects compared associative category hits to all other memory outcomes (i.e., associative misses) on the immediate cued recall data on day 1. This analysis included the within-subject factor Cued (cued and correct on day 2 versus not cued) and the between-subjects factor Group, and revealed no significant main or interaction effects of Cued or Group, suggesting comparable retrieval success-related neural correlates of memory for later cued and correct (day 2) and not cued pairs and in the two groups on day 1.

Day 2: Neural pattern reinstatement tracks successful memory reactivation

On day 2, participants returned to the MRI scanner and underwent a memory cueing task (2AFC cued recall; Fig. 1), which aimed to cue associative memory and neural reactivation of half of the word-picture pairs that were encoded on day 1. Groups did not differ in subjective mood, autonomic arousal, or salivary cortisol before memory cueing on day 2 (all Ps > 0.184). During the memory cueing task, participants saw 72 old cue words (36 that had been paired with scenes, 36 that had been paired with objects, along with 8 catch trials; see Materials and Methods). For each probe, they were instructed to retrieve the corresponding picture in as much detail as possible and to indicate whether it was an object or a scene. Overall, participants performed well in this task, choosing the correct picture category in 72.6% of trials (SE = 1.5%; chance = 50%). The associative hit rate during the memory cueing task did not differ between stress and control groups [$t(66.62) = -0.57$, $P = 0.569$, $d = 0.13$; stress: 73.5% (SE = 1.7%); control: 71.7% (SE = 2.6%)]. Because of the absence of new foils in this task (2AFC cued recall), memory outcomes were restricted to associative hits (i.e., correct trials) and associative misses (i.e., incorrect trials). To shed light on the neural signature of successful memory reactivation (i.e., retrieval success effects) on day 2, we first analyzed univariate brain activity related to associative hits versus associative misses in the memory cueing task. A whole-brain fMRI analysis across both groups revealed significant activation clusters that included regions previously associated with episodic retrieval (*54*, *55*, *63*), with a prominent spatial cluster that included the PCC, angular gyrus, superior parietal cortex, and medial prefrontal cortex (mPFC) [from here on called cortical reactivation cluster; (−8, −36, −42), $t = 9.93$, $P_{(FWE)} < 0.001$). Additional clusters were found in the ventral temporal/occipital cortices [from here on designated as VTC clusters; left: (−26, −52, −18), $t = 7.20$, $P_{(FWE)} < 0.001$; right: (32, −40, −12), $t = 6.19$, $P_{(FWE)} < 0.001$] and left hippocampus [(−30, −30, −14), $t = 6.66$, $P_{(FWE)} < 0.001$; see table S6]. We did not observe any group differences in retrieval success-related univariate brain activity during the memory cueing task.

Building on these univariate results, we used psycho-physiological interaction (PPI) analyses to investigate the functional connectivity between retrieval success–related areas. Seeds were based on our univariate findings and the existing literature on episodic retrieval (*64*) and included the hippocampus, the VTC clusters, and the PCC. Results revealed significant functional coupling between left hippocampus and left VTC [SVC; (−40, −52, −18), $t = 4.29$, $P\text{corr}_{(FWE)} = 0.024$] as well as between PCC and bilateral VTC (SVC; left: (−42, −54, −20), $t = 4.24$, $P\text{corr}_{(FWE)} = 0.012$; right: (42, −48, −24), $t = 4.68$, $P\text{corr}_{(FWE)} = 0.008$], highlighting the cross-talk of these regions during successful memory retrieval.

Next, we asked to what extent successful retrieval is linked to reactivation (i.e., pattern reinstatement) in visual cortical areas thought to represent scenes and objects. To address this question, we leveraged MVPA using a logistic classification approach (Fig. 2A). We trained a classifier on data from an independent functional localizer task to distinguish scenes from objects in the VTC (see results S1 for localizer training performance). Testing the classifier on all memory cueing task trials confirmed that associative hits were accompanied by higher cortical reinstatement of visual category evidence in VTC compared to associative misses [$F_{(1,78)} = 29.33$, $P < 0.001$, $\eta^2 = 0.16$]. There were no significant differences between the stress and control groups (all main and interaction effects, Ps > 0.121; Fig. 2B).

We then applied the trained classifier selectively to associative hits of scenes and objects during the memory cueing task. Overall, the classifier was able to distinguish associative hits of scenes from objects, performing significantly above chance-level [M(±SE) = 55.0% (±1.3%); chance = 50%; $t(79) = 5.40$, $P < 0.001$, $d = 0.60$]. By contrast, the classifier did not distinguish associative misses of scenes from objects [M(±SE) = 48.2% (±1.6%); $P = 0.266$]. Mean category pattern reinstatement strength (logits) of associative hit trials in VTC did not differ between groups [$t(74.88) = -1.14$, $P = 0.258$, $d = 0.25$]. Last, using an individual-difference approach, we tested whether mean category pattern reinstatement (logits) was related to the day 2 associative hit rate. A multiple regression model, including the classifier evidence from associative hits of scenes and objects, revealed a main effect of Reinstatement ($b = 20.47$, $P = 0.019$, $R^2_{multiple} = 0.14$, model $P = 0.009$; Fig. 2C), but no effect of Group and no Group × Reinstatement interaction (both Ps > 0.776), confirming that the extent of category-specific neural reinstatement (i.e., reactivation) during associative hits in the VTC predicted memory performance during the memory cueing task (which occurred before the stress manipulation), without differences between groups.

Next, we tested whether the retrieval-related univariate activity varied with a behavioral marker of the strength of memory retrieval. To this end, we used participants' reaction times during associative hits on the memory cueing task as a proxy of memory strength/confidence (*65*, *66*). More specifically, we used LMMs predicting day 2 single-trial estimates of hippocampal, PCC, and VTC univariate activity by their corresponding reaction times. For hippocampus, VTC, and PCC, we found that higher activity was related to faster reaction times and by implication higher memory strength/confidence (main effect Hippocampus RT: $\beta = -0.34 \pm 0.13$, $t = -3.72$, $P < 0.001$, $R^2_{marginal} = 0.01$; main effect VTC RT: $\beta = -0.35 \pm 0.11$, $t = -3.13$, $P = 0.002$, $R^2_{marginal} = 0.01$; main effect PCC RT: $\beta = -0.44 \pm 0.11$, $t = -3.89$, $P < 0.001$, $R^2_{marginal} = 0.01$; Fig. 2D). We observed no significant group difference in any of the regions (all interaction Ps > 0.110). These findings suggest that, on associative hits, hippocampal, VTC, and PCC activity tracks the strength of

