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On the Trail of Memory Traces:

How Stress Affects Initial Memory Formation and Updating Processes

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Abstract

Forming and updating memories are central aspects of human cognition, which are strongly affected by stressful encounters. Due to the large variety in study designs and lack of neural correlates, our understanding of how stress affects encoding and post-retrieval memory processes is limited. To uncover the underlying mechanisms, three multi-day neuroimaging studies were conducted as part of this thesis. Using Magnetoencephalography (MEG), study I investigated the role of theta oscillations in emotional encoding under stress. Studies II and III aimed to further delineate the interaction between stress and memory updating processes by employing functional Magnetic Resonance Imaging (fMRI) in a three-day associative memory task. While studies I and II employed a behavioral stress induction, study III leveraged a pharmacological intervention to increase either noradrenergic activity or cortisol levels. Despite differing methodologies, results of all three studies consistently highlight the critical role of the hippocampus and connected occipito-parietal areas in memory formation and updating under stress. While study I revealed that increased theta oscillations in this cortico-hippocampal network during the encoding of emotionally negative images were linked to memory enhancements, results from studies II and III showed that stress, and especially noradrenaline, following a strong activation of a similar network during reactivation, significantly impaired subsequent memory. These findings suggest the cortico-hippocampal network to reflect a critical yet vulnerable target to stress across the whole memory formation process, yielding major relevance for (i) understanding the pathogenesis of stress-related disorders and (ii) developing targeted interventions to alleviate symptoms emerging from maladaptive memories.

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List of abbreviations

BOLD = Blood Oxygen Level Dependency

dlPFC = Dorsolateral Prefrontal Cortex

EEG = Electroencephalography

MEG = Magnetoencephalography

fMRI = functional Magnetic Resonance Imaging

MVPA = Multivariate Voxel Pattern Analysis

PTSD = Post Traumatic Stress Disorder

RSA = Representational Similarity Analysis

SNS = Sympathetic Nervous System

PNS = Parasympathetic Nervous System

ANS = Autonomic Nervous System

HPA = Hypothalamus-Pituitary Axis

GC = Glucocorticoids

CORT = Cortisol

NA = Noradrenaline

MR = Mineralocorticoid Receptors

PLAC = Placebo

VTC = Ventral Temporal Cortex

VTA = Ventral Tegmental Area

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1 General introduction

Every one of us has experienced stressful situations such as public speaking, tight deadlines, or sudden unexpected events; making us sweat, nervous, and act less controlled. This kind of acute stress is characterized by intense yet short-lived pressure, which significantly shapes our actions and responses, and necessitates ongoing coping mechanisms as well as adaptive responses. Under stress, our cognitive processes and the resulting behaviour shift from controlled planning to habit-guided processing (Schwabe et al., 2011; Schwabe & Wolf, 2011, 2013), specifically affecting learning and memory processes (Sandi & Pinelo-Nava, 2007; Schwabe et al., 2022). Great efforts have been made to shed light on the exact impact of stress in this regard, yet many contradictions remain, specifically in human studies, due to the vast range of applied study designs, use of different stimuli, and an incompetent understanding of underlying memory trace dynamics. A clear insight of these mechanisms is however of major importance, as a more detailed picture of the underlying processes could shed light on the dynamics of stress-related disorders, such as PTSD. This could on the one hand aid in explaining its pathogenesis, but also provide knowledge for developing effective interventions and support mechanisms for individuals experiencing stress-related memory impairments. In order to approach such an ambitious goal, illuminating the complex stress-induced neurophysiological effects on memory formation seems critical. Therefore, the underlying neural signature of each memory formation stage needs to be related to the time-dependent cascade of the physiological stress response.

1.1 Stress response

Stress prepares the body to deal with perceived threats or stressors, ensuring survival in challenging situations. The human stress response is a complex interplay of various physiological systems, primarily governed by the Autonomic Nervous System (ANS) and the Hypothalamic-Pituitary-Adrenal (HPA) axis (Ulrich-Lai & Herman, 2009; Figure 1A). The ANS serves as the primary regulator of involuntary bodily functions, including heart rate, digestion, respiratory rate, and pupillary response (Yamaji et al., 1997). It comprises two branches: the Sympathetic Nervous System (SNS) and the Parasympathetic Nervous System (PNS; McCorry, 2007; Figure 1B). During stress, the SNS becomes activated, initiating the well-known "fight-or-flight" response (Richter & Wright, 2020). Activation of the SNS triggers the release of catecholamines, such as adrenaline and noradrenaline, from the adrenal medulla into the bloodstream (De Kloet et al., 2005; Joëls & Baram, 2009). These neurotransmitters act on various target organs, inducing physiological changes aimed at preparing the body to