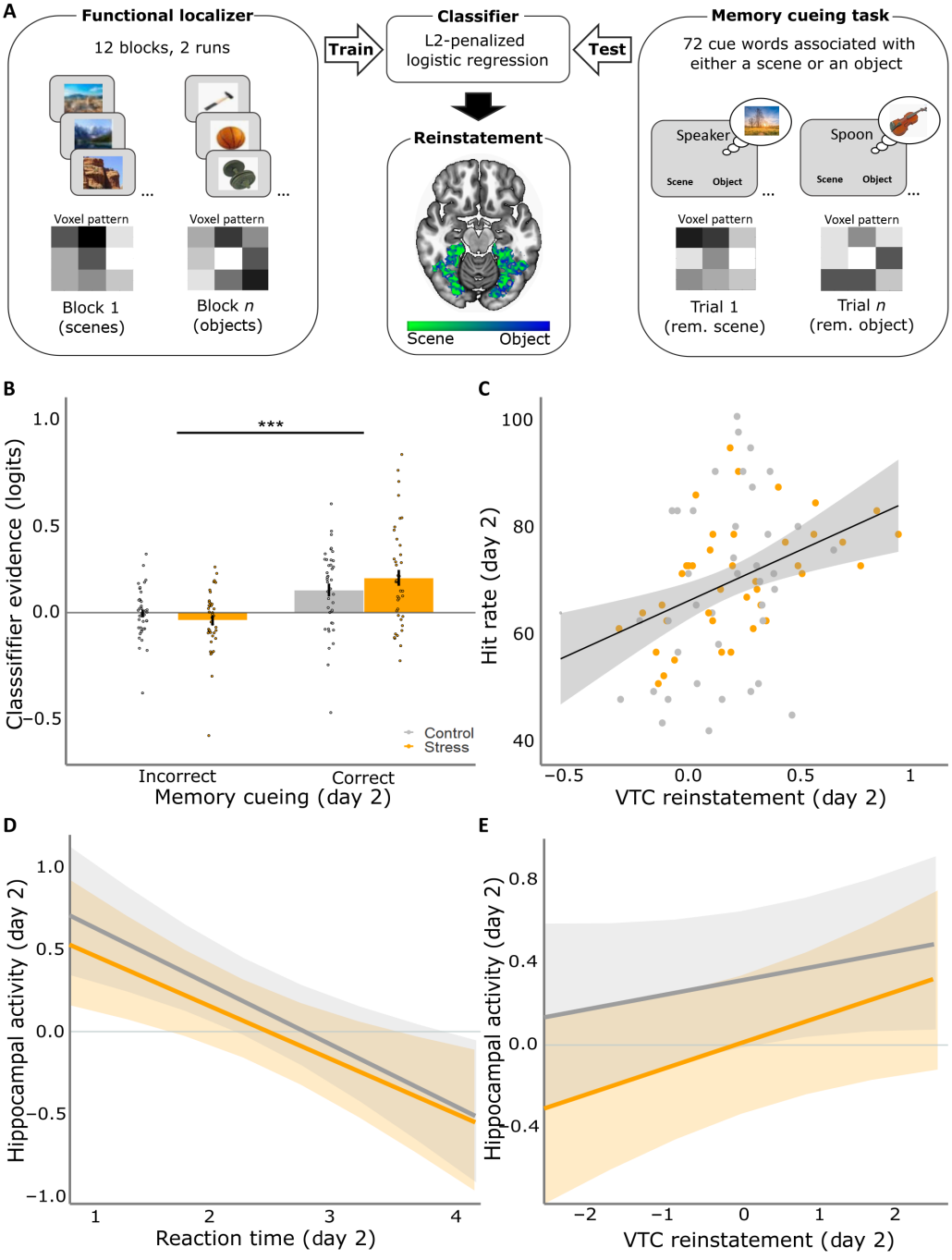

Fig. 2. Tracking memory reactivation by hippocampal activity and category pattern reinstatement in the ventral temporal cortex (VTC). (**A**) Trial-wise category pattern reinstatement was derived from multivariate voxel pattern analysis in the VTC. The logistic classifier (L2 penalized logistic regression) first received data from an independent visual localizer task, in which participants were presented with images of scenes, objects, and faces in two runs. The algorithm was trained to classify VTC activity category patterns between scenes and objects. The trained classifier was then tested on data from the day 2 memory cueing task, probing to what extent the classifier could detect a category pattern corresponding to the participants' correct choice ("scene" or "object") as the associate belonging to the presented cue word. Average classification performance in the memory cueing task of one subject is depicted on an MNI brain template. (**B**) The application of the classifier to the memory cueing task showed that the associative hit rate in the memory cueing task was associated with higher classifier accuracy. (**C**) Next, when probing the relation of VTC category pattern reinstatement during memory cueing and actual task performance, results showed that the average VTC category pattern reinstatement strength significantly predicted day 2 associative hit rate (without difference between groups). (**D**) Decreasing reaction times (as a proxy for memory strength/confidence) of associative hit trials were accompanied by increasing hippocampal activity, suggesting that hippocampal activity tracks the strength of memory reactivation. (**E**) In addition to reaction times, category pattern reinstatement of associative hit trials in the VTC (derived from MVPA) was positively related to hippocampal activity (*z*-scored beta) on a single-trial level, highlighting the role of the hippocampus in successful memory reactivation and supporting the idea that the hippocampus couples with information in cortical areas (i.e., VTC) during successful retrieval. Data represent means (±SE); ***$P < 0.001$.

memory reactivation. Further supporting this interpretation, we also observed that the strength of category-level VTC pattern reinstatement on associative hits (as measured with trial-level MVPA logits) was positively related to univariate hippocampal activity ($\beta = 0.08 \pm 0.03$, $t = 2.23$, $P = 0.026$, $R^2_{marginal} = 0.01$; Fig. 2E). Again, the association between hippocampal activity and VTC pattern reinstatement did not differ between the stress and control groups (interaction $P = 0.620$).

Collectively, these findings show that successful retrieval during the memory cueing task on day 2 was associated with (i) activation of the hippocampus, PCC, and VTC; (ii) functional connectivity of the VTC with both the hippocampus and PCC, as well as between the hippocampus and a network of cortical memory areas (resembling the default mode network); and (iii) category-specific pattern reinstatement in the VTC. Moreover, hippocampal activity appeared to track memory reactivation strength, as reflected in associations with reaction time (indicative of memory strength/confidence) and the degree of VTC pattern reinstatement during associative hits in the memory cueing task.

Day 2: Successful stress induction after memory cueing

About 5 min after the memory cueing task on day 2, participants underwent, out of the scanner, either the TSST ($n = 40$) or a non-stressful control manipulation ($n = 40$). Significant changes in subjective mood, autonomic arousal (expressed as changes in blood pressure and heart rate), and salivary cortisol confirmed successful stress induction by the TSST.

Specifically, analyses of subjective ratings revealed that negative mood significantly increased after the stress but not after the control manipulation (Time × Group interaction: $F_{(4,312)} = 10.85$, $P < 0.001$, $\eta^2 = 0.02$). Post hoc t tests showed higher negative mood ratings in the stress compared to the control group after the experimental manipulation [$t(77.32) = 2.79$, $P = 0.001$, $d = 0.62$], while there were no significant group differences at any other time point of measurement (all Ps > 332). Similarly, restlessness increased after the experimental manipulation [Time × Group interaction: $F_{(4,312)} = 11.11$, $P < 0.001$, $\eta^2 = 0.02$; table S5]. Tiredness did not differ between groups across day 2 [Time × Group interaction: $F_{(4,312)} = 0.99$, $P = 0.411$, $\eta^2 = 0.01$]. Last, participants in the stress group rated the experimental manipulation as significantly more stressful [M(±SE): stress = 7.25 (0.41), control = 3.95 (0.37); $t(77.36) = -5.95$, $P < 0.001$, $d = 1.33$], unpleasant [M(±SE): stress = 6.52 (0.50), control = 3.67 (0.37); $t(72.17) = -4.53$, $P < 0.001$, $d = 1.01$], and difficult [M(±SE): stress = 6.55 (0.46), control = 3.67 (0.38); $t(75.52) = -4.80$, $P < 0.001$, $d = 1.07$; table S5] than those in the control group.

Analyses of physiological measures revealed the following: (i) systolic blood pressure, (ii) diastolic blood pressure, (iii) heart rate, and (iv) salivary cortisol concentrations all significantly increased in stressed but not in control participants [Time × Group interactions: (i) $F_{(5,390)} = 45.37$, $P < 0.001$, $\eta^2 = 0.13$; Fig. 3A; (ii) $F_{(5,390)} = 31.30$, $P < 0.001$, $\eta^2 = 0.12$; Fig. 3B; (iii) $F_{(5,390)} = 18.41$, $P < 0.001$, $\eta^2 = 0.06$; Fig. 3C; (iv) $F_{(4,312)} = 12.43$, $P < 0.001$, $\eta^2 = 0.07$; Fig. 3D]. Post hoc t tests showed significantly higher systolic and diastolic blood pressure in the stress compared to the control group during [+5 min relative to treatment onset; systolic: $t(70.92) = -7.13$, $P < 0.001$, $d = 1.59$; diastolic: $t(77.28) = -8.30$, $P < 0.001$, $d = 1.85$) and immediately after [+15 min relative to treatment onset; systolic: $t(68.83) = -2.49$, $P = 0.015$, $d = 0.55$; diastolic: $t(76.77) = -2.01$, $P = 0.047$, $d = 0.45$] the experimental manipulation, while there were no significant differences at any other time point (systolic: all Ps > 0.111; diastolic: all Ps > 378).

Similarly, post hoc t tests also showed significantly higher heart rates in stressed compared to control participants during the experimental manipulation [+5 min relative to treatment onset; $t(65.95) = -4.95$, $P < 0.001$, $d = 1.10$], but not at any other time point (all Ps > 0.543). Last, stressed participants had significantly higher salivary cortisol concentrations compared to controls immediately after the experimental manipulation [+15 min relative to treatment onset: $t(64.47) = -5.80$, $P < 0.001$, $d = 1.29$], which remained elevated during the rest period [+30 min: $t(48.95) = -6.15$, $P < 0.001$, $d = 1.37$; +45 min: $t(51.69) = -4.35$, $P < 0.001$, $d = 0.97$], while there were no significant group differences in cortisol before the experimental manipulation (both Ps > 0.554). In sum, the TSST led to a significant subjective, autonomic, and endocrine stress response after memory cueing, during the putative reconsolidation window.

Day 3: Post-retrieval stress disrupts subsequent remembering depending on neural memory reinstatement during reactivation

On day 3, 24 hours after memory cueing and stress manipulation, participants returned to the MRI scanner and underwent a final 4AFC cued recall task, to probe the impact of post-retrieval stress on subsequent memory (Fig. 1). On day 3, the groups did not differ in subjective mood, autonomic arousal, or salivary cortisol (all Ps > 0.248; see table S4). This cued recall test was identical to the immediate 4AFC cued recall test on day 1, except that the test included foils that had not been presented before. Overall, the average associative d' was 1.69 (SE = 0.09), indicating good memory performance. Across groups, memory was significantly better for category-level associations that were cued and correct (i.e., associative hits) compared to cued and not retrieved (i.e., associative misses) on day 2 [$F_{(1,78)} = 213.11$, $P < 0.001$, $\eta^2 = 0.55$] and those not cued on day 2 [$F_{(1,78)} = 35.10$, $P < 0.001$, $\eta^2 = 0.14$; Fig. 4A]. These findings show that the memory cueing manipulation was effective. According to the memory reconsolidation concept as well as interference accounts of post-retrieval manipulations that disrupt later remembering, stress should affect subsequent memory only for associations that were cued and correct (i.e., associative hits) before the stress manipulation on day 2 but not for not cued associations. A mixed-design analysis of variance (ANOVA) revealed neither a Cued × Group interaction nor a main effect of Group (all Fs > 1.33, all Ps >0.251), suggesting that the presentation of the word cue on day 2 alone was not sufficient to induce a stress-related modulation of the testing effect. Likewise, univariate and multivariate analyses revealed no Cued × Group interactions in whole-brain or region of interest (ROI) activity, PPI connectivity strength, or cortical reinstatement. Because the day 2 memory cueing task was 2AFC, one possibility is that some associative hits, while correct category responses, were not based on memory reactivation (i.e., the word cue was recognized without associate reactivation and the participant guessed the correct category or the word cue was not recognized and the participant guessed the correct category). It is for this reason that neural assays of memory reactivation were thought to be incisive.

Specifically, we reasoned that for post-retrieval stress to affect subsequent memory performance, a memory representation needs strong reactivation before the stress manipulation on day 2. Therefore, we next tested whether the strength of the neural signals during associative hit trials (day 2) predicts whether post-retrieval stress influences subsequent memory. We did not observe any group interaction

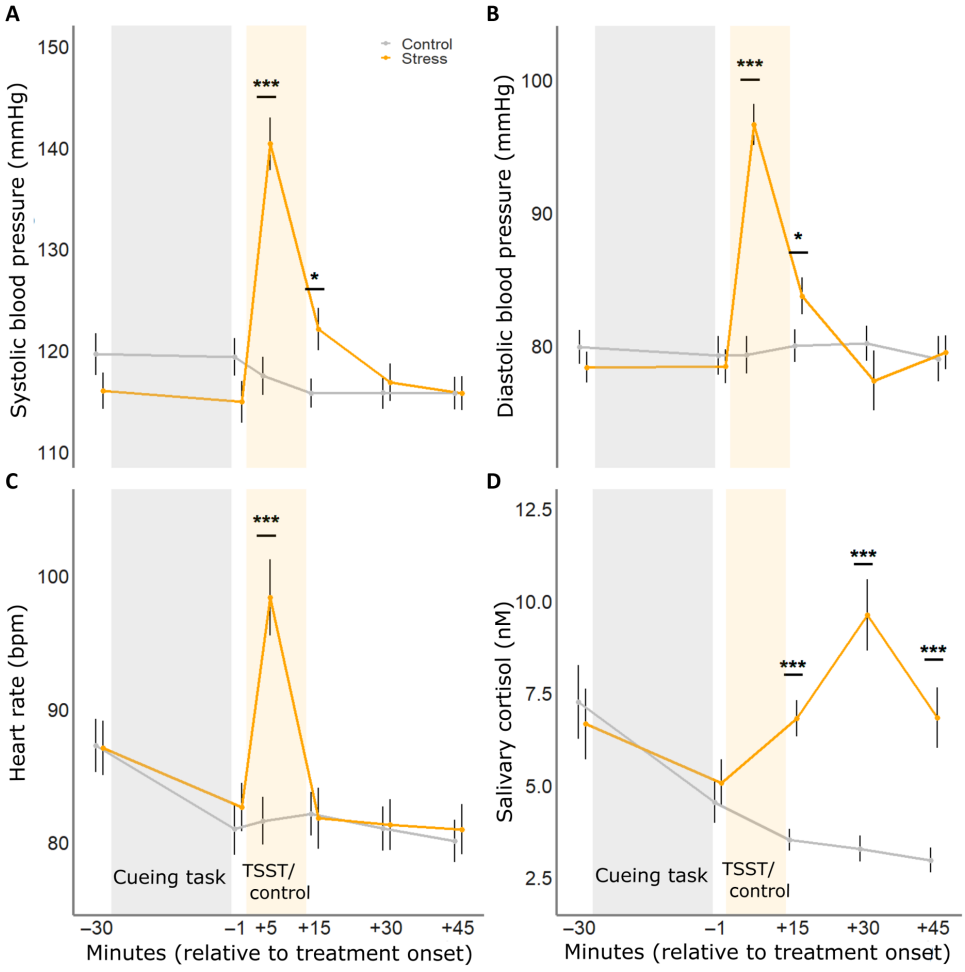

Fig. 3. Physiological stress response to the TSST and control procedurerespectively. Significant increases in (**A**) systolic and (**B**) diastolic blood pressure as well as (**C**) heart rate in response to the TSST but not in response to the control manipulation. (**D**) The stress group further showed a significant increase in concentrations of salivary cortisol up to 45 min after the TSST. Groups did not differ in either physiological measure before the memory cueing task or before the treatment. Gray shades indicate the periods of the memory cueing task serving neural reactivation, and yellow shades indicate the onset and duration of the TSST/control procedure. Data represent means (±SE); *$P < 0.05$ and ***$P < 0.001$.

on subsequent memory using univariate retrieval-related activity (day 3) in single brain areas (i.e., hippocampus, PCC, and VTC) as predictors, suggesting that activation in a single brain area may not be sufficient to enable effects of post-retrieval stress. Therefore, we next used functional connectivity between PCC, VTC clusters, hippocampus, and the cortical reactivation cluster during associative hits (day 2) to predict whether post-retrieval stress influences day 3 memory. Whereas strong connectivity between hippocampus and the cortical reactivation cluster during associative hits (day 2) was linked to increased day 3 associative category hit rate in the control group, high cortical-hippocampal connectivity on day 2 was associated with an impaired associative category hit rate on day 3 in the stress group [Group × Cued interaction: $\beta = -17.83$, $t(76) = -2.77$, $P = 0.007$, model $P = 0.047$, $R^2_{multipal} = 0.09$; Fig. 4B]. Thus, reactivation-related patterns of functional connectivity were associated with memory strengthening when post-retrieval conditions were not stressful (i.e., a positive testing effect) but were associated with increased forgetting when individuals experienced stress after day 2 cued recall (i.e., a negative testing effect). While these findings were based on a PPI across the entire memory cueing session, to further examine the relationship between the strength of memory reactivation and the effects of post-retrieval stress, we next tested whether hippocampus-PCC connectivity at the single-trial level (day 2) predicts effects of post-retrieval stress on day 3 memory. A generalized linear mixed model (GLMM) that predicted the day 3 probability of associative category hits showed a significant interaction of Group with hippocampal and PCC activity during associative hits ($\beta = -0.12 \pm 0.01$, $z = -2.27$, $P = 0.023$, $R^2_{marginal} = 0.03$, post hoc slope test: beta $= -0.24 \pm 0.10$, $z = -2.17$, $P = 0.027$, $R^2_{marginal} = 0.03$; Fig. 4C), suggesting that post-retrieval stress differentially impaired 24-hour–delayed memory when the associative hit trials on day 2 were accompanied by stronger trial-wise coactivation of hippocampus and PCC (i.e., strong neural reactivation).

Another important neural measure of reactivation strength is the extent of cortical reinstatement (*67*). Consistent with prior work, category pattern reinstatement (assessed by MVPA) in the VTC was linked to successful retrieval on day 2 (*68*). Accordingly, we further analyzed whether the mean strength of VTC category pattern

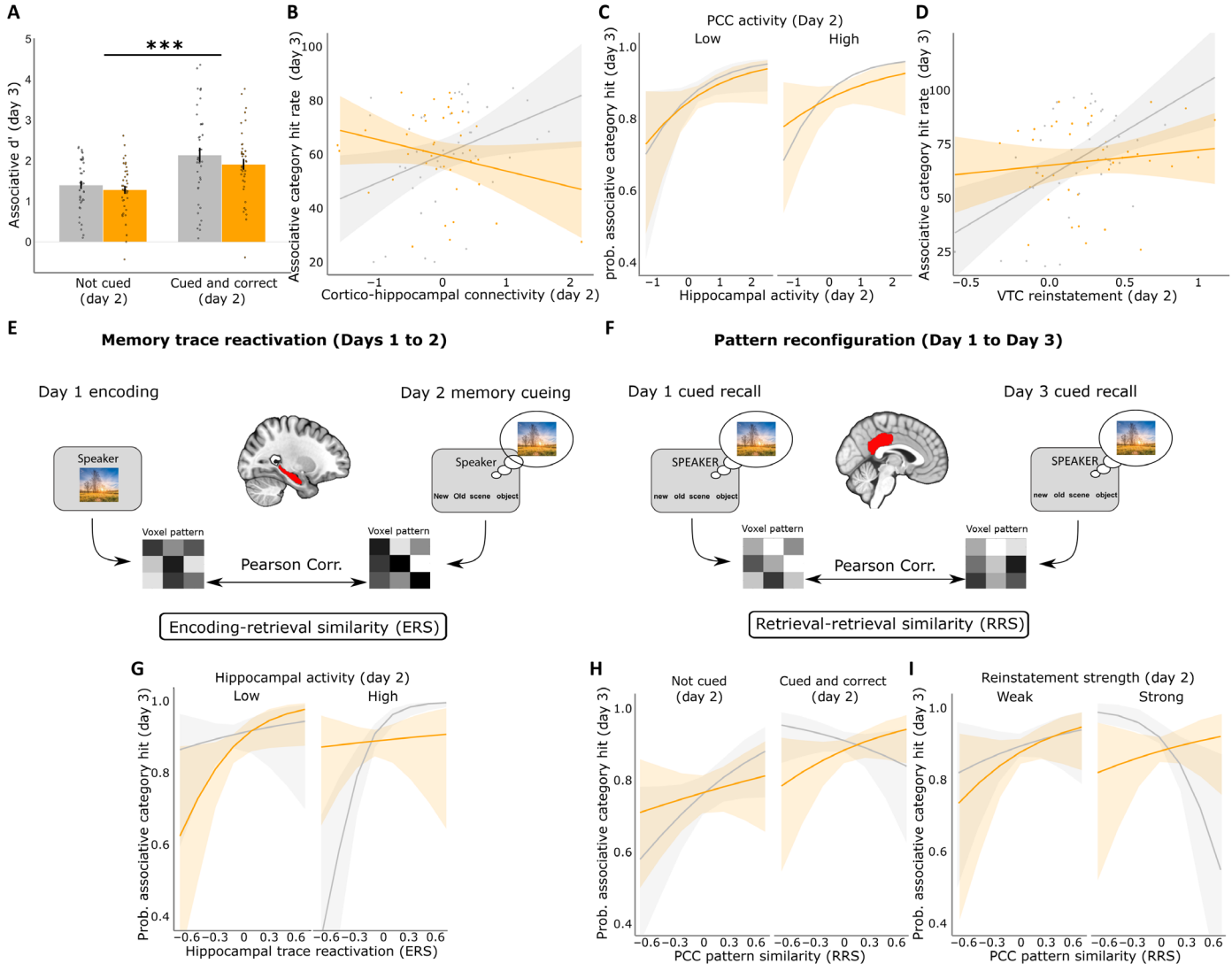

Fig. 4. Post-retrieval effects of stress on memory linked to trace reactivation on day 2 and neural pattern reconfiguration from days 1 to 3. (**A**) On day 3, memory (associative *d'*) was significantly better for pairs that were successfully retrieved on day 2 compared to those that were not successfully retrieved and those that were not cued on day 2, without group differences. (**B**) Higher cortical-hippocampal connectivity (PPI) on day 2 was associated with decreased day 3 performance in the stress group but with increased day 3 memory in controls. This pattern was found on single-trial level (**C**) including the BOLD activity of PCC and hippocampus, showing a stress-induced performance decrease when both regions were highly active during memory cueing. (**D**) Average category pattern reinstatement in the VTC during day 2 correlated positively with day 3 memory in controls. Post-retrieval stress abolished this association, leading to impaired performance when VTC reinstatement was high. (**E**) Memory trace reactivation was indexed by representational pattern similarity from days 1 to 2 (encoding-retrieval similarity, ERS). (**F**) Pattern reconfiguration was estimated by the cays 1 to 3 representational pattern similarity (retrieval-retrieval similarity, RRS). (**G**) Strong memory trace reactivation (day 1 to day 2 ERS) together with high hippocampal activity during day 2 increased day 3 performance in controls. In the stress group, day 3 performance was reduced when hippocampal activity and hippocampal ERS were high during day 2 reactivation. (**H**) Successful retrieval of cued trials on day 3 relied on a decrease in PCC pattern similarity from days 1 to 3 in controls. This relation was reversed in the stress group, which further relied on high pattern similarity in the PCC. (**I**) In controls, strong VTC reinstatement together with low PCC pattern similarity was related to successful retrieval. In the stress group, this effect was reversed resulting in lower memory. ***$P < 0.001$.