confront or flee from the perceived threat. For instance, heart rate increases to enhance blood flow and oxygen delivery to muscles, while blood vessels constrict in non-essential organs to redirect blood flow to vital areas. These changes result in increased blood pressure, heightened alertness, and dilated pupils, geared to optimizing sensory perception (De Kloet et al., 2005; Joëls & Baram, 2009). Respiratory rate also rises to meet increased oxygen demands, thereby facilitating greater energy production (Ulrich-Lai & Herman, 2009; Vicennati et al., 2011). Together, these responses prime the body for immediate action in the face of danger. In addition to the rapid activation of the ANS, the stress response also involves the Hypothalamic-pituitary-adrenal (HPA) axis, a complex neuroendocrine cascade (Papadimitriou & Priftis, 2009; Ulrich-Lai & Herman, 2009). The HPA plays a crucial role in regulating the body's response to stress over a more prolonged timeframe and involves three main components: the hypothalamus, the pituitary gland, and the adrenal glands. This hormonal cascade starts with the release of Corticotropin-Releasing Hormone (CRH) from the hypothalamus in response to stress. CRH then stimulates the anterior pituitary gland to release adrenocorticotropic hormone (ACTH) into the bloodstream. ACTH then travels to the adrenal glands, situated atop the kidneys, where it triggers the synthesis and release of glucocorticoids, primarily cortisol in humans. (Papadimitriou & Priftis, 2009; Ulrich-Lai & Herman, 2009). Cortisol serves as the body's primary stress hormone and plays a vital role in mobilizing energy reserves, regulating metabolism, and modulating the immune response during periods of stress (Ulrich-Lai & Herman, 2009). To achieve this goal, cortisol exerts widespread effects throughout the body by binding to glucocorticoid receptors (GRs) located in various tissues and organs. Unlike catecholamines, cortisol can traverse the blood-brain barrier (Banks, 2012), exerting its biological action via mineralocorticoid receptors (MRs) and glucocorticoid receptors (GRs) distributed throughout the brain. Crucially, besides intracellular MRs and GRs acting as transcription factors in the cell nucleus, membrane-bound MRs facilitate rapid non-genomic actions with lower cortisol affinity (Karst et al., 2005). The differing affinities of GRs and MRs enable adaptive responses to stress and promote cognitive adaptation under stress (Joëls & Baram, 2009). The swift activation of membrane-bound MRs enhances initial stress responses, assists in situational assessment, and supports the adoption of optimal coping strategies. This is counterbalanced by the slower GR-mediated activation, preventing an excessive initial stress response and restoring homeostasis (Joëls & Baram, 2009; Figure 1C). Given the distribution of these receptors in the brain and their convergence in regions critical for memory and learning, extensive research has explored their role in modulating memory formation processes (Diamond et al., 2007; Roozendaal, 2002; Roozendaal et al., 2006; Sandi & Pinelo-Nava, 2007).