reinstatement during associative hits on day 2 predicted the influence of post-retrieval stress on day 3 memory. Linear regression analysis showed a significant Group × Reinstatement interaction [$\beta = -38.40$, $t(76) = -2.33$, $P = 0.023$, model $P = 0.005$, $R^2_{marginal} = 0.10$; Fig. 4D]. Whereas a high level of VTC pattern reinstatement was linked to an enhanced associative category hit rate (day 3) in control participants (i.e., a positive testing effect), stronger VTC category pattern reinstatement associative hits on day 2 was not associated with an enhanced subsequent associative category hit rate (day 3) in the stress group (i.e., a null testing effect) further documenting the disruptive effects of post-retrieval stress on subsequent memory for strongly reactivated memories.

While these participant-level findings document a relationship between VTC category pattern reinstatement and the effects of post-retrieval stress, we next tested whether the strength of reactivation of individual associative pairs (i.e., trial-level effects) interacts with

the impact of post-retrieval stress on later memory. We derived an index of memory trace reactivation, separately for the hippocampus, VTC, and PCC (Fig. 4E), by calculating the neural similarity of the pattern elicited by each word-picture pair from encoding (day 1) to each pair's elicited pattern during memory cueing before the stress/control manipulation (day 2), i.e. encoding-retrieval similarity (ERS) as an indicator of neural reinstatement (*69*–*71*). The resulting index reflects the extent to which a neural pattern was reinstated (at the trial level) during memory cueing 24 hours later. Initial analysis of the ERS estimates revealed significantly higher hippocampal similarity on the category level compared to the event level [$t(77) = -2.82$, $P = 0.006$, $d = 0.48$). We used a GLMM predicting the day 3 probability of associative category hits with the predictors Group, Hippocampal reactivation (ERS), and univariate Hippocampal activity from day 2. We included hippocampal activity from day 2 because of its high predictive power in relation to pattern reinstatement as well as memory confidence during the memory cueing session. Moreover, a high ERS could also result from a very low activation of a brain region during both encoding and retrieval, but we predicted that post-retrieval stress would affect memory in particular when memory cueing was associated with hippocampal ERS associated with a high level of hippocampal involvement. In line with this hypothesis, our results showed a significant interaction of the three predictors, indicating that successful recall in the control group is associated with strong memory trace reactivation (i.e., higher ERS) in the hippocampus accompanied by high hippocampal activity. In contrast to this pattern in the control group, there was a weaker positive relationship between the co-occurrence of high hippocampal ERS and strong hippocampal activity on day 2 and 24-hour-delayed recall in stressed participants (Group × ERS × HC activity interaction: $\beta = -2.36 \pm 0.85$, $z = -2.76$, $P = 0.006$, $R^2_{\text{marginal}} = 0.02$; post hoc slope test: $\beta = -0.20 \pm 0.09$, $z = -2.20$, $P = 0.028$, $R^2_{\text{marginal}} = 0.03$; Fig. 4F). That is, stress tempered the benefits of the testing effect especially for the memories most strongly reactivated on day 2. As it is possible that similarity estimates are artificially inflated by univariate activity from the same region (*72*), we used a two-step control analysis. First, we submitted both factors to a linear mixed model predicting Hippocampal ERS with hippocampal activity from day 2, which did not yield a significant linear relation of the two ($\beta = -0.45 \pm 0.65$, $t = -0.69$, $P = 0.512$, $R^2_{\text{marginal}} > 0.001$). Moreover, the resulting residuals of the prediction were treated as "true" similarity values, now independent from any univariate relation. These residual similarities were then used in the above described GLMM and confirmed our previous results (Group × $\text{ERS}_{\text{residual}}$ × HC activity interaction: $\beta = -0.34 \pm 0.12$, $z = -2.76$, $P = 0.006$, $R^2_{\text{marginal}} = 0.02$; post hoc slope test: $\beta = -0.17 \pm 0.07$, $z = -2.20$, $P = 0.028$, $R^2_{\text{marginal}} = 0.02$), thus ruling out that our ERS findings are driven by univariate activity. Further models using data derived from the PCC and VTC [including the predictors Group, Memory trace reactivation (ERS), and univariate activity (day 2)] did not yield a significant main effect or interaction with Group in either model (all Ps > 0.082).

Day 3: Post-retrieval stress inhibits pattern reconfiguration of highly reinstated memories

Last, and perhaps most critically from a mechanistic perspective, we leveraged representational similarity analysis (RSA) to track changes in association-specific neural patterns (i.e., pattern reconfiguration) from day 1 immediate recall to day 3 final recall (see Materials and Methods). In the first step, we estimated the trial-wise representational similarity across cued recall tests in the hippocampus, VTC, and PCC (days 1 to 3; Fig. 4G). Next, we used GLMMs using single-trial Representational similarities, Group, and Cued as predictors of the day 3 associative category hit probability. For the hippocampus and VTC, there were no significant interaction effects (all interaction Ps > 0.535; fig. S1). For the PCC, however, we observed a significant interaction of single-trial Representational similarity between days 1 and 3 recall, Group, and Cued ($\beta = 3.19 \pm 1.62$, $z = 1.97$, $P = 0.049$, $R^2_{\text{marginal}} = 0.06$; Fig. 4H). This interaction effect showed that subsequent retrieval (day 3) of cued and correct trials on day 2 (i.e., associative hits), but not of not-cued trials on day 2, was associated with an increase in pattern dissimilarity in the PCC from days 1 to 3 in controls, whereas in stressed participants increased pattern similarity in the PCC from days 1 to 3 was linked to subsequent retrieval on day 3 of associations cued and correct on day 2 (i.e., associative hits). The post hoc slope test, however, showed only a trend-level difference for subsequently retrieved trials (day 3) between groups ($\beta = -2.28 \pm 1.29$, z-ratio $= -1.76$, $P = 0.076$). These results point to a potential impact of stress on the mechanisms of consolidation and/or reconsolidation of the reactivation event on day 2—that is, stress may foster competition, and thus interference, between the memory traces on day 1 and the memory traces that are encoded during day 2 memory cueing. The above pattern was only observed at the event level but not at the category level, suggesting that post-retrieval stress specifically affected the trial-specific representations [event-level ERS Cued and correct (day 2) – event-level ERS Not Cued: $t(79) = -2.82$, $P = 0.006$, $d = 0.33$; event-level ERS Cued and correct (day 2) – category-level ERS Cued and correct (day 2): $t(79) = 4.57$, $P < 0.001$, $d = 0.66$].

To further pursue this possibility, we next included the day 2 Reinstatement index derived from the MVPA to test whether the effect of stress on representational pattern change from days 1 to 3 in the PCC is predicted by day 2 category pattern reinstatement in the VTC. To this end, we classified associative hit (day 2) trials as strongly reactivated and weakly reactivated based on a median split on the MVPA category pattern reinstatement. This median-split approach allowed us to incorporate all associative hit trials as a function of the reinstatement index (day 2) as well as not-cued trials within one model, i.e., we distinguished not reactivated, weakly reactivated, and strongly reactivated events and tested whether Reactivation level interacted with Group and single-trial pattern similarities between days 1 and 3 in the PCC, to predict 24-hour–delayed probability of associative category hits. This analysis yielded a significant three-way interaction ($\beta = 5.49 \pm 2.11$, $z = 2.59$, $P = 0.009$, $R^2_{\text{marginal}} = 0.06$; Fig. 4I). In the control group, increased pattern dissimilarity in the PCC from days 1 to 3 was linked to enhanced memory only when the memory reinstatement was strong on day 2. This raises the possibility that day 3 recall in the control group was probabilistically more likely to be based on memory traces that were encoded during memory reactivation on the day 2 memory cueing test than on the traces encoded on day 1 (i.e., a shift away from reactivating day 1 traces in favor of strongly represented day 2 traces that were then consolidated post-retrieval). In the stress group, in turn, increased pattern similarity between days 1 and 3 in the PCC predicted a higher probability of day 3 associative category hits. Post hoc slope tests between groups showed that especially strongly reactivated trials remained unaffected by stress, as successful retrieval did not rely on an increase in pattern dissimilarity, which was the

case in the control group (not reactivated: $\beta = 0.91 \pm 0.99$ *z*-ratio = 0.92, *P*corr = 1; weak reactivation: $\beta = -0.54 \pm 1.76$, $z = -0.31$, *P*corr = 1; strong reactivation: $\beta = -4.58 \pm 1.88$, $z = -2.43$, *P*corr = 0.045). This raises the possibility that stress disrupted consolidation of the memories encoded during day 2 reactivation, resulting in day 3 recall more likely being based on the original day 1 memory traces.

Whereas the previous analysis distinguished trials based on day 2 VTC category pattern reinstatement (as derived from MVPA), we next investigated the interplay of memory trace reactivation with the observed changes in pattern similarity from days 1 to 3 during memory retrieval by subdividing trials into strongly and weakly reactivated trials based on the days 1 to 2 ERS, i.e., the degree of neural reinstatement during associative hits during the memory cueing task. In a GLMM, we predicted the probability of day 3 associative category hits by Memory trace reactivation strength (ERS) in the hippocampus on day 2, Group, and D1-to-D3 pattern similarity. However, for the hippocampus, no main effect or interaction including the factor Group reached significance (all *P*s > 0.375). Results for the PCC model showed a nonsignificant trend for a three-way interaction of the three predictors, providing trend-level evidence that stronger pattern reactivation (ERS) and pattern reconfiguration (days 1 to 3) predict associative category hits depending on the experimental group ($\beta = 3.75 \pm 1.93$, $z = 1.93$, $P = 0.053$, $R^2_{\text{marginal}} = 0.06$). In the control group, a strong memory trace reactivation accompanied by an increase in pattern dissimilarity from days 1 to 3 appeared to facilitate subsequent retrieval on day 3. In contrast to the control participants, strong pattern reactivation was coupled to an increase in pattern similarity from days 1 to 3 in stressed participants. However, since this interaction effect was only a trend, it needs to be interpreted with caution.

DISCUSSION

Future remembering is often affected by event retrievals that intervene between learning and the future attempt to remember. While positive "testing effects" are often observed (*73*), wherein prior retrieval increases the probability of future remembering, retrieval can sometimes lead to forgetting. Some attribute such memory impairments to a reconsolidation mechanism that involves reactivation-related changes to the original memory trace (*74*), while others emphasize the role of multiple memory traces formed at initial encoding and subsequent retrieval (*5*). Here, we aimed to shed light on the neural mechanisms underlying post-retrieval memory changes in general and those involved in post-retrieval stress effects on (re)consolidation in particular. Our findings show that post-retrieval stress can impair subsequent memory and that this effect depends critically on the degree to which neural event representations are reactivated in the hippocampus and VTC during the intervening retrieval.

Participants acquired (day 1) and retrieved (day 2) the word-picture associations overall very well, with cued recall performance being comparable to previous associative memory studies (*75*, *76*). The detrimental impact of post-retrieval stress on subsequent memory is in line with several previous studies suggesting that stress impairs a putative reconsolidation mechanism [(*35*, *37*, *38*, *50*, *51*); but see (*52*, *53*) for opposite findings], whereas initial consolidation is typically enhanced by (post-encoding) stress. The apparently opposite effects of stress on initial consolidation and post-retrieval (re)consolidation are in line with the idea that post-encoding consolidation and post-retrieval (re)consolidation are distinct processes that differ, for instance, with respect to the involved molecular and brain mechanisms (*77*). Our findings meaningfully extend previous behavioral studies on stress and reconsolidation by showing that the mere presentation of a reminder cue may not be sufficient for post-retrieval stress to alter memory, which accounts for the absence of a cued-by-group interaction at the purely behavioral level. In non-stressed controls, memory cueing was linked to enhanced memory performance 24 hours later, resembling the well-known testing effect (*73*, *78*). The overall enhancement for cued and correct compared to not cued events (word-picture pairs) is important as it suggests that the partial cueing procedure used was successful and that representations of non-cued events were not indirectly reactivated through the retrieval cueing of the other half of the events. At the least, the degree of reactivation appeared to be substantially stronger for cued and correct events and we did not observe any effects for non-cued associations, neither at the behavioral nor at the neural level.

As expected, several cortical and subcortical areas were involved in successful retrieval during the day 2 memory cueing scans. Among these, the hippocampus appeared to play a particularly important role. Hippocampal activity tracked not only participants' reaction times on successfully retrieved trials during memory cueing but also the strength of trial-wise VTC cortical reinstatement. In non-stressed controls, this VTC reinstatement and hippocampal-cortical connectivity predicted day 3 memory performance. Similarly, reinstatement of the day 1 encoding representation during day 2 memory cueing (i.e., ERS) was predictive of day 3 memory performance when ERS was accompanied by high hippocampal activity, thus demonstrating again a key role of the hippocampus in the post-retrieval modification of memory. These findings in the control group are compatible with two possible interpretations: (i) the idea that memory can be strengthened by reconsolidation mechanisms, as long as there are no factors that interfere with the post-retrieval re-stabilization (*50*); or, alternatively, (ii) accounts that posit that a new memory trace is formed during neural reactivation that may then support future remembering (*5*, *79*).

We observed a markedly different pattern of results in the stress group. For stressed participants, there was no benefit of day 2 VTC reinstatement for day 3 memory, and day 3 performance was even impaired when hippocampal-cortical connectivity and episodic reinstatement were high during day 2 memory cueing. Thus, the same reactivation events that enhanced subsequent memory in controls were linked to diminished memory in participants who were exposed to stress after memory cueing. Again, these findings are compatible with two possible interpretations. First, based on reconsolidation theory, it could be argued that the stressor after memory cueing interfered with the re-stabilization of the reactivated and hence labile memory representation, thus negatively affecting subsequent memory on day 3. Our finding that the disruptive effect of post-retrieval stress depends on the successful behavioral and strong neural reactivation of the day 1 event representation on day 2 dovetails with recent evidence from rodents (*62*), suggesting a critical role of the original memory trace in memory changes during post-retrieval memory changes. Second, and alternatively, from a multiple memory trace perspective, these observations are consistent with the possibility that consolidation of newly formed retrieval-based memories is disrupted by stress, thus diminishing or eliminating

the potential testing effect. Notably, however, it is hardly possible in humans to distinguish a new trace formed during retrieval from an altered original trace. While the formation of a new trace would favor Multiple Trace Theory (MTT), the modification of an existing memory representation by stress would be more in line with reconsolidation theory.

From the perspective of canonical reconsolidation theory, the outcomes of our representational analyses may present a challenge. Specifically, while we observed that post-retrieval stress disrupts subsequent memory depending on hippocampal memory reinstatement during memory cueing, our data further revealed that post-retrieval stress altered the neural underpinnings of subsequent successful remembering. The PCC has been implicated in memory retrieval, the integration of information into memory networks, and the modification of behavior (*80*–*82*). Thus, the PCC appeared to be a prime candidate for the representation of new memory traces formed during retrieval. In line with this idea, in the control group, subsequent memory was not only linked to strong neural reactivation on day 2, reflected in VTC reinstatement and ERS, but was also associated with increased pattern dissimilarity between the days 1 and 3 representations in the PCC. By contrast, the stress group did not show such an increase in dissimilarity; instead, high similarity of neural patterns in the PCC from days 1 to 3 related to successful retrieval. In other words, whereas successful day 3 retrieval appeared to be based on a memory representation that was dissimilar from the original day 1 representation in controls, successful retrieval appeared to differentially rely on the original memory representation in stressed controls. Assuming that day 2 retrieval resulted in the reactivation, modification, and reconsolidation of the original trace in control participants, then the observed pattern dissimilarity in controls could be explained by a reconsolidation account. The increased pattern dissimilarity would reflect the altered (reconsolidated) memory representation. However, the pattern observed in stressed participants is more difficult to explain by reconsolidation theory. According to the reconsolidation concept, stress after reactivation should have weakened (or, more broadly, altered) the original memory trace, which would not explain why stressed participants, relative to controls, relied more on the original day 1 event representation during successful day 3 retrieval. In an attempt to reconcile this finding with reconsolidation theory, one might argue that stress impairs the reconsolidation of the reactivated memory representation and that subsequent memory depends on the extent to which memories underwent reconsolidation. In other words, one would have to assume that not all event representations underwent reconsolidation and that those that did not (and hence remained similar to the original representation) are better remembered than those that were reactivated and then affected by stress while being in the proposed labile state.

While the above reconsolidation account of the outcomes of our representational analyses may be viable, the collective pattern of results in controls and stressed participants can be readily accounted for by multiple trace theory (*79*). According to this account, in controls, a new trace is formed during day 2 retrieval, which may then differentially support subsequent memory on day 3. For this reason, the day 3 memory representation is less similar to the day 1 memory representation. By contrast, stress seems to interfere with the consolidation of the new day 2 retrieval-based trace, thus leaving stressed participants differentially dependent on the availability of the original (day 1) representation during day 3 recall. Again, this effect of post-retrieval stress was critically dependent on the neural reinstatement of the memory trace during day 2 memory cueing. While our pattern of results appears to be overall more in line with a multiple trace theory account than with a reconsolidation-based account, it is important to note that these two accounts need not be mutually excluded and that the conclusions drawn may depend on the level of analysis. In particular, our conclusions are based on evidence at the cognitive and systems level and we cannot rule out that data at the molecular or cellular level would provide evidence more in line with a reconsolidation account. Moreover, we note that the evidence in favor of the multiple trace theory–based account came mainly from the single RSA model comparing the neural representation patterns on days 1 and 3.

Classical studies of the testing effect also included a group that simply re-studied the learning material, to show the beneficial effects of retrieval practice (*73*, *83*). Here, we did not aim to specifically probe the testing effect, and for the putative reconsolidation mechanism, a re-study group would have been less informative. In particular, it is assumed that unexpected events reactivate a memory trace and open the putative reconsolidation window (*43*–*45*). Although no feedback was provided in our task, a prediction error was represented in the incomplete reminder structure of the cued recall (*29*, *84*). In a re-study group, there may not be meaningful reactivation due to the absence of any prediction error given a partial cue. Moreover, there would be no explicit retrieval demands associated with a re-study condition, which may further decrease the extent of memory reactivation. Thus, for a mere re-study group, we would expect limited memory reactivation, which appears to be critical for the observed effects of post-retrieval stress on subsequent remembering.