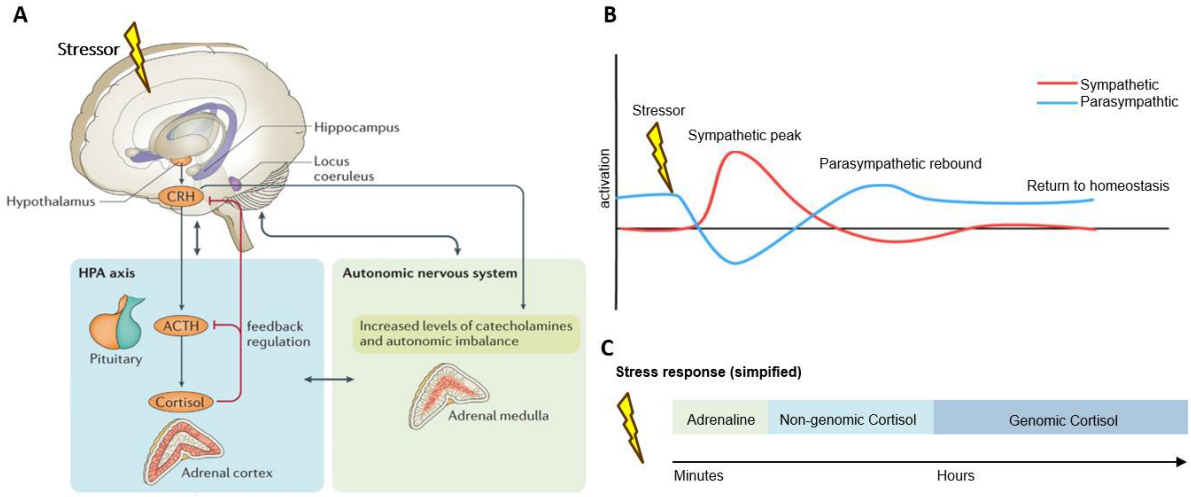

Figure 1. Physiological stress response. **A** Confronted with a stressor, the body activates the ANS, increasing noradrenaline levels. Noradrenaline directly affects the neural system but also interacts with the slower HPA-axis, increasing cortisol levels (Figure partly adapted and modified from Otte et al., 2016; permission license: 5812410765765). **B** ANS and PNS work mostly contrary against another in order to restore homeostasis in the body. **C** The simplified stress response, reduced to noradrenergic and glucocorticoid activity. The body initially increases noradrenaline levels, serving the fight-or-flight response. This is followed by the relatively fast non-genomic cortisol response, which peaks around 20 minutes after experiencing the stressor. Finally, hours after the stressor, the body further reacts with the rather slow genomic cortisol response.

1.2 Initial memory formation under stress

While sensory input is encoded, external stimuli are processed and selectively transferred to short-term memory. Following initial encoding, a fragile memory representation undergoes stabilization through synaptic and systems consolidation. Synaptic consolidation stabilizes short-term changes in synaptic strength via long-term potentiation (LTP) or long-term depression (LTD; Bailey et al., 2015; Clopath, 2012). This process typically occurs within minutes to hours after learning and involves structural changes in dendritic morphology and spine density (Steward & Worley, 2002). In contrast, systems consolidation is a gradual process where memories become less reliant on the hippocampus and more dependent on distributed cortical networks, facilitating long-term storage over a longer period (days to years after learning; Dandolo & Schwabe, 2018; Squire et al., 2015; Takashima et al., 2009). Both, synaptic and systems consolidation work together to transform newly encoded information into stable and enduring memories (Squire et al., 2015; Tononi & Cirelli, 2014; Figure 2). Stress interacts with each memory stage differentially (i.e., encoding, (re-)consolidation), rendering it a powerful modulator of essentially every memory process (Luksys & Sandi, 2011; Schwabe et al., 2022). Yet whether stress enhances or impairs subsequent memory depends on its timing

(Quaedflieg & Schwabe, 2018). To grasp the overall reason for these heterogeneous effects, and derive an overarching understanding of the dynamics at play, one needs to visit the existing evidence concerning stress effects on specific stages of memory formation. On that account, it is well established that stress can have a profound influence on initial memory formation by interacting with both, the encoding, and later consolidation processes (Joëls et al., 2006; Roozendaal & McGaugh, 2011; Sandi & Pinelo-Nava, 2007; Schwabe et al., 2012).

1.2.1 Stress effects during encoding – missing the temporal glue

Stress effects around the time of encoding have been extensively researched. Evidence suggests that stress either improves (Domes et al., 2002; Schwabe et al., 2008; Smeets et al., 2008) or hinders (Diamond et al., 2007; Elzinga et al., 2005; Kirschbaum et al., 1996) memory formation, varying, depending on factors such as the emotional nature of the material or the time elapsed between stress and encoding. A closer look at these findings reveals however major design differences. One highly relevant factor that differs between studies is the timing of memory assessment after learning, with some studies administering the memory test while participants were still stressed (e.g., Domes et al., 2002). Such a procedure is highly problematic as it is well known that retrieval performance decreases under stress (Buchanan et al., 2006; De Quervain et al., 2000; de Quervain et al., 1998; Kuhlmann et al., 2005), making it impossible to disentangle the precise effect of stress being related to either the encoding, retrieval, or both. As such, a specific statement about a potential stress effect is rendered invalid in this regard. To bypass such a bias, one needs to conduct the memory test in the absence of any stress-related neurophysiological effect, i.e. one day later. Besides this challenge, efforts in both, animal and human studies have been made to explain the underlying neuro-physiological interaction, converging on the idea that simultaneous activation of cortisol and noradrenaline serves to facilitate memory encoding, most likely due to the modulation of noradrenergic activity both pre-synaptically and post-synaptically, through interactions with adreno-receptors (Krugers et al., 2012). Critically, this neuro-physiological interaction seems to be most pronounced in light of emotional events. Extensive research supports that emotionally arousing events are more effectively remembered, compared to non-emotional ones. This phenomenon is underscored by studies showing that information encoded under stress, or heightened emotional states, is selectively stored in memory (Joëls et al., 2006; Kalbe et al., 2020; Sandi & Pinelo-Nava, 2007; Wiemers et al., 2013). This memory enhancement is primarily attributed to the release of hormones and neurotransmitters such as glucocorticoids (e.g.cortisol in humans), and noradrenaline (Joëls et al., 2006; Schwabe et al., 2012), which directly impact brain regions