A major advantage of whole-brain fMRI studies in humans, compared to animal studies, is that they allow analyses of the connectivity among multiple brain areas and networks. Here, we observed a large network of brain regions involved in successful memory reactivation, which included, in addition to the hippocampus and VTC, core areas of the default mode network (*85*). Traditionally, the DMN has been associated with self-referential and internally focused mental processes when individuals were not engaged in a specific task (*86*, *87*). Accumulating evidence further suggests that the DMN is involved in a range of cognitive functions (*88*–*90*). In line with this notion of "the not-so-default mode network," areas of the DMN were associated with successful memory cueing, with the PCC, a central node of the DMN, appearing to represent reactivation-related changes in memory. In addition to the DMN, the connectivity between the hippocampus and VTC was relevant for memory cueing as well as for the reactivation-dependent change in subsequent memory. This pattern is in line with the postulated "pointer" function of the hippocampus, which assumes that the hippocampus binds cortical activation patterns during encoding and then "points" again to these areas during retrieval, thus reactivating the cortical representation patterns associated with the encoding of an event (*91*, *92*). Our data show that this cross-talk between hippocampus and cortical representation sites (such as the VTC) is not only relevant for successful retrieval but also for the modification of memory after retrieval [i.e., during the postulated (re)consolidation window], suggesting that the hippocampus might orchestrate the post-retrieval modification of memory. In line with this latter idea, the effect of post-retrieval stress was also linked to the cross-talk of the hippocampus with a cortical representation

network, which largely overlaps with the DMN. Together, our data suggest that hippocampal mechanisms are essential for reactivation effects and that these further depend on hippocampal cross-talk with neocortical brain areas, pointing to a coordinating role of the hippocampus in post-retrieval memory changes. Acute stress shortly after successful cued reactivation may interfere with the coordinating role of the hippocampus in the post-retrieval modification of memory or the stabilization of new, retrieval-related representations, in line with the reported impairment of hippocampal plasticity (*46*), retrieval of hippocampal memory (*68*, *93*), and hippocampus-mediated integration of incoming information into existing memory representations (*94*, *95*) after stress. Although our findings indicate a key role of the hippocampus in the effects of post-retrieval stress on subsequent remembering, it is to be noted that we tested associative episodic memories known to rely on the hippocampus (*96*, *97*). For other, non-hippocampal tasks, other brain regions might be more important. We assume that the reinstatement of the initial memory representation, whether hippocampal or non-hippocampal, is key for any changes in memory after retrieval.

To conclude, we show here that the impairing effect of post-retrieval stress on subsequent memory depends critically on hippocampal memory trace reinstatement during reactivation as well as the cross-talk of the hippocampus with neocortical representation areas. Although this reactivation dependency of post-retrieval stress effects would be in line with a posited reconsolidation mechanism, it is important to note that we did not obtain evidence for a weakening of the original memory trace. Instead, after reactivation, memory became even more reliant on the original memory trace in stressed compared to control participants, which appears to be more in line with the view that stress interfered with the consolidation of a retrieval-based, new memory trace that could support later remembering. Beyond their relevance for understanding a fundamental debate between reconsolidation and multiple trace theories of memory, our findings may also have important implications for attempts to debilitating memories in anxiety disorders or PTSD.

MATERIALS AND METHODS

Participants

Eighty-nine healthy, right-handed adults (45 women, 44 men) without a history of any neurological or psychiatric disease were recruited for this experiment. Further exclusion criteria included smoking, drug abuse, prescribed medication use, prior participation in the stress protocol, pregnancy, or lactation, as well as any contraindication for fMRI measurements (e.g. metal implants, pacemaker). Women were excluded if they used hormonal contraception and were not tested during their menses as these factors may affect the endocrine stress response (*98*). Participants were instructed to refrain from caffeinated beverages, exercise, and eating or drinking (with the exception of water) for 2 hours before the experiment. Exact testing times were pseudo-randomized to ensure even distribution across genders and groups. Groups did not differ in depressive mood, chronic stress, as well as state and trait anxiety. Respective scores were derived before the start of the actual experiment (see results S2 and table S7). All participants provided written informed consent before the start of the experiment and received monetary compensation for their participation. Nine participants were excluded from analyses due to not returning on day 2 or 3 ($n = 4$), acute claustrophobia ($n = 3$), or technical failure ($n = 2$), thus leaving a final sample of $n = 80$ participants (40 women, 40 men, age = 18 to 34 years, mean = 25.25 years, SD = 3.38 years). Participants were pseudo-randomly assigned to the stress group (20 women, 20 men, age = 18 to 33 years, mean = 24.25 years, SD = 3.96 years) or control group (20 women, 20 men, age = 19 to 34 years, mean = 25.97 years, SD = 3.60 years), to achieve a comparable distribution of men and women per group. An a priori power calculation with G*Power (*99*) indicated that a sample size of $N = 80$ is required to detect a medium-sized Group × Cued interaction effect with a power of 0.90. The study was approved by the ethics committee of the Medical Chamber of Hamburg (PV5960).

Experimental procedure

The experiment took place on three consecutive days at the MRI unit of the University Medical Center Hamburg-Eppendorf. On day 1, participants encoded word-picture pairs and completed an immediate cued recall test. On day 2, half of the encoded word-picture pairs were reactivated in a memory cueing task before participants underwent a standardized stress or control manipulation. On day 3, participants completed a final cued recall test as well as a functional localizer task. Critically, all tasks (except the stress/control manipulation) were performed in an MRI scanner. To account for the diurnal rhythm of the stress hormone cortisol, all testing took place in the morning between 8:30 a.m. and 12:30 p.m. To control for potential group differences in chronic stress, depressive mood, and anxiety, participants completed the Trier Inventory for Chronic Stress [TICS; (*100*)], Beck Depression Inventory [BDI; (*101*)], and State-Trait Anxiety Inventory [STAI; (*102*)] before the start of the experiment (see results S2 and tableS7).

Experimental day 1: Associative encoding task

Before the start of the encoding task (Fig. 1), participants underwent a brief (~5 min) training session out of the scanner to familiarize them with the task procedure. This training task followed the same structure as the overall 3-day paradigm, including a brief encoding session followed by a cued recall test, but involved different word-picture associations that were not used during the actual experiment. At the beginning of the encoding task, participants were instructed to memorize the presented word-picture pairs, as their memory for these pairs would be tested later. During the encoding task, participants were presented with 164 unique word-picture pairs in three runs, such that each pair was presented overall three times, once in each run (Fig. 1). The words were concrete German nouns with either negative (mean valence = 3.45, mean arousal = 5.72, mean concreteness = 4.62) or neutral valence (mean valence = 5.06, mean arousal = 2.15, mean concreteness = 4.41). These words were selected from the Leipzig Affective Norms for German database (*103*). Since there was no meaningful influence of word valence at the behavioral and neural levels, which may be due to the fact that the arousal evoked by emotional words is typically lower than for pictures or movies (*104*), we did not include the factor valence in the analyses reported here. The pictures consisted of outdoor scenes from the SUN database (*105*) and objects from the BOSS database (*106*). All scene pictures were selected to be emotionally neutral (e.g., excluding persons and avoiding arousing content, such as volcanos), yet ratings of valence or arousal were not available for them. The pairings of words and images were unique for each participant and were counterbalanced across picture categories (scene/object) and valence (negative/neutral). On each trial,

a word was presented at the top of the screen together with a picture in the middle for 3 s. Participants were asked to relate the word to the image and rate the fit of the word-picture pair using a button box with a four-point Likert scale (ranging from "very bad" to "very good"). Participants responded via an MRI-compatible button box held in their right hand. Between trials, a black fixation cross was displayed at the center of the screen for 5 to 9 s (jitter: 0 to 4 s, mean jitter: 2 s). One run of the encoding task took approximately 25 min. After each run, a 2-min break was provided, during which scanning was paused. However, participants remained in the scanner throughout all three encoding runs, for about 90 min in total.

Out of the 164 word-picture pairs presented during encoding, 20 pairs were designated as catch trials for the subsequent cued recall tasks. The selection of word-picture catch trial pairs was counterbalanced in terms of valence (negative/neutral) and categories (scene/object). Catch trials served to maintain participants' attention during the cued recall tests and to motivate participants to retrieve the associated picture while seeing the associated word. To further motivate participants to recall the associated picture in as much detail as possible when seeing the word cue, participants were informed that correctly answered catch trials would increase their financial compensation. The cued recall tests on days 1 and 3 included eight catch trials each, while the shorter day 2 memory cueing task included four catch trials. The temporal position of catch trials was distributed within a task, ensuring equal spacing between them. A catch trial was triggered when participants correctly designated the presented word as "old," "old/scene," or "old/object." Upon this choice, either the corresponding or a semantically similar picture probe was displayed on the screen for 0.5 s and participants had to judge whether the probe was the studied associate of the word, responding "yes" or "no" within 1 s. Catch trial performance did not differ between groups on any experimental day (all Ps > 0.200). All catch trials were subsequently excluded from the analyses to prevent potential biases in memory effects due to the representation of correct or semantically similar picture probes together with old words. Hence, all memory analyses were based on 144 word-picture pairs.

Experimental day 1: Immediate cued recall

After completing the encoding task, participants were taken out of the MRI scanner and given a break of 15 to 20 min. Next, participants received instructions for the immediate cued recall task. Upon re-entering the MRI scanner, participants were presented with 152 words (including eight catch trials) from the previous study phase ("old"), as well as 152 new words that had not been presented before (Fig. 1). The test words were displayed on the top of the screen for 4 s, and participants were instructed to make one of four memory decisions: "new," "old," "old/scene," and "old/object." Index finger presses indicated "new" responses (i.e., they do not recognize the word as studied), while middle finger presses indicated "old" responses (i.e., they recognize the word as studied but do not remember the associated picture). The positions of "old/scene" and "old/object" were randomized between the ring finger and little finger, with a 50% chance on each trial. Participants used these responses when they remembered the associated picture, making a categorical decision to indicate the recalled pictures category. Participants were instructed to respond quickly and accurately on an MRI-compatible response box and were informed that responses given after the word disappeared from the screen would be considered invalid. An inter-trial interval (ITI) of 5 to 9 s separated test trials, during which a black fixation cross was presented. The cued recall task lasted 60 min and was divided into two 30-min sessions, separated by a 2-min break.

Upon word recognition, participants were instructed to also retrieve the corresponding picture as detailed as possible. However, per the fMRI task design, participants were to respond with category-level answers (e.g., old/scene). Prior evidence using a similar task setup, but with an additional post-scanning verbal report of retrieved associates, suggests strong alignment between correct category-level decisions (i.e., associative category hits) and successful verbal retrieval of the specific item associated with the word (*107*).