crucial for memory formation, such as the amygdala, hippocampus, prefrontal cortex (PFC) or the dorsal striatum (de Quervain et al., 2017; Joëls et al., 2006; Barsegyan et al., 2010; Buchanan et al., 2006; Cahill et al., 2003; de Quervain et al., 2007; Karst et al., 2005; Roozendaal et al., 2008; Van Stegeren, 2008). However, these findings solely rely on fMRI data, limiting our knowledge about the underlying process significantly, as essentially no temporal information exists. While evidence including the temporal correlates affected by stress during encoding is largely missing, the few existing pieces of evidence include findings suggesting that stress affects event-related potentials depending on emotional valence (Quaedflieg et al., 2013; Weymar et al., 2012; Wirkner et al., 2013; Wirz & Schwabe, 2020). The effect of stress on brain oscillations in the context of emotional memory formation remains however elusive in humans as, so far, solely animal studies suggest that stress may specifically impact theta activity (4-7 Hz) in the MTL (Ghosh et al., 2013; Jacinto et al., 2013). Theta oscillations primarily originate from structures deep within the MTL, including the hippocampus, critically involved in the formation and retrieval of declarative memories (Buzsáki, 2002). During memory encoding, theta oscillations help synchronize neuronal activity across different brain regions, facilitating the integration of incoming information into existing memory networks (Karakaş, 2020; Muthukrishnan et al., 2020). Such synchronization is thought to enhance memory efficiency (Hsieh & Ranganath, 2014) by coordinating the activity of neurons involved in binding various elements of the incoming stimuli creating a coherent memory representation. This binding mechanism has characterized theta oscillations as the 'glue' for episodic memories (Clouter et al., 2017). In sum, the role of theta oscillations as well as the fact that they originate from the MTL renders these oscillations as prime candidates for any (emotional) episodic memory process in general, and interactions with stress in particular. Until now, there is no human evidence explaining the role of theta oscillations in emotional memory encoding under stress, posing a major gap in the literature, hampering our knowledge of this process significantly.

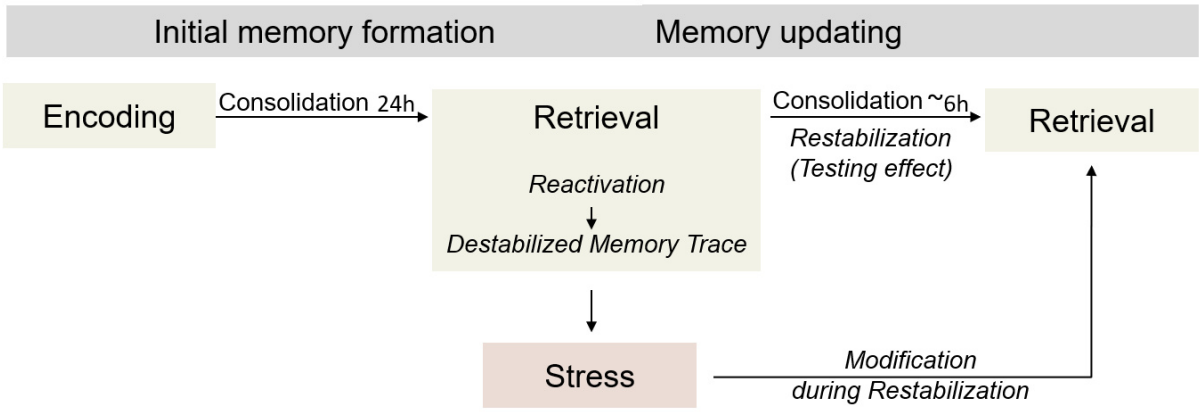

Figure 2. General model of memory formation and updating. Upon encoding, events are consolidated on a systems and synaptic level, which is supposed to take hours and necessitates sleep. During retrieval, the underlying neural signatures may get reactivated, which can lead to a destabilization of the original memory trace (according to reconsolidation theory). Without any intervention, this memory trace is re-stabilized and tempered, resulting in a stronger event memory, and easier recall on subsequent days (reflecting the testing effect). If however stress occurs directly after the retrieval, the re-stabilization is modified, leading to a potential impairment of subsequent memory.

1.2.2 Stress after encoding filters emotional events

Stress around the time of encoding may preferentially enhance memory for emotional material (Domes et al., 2002; Schwabe et al., 2008). During, and especially after encoding, the memory formation process engages in consolidation processes. How does our memory change, when we encounter a stressful situation during initial memory consolidation compared to stress during encoding? One might assume that post-encoding stress effects also depend on the emotionality of the material. While this seems to be true in general, the direction of this effect seems to be flipped, compared to stress during encoding. In fact, some studies report an emotional memory enhancement (Cahill et al., 2003; Smeets et al., 2008) but, interestingly, there is also evidence for an even larger enhancement of neutral information (McCullough & Yonelinas, 2013; Preuß & Wolf, 2009). On this behalf, it has been suggested that stress might act as a filter, prioritizing non-emotional over emotional events, protecting us from the storage of overly negative and the potential formation of maladaptive memories (Ritchey et al., 2017). It is not surprising that, on the neural level, the MTL, and specifically the amygdala and hippocampus are central for post-encoding stress effects on subsequent memory, supporting prioritization (Kensinger, 2009; Mather et al., 2016) and recollection (Diana et al., 2007; Yonelinas & Ritchey, 2015). The physiological explanation involves, similar to the encoding stage, the collaborative action of cortisol and noradrenaline. Particularly, the activity within the basolateral amygdala plays a

pivotal role in this process (Roozendaal et al., 2006; van Stegeren et al., 2007). In line with this idea, it has been shown that increased cortisol levels post-encoding, render item recollection more dependent on the initial MTL representations during encoding (Ritchey et al, 2017). As post-encoding processes establish event-specific memory traces (Miyashita et al., 2008) by tempering the neural signal from the encoding stage (Axmacher et al., 2009; Dudai et al., 2015), such a mechanisms points at a specific interaction of stress with the original memory trace. In short, stress during the post-encoding consolidation period engages the same brain areas as during encoding but instead of boosting emotional content, stabilizes or even amplifies memory storage of non-emotional events.

1.3 Memory updating under stress

The process of post-encoding consolidation provides us with a mechanism of how our brain transforms short events into lasting memories, thus being essential for stabilizing new information, and allowing them to be integrated into the vast network of our existing knowledge. But what happens to these stabilized memories after remembering them? On first glance, post-retrieval processes seem very similar to post-encoding processes, as memories are generally also stabilized, ensuring their storage, facilitating swift recall in the future. This process, reflected in the well-known testing effect (Roediger III & Karpicke, 2006; Figure 2), is crucial for maintaining the integrity of memories over time, as it reinforces the synaptic connections and underlying neural networks. However, research from the last two decades has demonstrated that memories undergo modification or updating upon each retrieval (Dudai & Eisenberg, 2004; Hardt et al., 2010; Nadel et al., 2012), allowing us to adapt to an ever-changing environment. So, obviously memories do not remain static after consolidation, but rather stay dynamic ever after. Reconsolidation theory as well as Multiple Trace Theory (MTT) offer different mechanistic explanations of this phenomenon. Reconsolidation theory posits that when a memory is retrieved, it becomes temporarily labile and susceptible to modification, requiring re-stabilization (Lee et al., 2017; Nader & Einarsson, 2010; Schwabe et al., 2014). In support of this theory, animal studies have provided important insights into the mechanisms of reconsolidation-based memory modifications, elucidating the underlying molecular mechanisms (Tronson & Taylor, 2007) and demonstrating that reconsolidation is protein synthesis-dependent (Nader, 2015; Ressler et al., 2021). MTT, on the other hand, suggests that memories are stored as a network of traces in the brain, with each retrieval episode leading to the formation of a new memory trace (Nadel et al., 2000; Polyn et al., 2009; Sederberg et al., 2011). According to this theory, even remote memories retain their dependence on the