Experimental day 2: Memory cueing

On day 2, participants returned to the MRI scanner for the memory cueing task. During this task, half of the previously studied old words (plus four catch trials) from day 1 were represented for 4 s, with an ITI of 5 to 9 s (Fig. 1). Of the 72 critical cued trials, 36 probed word-scene and 36 probed word-object associations; of the four catch trials, two probed word-scene and two probed word-object associations. On each trial, participants were instructed to remember the corresponding picture and to indicate whether the word was paired with an object or scene (category level 2AFC). The positions of the response options were randomly switched between the ring finger and the little finger with a 50% chance during each trial; response mapping was indicated at the bottom of the screen. This memory cueing procedure aimed to reactivate half of the word-picture pairs, thus enabling examination of "testing effects" and, from one perspective, opening a putative window of reconsolidation for these associations. By contrast, the remaining half of the words were not cued and thus served as baseline/control memories.

Experimental day 2: Stress manipulation

After leaving the MRI scanner, participants were directed to another room specifically prepared for the induction of acute psychosocial stress. The stress (or control) manipulation started 5 min after the end of the memory cueing procedure. In the stress condition, participants underwent the TSST, a standardized paradigm in experimental stress research (*108*). Participants were given a 3-min preparation period, which was part of the stress procedure as this preparation took place while participants were observed by the panel and video-recorded. Afterward, participants were asked to give a 5-min free speech about their qualifications for a job tailored to their interests. Next, participants had to perform a 5-min mental arithmetic task, counting backward from 2043 in step of 17. Both tasks were conducted in front of a panel consisting of two non-reinforcing committee members (1 man, 1 woman) dressed in white lab coats. The panel members were introduced as experts in behavioral analysis and were instructed to maintain a cold, non-reinforcing demeanor and refrain from responding to questions. In addition, participants were video-recorded during the TSST, and the recording was played on a TV screen placed behind the TSST panel. In the control condition, participants performed two non-stressful control tasks of the same duration. The first task involved giving a free speech about the last book they read, a movie they watched, or a holiday destination they visited. The second task required counting forward in steps of 15. No panel was present in the control condition, and no video recordings were taken.

To assess the effectiveness of the stress induction, we measured participants' subjective mood, blood pressure, and heart rate and collected saliva samples at several time points before and after the experimental manipulation. Mood changes were evaluated using the Mehrdimensionalen Befindlichkeitsfragebogen (MDBF) (*109*),

a German multidimensional mood questionnaire. The MDBF includes 24 items which are answered on a 1 to 5 Likert scale (never-always), probing three bipolar dimensions (eight items each) of current subjective mood: good to bad mood, energetic to tiredness, and calmness to wakefulness. Subscale values are summed up, with low values reflecting, e.g., good mood, while high values reflecting, e.g., bad mood. The internal consistency (Chronbach's alpha) of the MDBF scales ranges from 0.73 to 0.89. Participants further provided ratings of the stressfulness, unpleasantness, and difficulty of the TSST/control task on a visual analog scale ranging from 0 (not at all) to 10 (extremely) immediately after the manipulation. Blood pressure and heart rate were measured (Omron Healthcare Europe BV) at baseline, before, during, and after the experimental manipulation (i.e., −30, −1, +5, +15, +30, and +45 min relative to TSST/control task onset). Saliva samples were collected before and after the experimental manipulation (i.e., −30, −1, +15, +30, and +45 min relative to the onset of the experimental manipulation). Cortisol levels were analyzed from saliva samples using a luminescence assay (IBL International, Hamburg, Germany) at the end of data collection. After the TSST or control manipulation, participants were seated in a quiet room and provided with magazines to read. They were not allowed to engage in other activities, such as using smartphones. Participants were dismissed 45 min after the onset of the TSST/control task.

Experimental day 3: Cued recall

Twenty-four hours after the memory cueing session, participants returned to the MRI unit for the final cued recall task, which was identical to the immediate cued recall task on day 1 (Fig. 1). Upon entering the MRI scanner, participants were presented with 152 words from the initial encoding phase (144 old words from day 1, half of which were probes during word-picture memory cueing on day 2, along eight catch trials) randomly intermixed with 152 new words (not presented before). Words were displayed for 4 s (ITI: 5 to 9 s) on the top of the screen and participants were instructed to make one of four memory decisions: "new," "old," "old/scene," and "old/object." Participants were instructed to respond as quickly and accurately as possible on an MRI-compatible response box and that their responses would be considered invalid if given after the word disappeared from the screen. The cued recall task lasted 60 min, divided into two sessions of 30 min each, with a 2-min break in between.

Experimental day 3: Functional localizer

Following the final cued recall task, participants completed two runs of a visual category localizer task inside the MRI scanner, which served to later identify subject-specific patterns of category-level visual representations (especially in VTC). This task involved judgments about images from three categories: faces [CFD database; (*110*)], objects [BOSS database; (*106*)], and scenes [SUN database; (*105*)]. The localizer task included 120 novel pictures (40/category; repeated in run 2) that were not part of the memory task. Each run consisted of 12 mini-blocks, with 4 mini-blocks of 10 pictures per category, resulting in a total of 120 trials per run. During each trial, an image was presented for 0.5 s, followed by a 1-s ITI. Mini-blocks were separated by fixation periods lasting 10.5 s. Participants were instructed to respond manually to each image as quickly and accurately as possible, indicating whether the face was male or female, whether the object was manmade or natural, or whether the scene was indoors or outdoors (*111*). Each localizer run lasted approximately 5.5 min.

Behavioral memory data analysis

In our analysis of word-picture associative memory for the cued recall tasks on days 1 and 3 (4AFC), associative category hits were defined as trials in which old word cues were presented and participants responded with the correct picture category (e.g. "old/scene" when the associate had been a scene), indicating the recognition of the presented word as old and category-level retrieval of the associated picture category. Associative category errors included all trials in which an old word was recognized, but the wrong category was chosen (e.g., "old/object" when the associate had been a scene). We use the broader term associative misses to refer to all old trials that were not associative category hits (i.e., an old word was presented and the participant responded "new," "old," or "old" with the wrong category). The average associative category hit, miss, and error rates were calculated as the sum of correct/incorrect responses relative to the total number of cued and correct (day 2 memory cueing task) and not-cued trials, respectively.

In the case of the 2AFC memory cueing task on day 2, participants could only respond with "scene" or "object." Hence, associative hits were defined as trials in which participants responded with the correct picture category (e.g., "object" when the associate had been an object) and associative misses were trials in which participants responded with the incorrect category. Because the task was 2AFC for categories, hits and misses could reflect correct/incorrect retrieval of the associated category but also could reflect recognition of the word as old and a correct/incorrect guess about the associated category remembered or a failure to recognize the word along with a correct/incorrect category guess. It is for this very reason that the neural measures of memory reactivation are incisive, as they provide a means of differentiating 2AFC associative hits that were based on strong associative memory reactivation from those based on moderate reactivation from those based on little to no reactivation. The average associative hit and associative miss rates were calculated as the sum of correct/incorrect responses relative to the total number of trials during the day 2 memory cueing task. For an overview of memory performance (e.g., associative hit rate) across all days see table S1, and for trial counts table S2.

Imaging methods

fMRI acquisition

Functional imaging data were acquired using a 3T Magnetom Prisma MRI scanner (Siemens) equipped with a 64-channel head coil. Gradient-echo T2*-weighted echoplanar images (EPIs) were acquired for functional volumes. The imaging parameters included a slice thickness of 2 mm and an isotropic voxel size of 2 mm^2. Sixty-two slices were aligned to the anterior commissure–posterior commissure line using a descending interleaved multiband method. The repetition time (TR) was 2000 ms, the echo time (TE) was 30 ms, the flip angle was 60%, and the field of view was 224 × 224 mm^2. Before the day 2 memory cueing task, high-resolution T1-weighted structural images were acquired for each participant using a magnetization-prepared rapid acquisition gradient echo (MPRAGE) sequence. The structural images had a voxel size of 0.8 × 0.8 × 0.9 mm^3 and consisted of 256 slices. The imaging parameters for the MPRAGE sequence were a TR of 2.5 s and a TE of 2.12 ms.

fMRI preprocessing

The structural and functional images underwent preprocessing using SPM12 (www.fil.ion.ucl.ac.uk/spm/) implemented in MATLAB. The first three functional images of each run were discarded to avoid T1

saturation effects. Preprocessing steps included spatial realignment, slice time correction, co-registration to the structural image, normalization to the Montreal Neurological Institute (MNI) standard space, and spatial smoothing with a 6-mm full width at half maximum Gaussian kernel.

fMRI whole-brain GLM analysis of cued recall on days 1, 2, and 3

A general linear model (GLM) was estimated for each participant, using smoothed (and normalized) functional images of all tasks. This GLM allowed for whole-brain contrasts within and between different tasks and experimental days. Task-related regressors were modeled as boxcar functions (4 s for all retrieval tasks, 15 s for each block in the localizer) convolved with a canonical hemodynamic response function. A high-pass cutoff filter of 128 s was applied to remove low-frequency drifts. The GLM analyses produced t-statistic maps representing the contrasts of interest. Cluster correction using Gaussian random fields theory was applied to correct for multiple comparisons, with a significance threshold of $P > 0.05$. Within the overall GLM, we incorporated regressors for each given trial type, along with six regressors for movement realignment parameters two run-specific and one session-specific regressor for each day, respectively. In total, the overall GLM included 35 regressors. Before group analyses of days 1 and 3 cued recall data, we subtracted the estimates of associative misses from associative category hits (for cued and correct as well as not-cued trials) within first-level estimations of each subject. Group-level analyses were conducted using a two-factorial model including the between-subjects factor Group (stress versus control) and the within-subjects factor Cued (Cued and correct$_{\text{associative category hit – associative miss}}$ and Not Cued$_{\text{associative category hit – associative miss}}$) to examine a Group × Cued interaction. On the basis of the same first-level model, we further calculated a flexible factorial model based on three factors (Group, Cued, Day) to investigate group-level changes in neural activity from days 1 to 3. Day 2 group-level analyses involved two-sample unpaired *t* tests to compare group means for participant-level contrasts (e.g., associative category hit > associative miss). The memory cueing task on day 2 was executed before the stress/control manipulation, so this model identified ROIs more active during the successful (associative hits) versus unsuccessful (associative misses) retrieval of previously encoded word-picture associations (independent of Group). This analysis also served to validate the ROIs selected based on the existing memory literature and to identify sample-specific regions relevant to memory (see ROI Analyses).

fMRI psycho-physiological interaction analyses

We performed a PPI analysis based on the day 2 data (associative category hit > associative miss), using the PPI approach implemented in SPM12. In the first-level PPI model, we included contrast-specific regressors, a PPI interaction term, and the time course from the seed region. The seed and target regions were defined using masks obtained from the day 2 whole-brain contrast maps, which highlighted the most functionally relevant voxels within each region. The resulting PPI estimates between the seed and target regions for each subject served as reactivation-related connectivity indices during memory cueing.

fMRI single-trial GLM analysis

After conducting whole-brain GLM analysis, we computed single-trial beta estimates for all days and tasks to provide a more detailed characterization of memory-related neural responses. Trial-level regressors were modeled as boxcar functions convolved with a canonical hemodynamic response function. To remove low-frequency drifts, a 128-s high-pass cutoff filter was applied. The model followed the "least-squares all" approach [preserving the fine-grained temporal dynamics in comparison to "least-squares separate"; (*112*)], generating one whole-brain beta map per trial. The single-trial GLM was performed on realigned, slice-time corrected, native space images (maximizing across-task realignment accuracy) to be used in subsequent multivariate analyses (MVPA and RSA).

ROI analyses

Task-evoked activation was examined in the following ROIs, which were chosen on the basis of the existing literature on the neural underpinnings of episodic memory (*54*, *55*, *63*) and our whole-brain GLM results from the day 2 memory cueing task: hippocampus, PCC, angular gyrus, mPFC, and VTC. ROI masks were derived from the Harvard-Oxford cortical and subcortical atlas using a probability threshold of 50%. The VTC mask was generated by combining relevant regions from the Harvard Oxford Atlas, including the fusiform, inferior temporal, and parahippocampal regions (excluding the hippocampus). In the case of overall GLMs, which were previously used for whole-brain analysis, the same regressors were used, but voxels were masked by a given ROI; ROI-specific effects were small volume–corrected. We further accounted for the number of ROIs by applying Bonferroni correction (*P*corr).

In the case of native-space single-trial analyses, ROI masks were back-transformed using the inverse deformation field derived from the segmentation during preprocessing. For all ROI analyses on voxel-wise modeled data, we calculated average ROI beta values using the least-squares separate approach. For each trial, a separate beta estimate was computed using a linear regression model. This means that each trial was treated independently, and a separate model was fit to estimate the beta value for that particular trial. The voxel-wise beta estimates for each trial were then averaged together to obtain a representative beta value for the ROI. The obtained single-trial estimates of each ROI were later related to one another LMMs and also used as predictors in GLMMs explaining day 3 associative category hits.

Multivariate voxel pattern classification

To assess trial-wise cortical reinstatement strength, we used multivariate/voxel pattern analyses (MVPA) using customized functions from The Decoding Toolbox (*113*). Three different MVPA models were applied to the VTC probing category-specific visual representations of scenes and objects, using betas obtained from the single-trial GLMs. All betas were z-scored, ensuring a mean of zero and unit variance for each voxel. L2-penalized logistic regression models with a regularization parameter ($C = 0.1$) were used for all models.

The first model evaluated the classification performance within the localizer task by using leave one-run-out cross-validation (scenes versus objects) to validate the overall quality of the task and associated data. Model performance was assessed using classification accuracy.

In the second model, a "category" detection model was trained using neural patterns derived from both runs of the visual localizer task and then tested using memory recall data to quantify category-level reinstatement. Specifically, this model distinguished between "scenes" and "objects" in the VTC, capturing higher-level visual representations (*59*, *114*). This model was tested on all items presented during the day 2 memory cueing task, regardless of response correctness. This model enabled testing on the single-trial reinstatement evidence of memory responses and later determined

whether reinstatement evidence was generally higher for cued and correct (i.e., associative hits) compared to cued and not retrieved trials (i.e., associative misses). Trial-wise category reinstatement evidence was assessed using logits, which represent the signed distance of each sample to the separating hyperplane between scenes and objects.

The third model followed a similar approach as the second model, training a "category" detection model using neural patterns derived from the visual localizer task and testing it on items presented during the day 2 memory cueing task. However, this time only items that were cued and correct on day 2 were included. Therefore, the classifier estimated the evidence between remembered scenes and remembered objects, serving as the reinstatement index in further analyses. Trial-wise category pattern reinstatement evidence was assessed using logits and balanced classification accuracy, which accounts for an unequal number of samples during testing.

Representational similarity analyses

To assess stress-related changes in day 3 neural patterns between cued and correct versus not-cued trials, we conducted an RSA using customized scripts from The Decoding Toolbox (*113*). Our hypotheses focus on the hippocampus, VTC, and PCC. These regions are known to be crucial for episodic memory, with the hippocampus supporting detailed memory (*115*), and the PCC, as a central hub of the default mode network, supporting context and semantic memory (*116*, *117*). The hippocampus and PCC not only make individual contributions to successful episodic retrieval but also exhibit strong functional coupling, which facilitates memory processes (*118*). Confirming the given evidence, both regions displayed significant univariate effects during the day 2 memory cueing task, with the PCC exhibiting the largest significant cluster in terms of voxels and effect size at the whole-brain level. To perform the RSA, beta vectors derived from the single-trial GLMs were extracted from each ROI. The RSA was conducted in the native space of each participant using participant-specific ROI masks.

In the first step, we calculated neural pattern similarity (Fisher *z*-transformed) within each word-picture associative pair from day 1 cued recall to day 3 cued recall. This allowed us to incorporate all trials (cued and correct day 2 and not cued), and specifically observe pattern changes in cued and correct trials due to the stress manipulation on day 2. We derived single-trial measures of pattern similarity change across days for each participant, which were later used as predictors in GLMMs to predict day 3 associative category hits on a trial-by-trial basis.

In the second step, we used RSA to obtain an index of hippocampal pattern reactivation on day 2. We computed the average representational similarity (Fisher *z*-transformed) from day 1 encoding (three runs) to day 2 memory cueing. This approach allowed us to compare trial-specific patterns without pruning them down to the category level (like in MVPA). That way, we were able to capture pattern similarities that are not bound to visual category reinstatement but represent the change in within-trial pattern activation from encoding to reactivation after consolidation (24 hours later).

Tracking trial-wise memory reactivation

During the day 2 memory cueing task, participants were cued to remember a picture and its corresponding category that had been associated with a word (i.e., the retrieval cue), indicating the category of the picture. Trials answered correctly were labeled as associative hits, yet this does not directly inform about the level of vividness or detail of the memory. This distinction is crucial because there are key differences between recalling a detailed versus gist-like associative memory (*119*, *120*). Examining the gradient between stronger and weaker reactivation is also pivotal for understanding the impact of post-retrieval stress on memory processes, as a strong reactivation during day 2 may make the memory more susceptible to the effects of stress.

To more comprehensively assess trial-wise neural reactivation on day 2, we examined the strength of memory reactivation using (i) reaction times; (ii) trial-wise univariate beta activity in PCC, hippocampus, and VTC; (iii) category pattern reinstatement index via MVPA in the VTC; and (iv) hippocampal pattern reactivation from encoding to reactivation (ERS via RSA). To examine the relationship of single-trial beta activity of the hippocampus, VTC, and PCC, as well as category reinstatement in terms of memory confidence, we used linear mixed models to predict either of these estimates using the trial-specific day 2 reaction time. We further fit an LMM to univariate hippocampal activity being predicted by category pattern reinstatement. This analysis served as a validation step, aligning with previous findings that showed a positive association between hippocampal activity and VTC category pattern reinstatement (*68*). The category pattern reinstatement index and hippocampal pattern reactivation were used to classify trials in either "high" or "low" reactivation, using a subject-specific median split. This factor was then used to predict day 3 performance in GLMMs, encompassing information from all available trials (high reactivation, low reactivation, and no reactivation/not probed on day 2).

Statistical analyses

Univariate and PPI fMRI statistical tests were conducted in the SPM12 environment (www.fil.ion.ucl.ac.uk/spm/). All other statistical models and tests were conducted in the R environment (version 3.3.4). Reported *P* values resulting from ANOVAs were Greenhouse-Geisser–corrected, when required; univariate fMRI voxel cluster results were initially FWE-corrected and further corrected (Bonferroni) for the number of ROIs (*P*corr).

Baseline and control variables on days 1 and 3 (e.g., blood pressure) were tested with two-sample *t* tests. Day 2 parameters validating the effective stress manipulation (i.e., blood pressure, heart rate, mood, and cortisol) were tested with repeated-measures ANOVAs (within-subject factor Time, between-subject factor Group) and subsequent post hoc *t* tests. Measures of task performance, including associative category hits, associative misses, and associative category *d′*, that investigated the effect of stress on later memory for cued and correct versus not-cued trials were subjected to repeated-measures ANOVAs (within-subject factor Cued, between-subject factor Group) and subsequent post hoc *t* tests. For calculations of associative *d′*, values of zero were replaced with 0.5/denominator and values of 1 with 1 to 0.5/denominator (*121*). Single-trial analyses were modeled using GLMM predicting associative category hits/errors on day 3, based upon several different predictor variables (i.e., Cued, Group, and Day 2 reactivation strength). GLMMs were fitted with the lme4 statistical package [versions 1.1.14; (*122*)]. Models were estimated using a restricted maximum likelihood approach. Post hoc slope comparisons of GLMMs were conducted using the emtrends function from the corresponding R package (*123*). Visualization and analysis used various R packages, including ggplot2 (*124*), tidyr, dplyr, and MASS (*125*).

Supplementary Materials

This PDF file includes:

Results S1 and S2
Fig. S1
Tables S1 to S7

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