hippocampus, and each retrieval reactivates and updates the memory trace associated with that specific event (Nadel et al., 2000). While the mechanistic explanation may differ, it is well possible that both models are indeed parts of another more complex process. This idea gains support by the fact that, besides their discrepancies, both theories converge on the necessity of memory reactivation to initiate updating processes (Agren, 2014; Nadel et al., 2000; Przybyslawski & Sara, 1997).

1.3.1 Memory trace reactivation

But what exactly does 'memory reactivation' mean? Generally, the concept of memory reactivation includes neural representations that were active during initial memory formation or encoding, being activated again to facilitate retrieval (Kragel et al., 2017; Ritchey et al., 2013). The success and quality of retrieval strongly relates to the underlying confidence (de Zubicaray et al., 2011; Moritz et al., 2006; Odinot et al., 2013). Hence, the neural reactivation itself might follow a gradient, directly tracking retrieval quality or vividness. This would mean that a less well-established memory might be reactivated with an overall weaker neural signal. Consequently, the efficiency of following manipulations would directly depend on this reactivation strength. Investigating such a dynamic would however demand a clear estimation of event-specific markers reflecting the neural reactivation. Capturing such correlates remains challenging especially in humans, demanding different approaches and perspectives (i.e. neural activity, pattern-similarity) in order to obtain robust and interpretable estimates. On the lowest level, one could utilize the average retrieval-specific neural activity from designated brain areas (i.e., hippocampus). Beyond this univariate approach, multivariate measures can be employed, which estimate the (dis-)similarity of neural patterns across distinct memory stages. On this account, Representational Similarity Analysis (RSA) has emerged as the gold standard to tackle such approaches. By using RSA, it is possible to correlate event-specific patterns from encoding with corresponding patterns from retrieval (and underlying reactivation). The resulting Encoding-Retrieval-Similarity (ERS) has been suggested to be strongly correlated with retrieval success, especially in the hippocampus (Pacheco Estefan et al., 2019). Notably, the neural representation from encoding can be interpreted as a reflection of the initial memory trace, a view that is supported by recent research in transgenic mice (Wally et al., 2022). Interestingly, evidence suggests that effective post-reactivation interventions require the reactivation of specific neuronal subsets within the engram (cognitive information imprinted in a physical substance), underscoring the significant contribution of the original memory trace to changes during the proposed updating window (Khalaf et al., 2018). Notably, there is also

evidence that the reactivation of the engram is accompanied by molecular cascades that enable the modification of a memory based on current experiences or contexts, offering a mechanistic explanation (Bellfy & Kwapis, 2020; Flavell et al., 2013; Rich & Torregrossa, 2018). Beyond the ERS, RSA may be conducted for any kind of memory stage-comparison, estimating for example the pattern reconfiguration across retrieval tasks, and investigating potential differences between initial and final pattern representations across days. Finally, it is also possible to estimate category-level reinstatement via Multivariate Pattern Analysis (MVPA). Here, multivariate classifiers are usually trained on specifically designed external localizer datasets, which are employed independently of the task (Gagnon et al., 2019; Kraft et al., 2005). Such a procedure renders the resulting estimates robust, and potentially even less noisy compared to RSA correlations (Haxby et al., 2001; Kriegeskorte et al., 2008). While on first glance the resulting category-level might not yield comparable explanatory potential as event-specific RSA, such analyses are specifically relevant for brain regions processing category information, such as the Ventral Temporal Cortex (VTC; representing scenes and objects; Bracci et al., 2017; Grill-Spector & Weiner, 2014). Thus, calculating both, event-specific RSA and category-specific MVPA, may account for heterogeneous roles across different brain areas, and their predictive power may increase drastically when employed together.

Beyond the question of 'how' to estimate neural reactivation, it is important to know 'when' to estimate it. Memory reactivation occurs not only during conscious retrieval (online) but also offline during post-retrieval rest periods. Online reactivation involves the immediate engagement of neural circuits during the retrieval process (J. D. Johnson & Rugg, 2007; Tanaka et al., 2014). This means that when a memory is being recalled, neural networks associated with that memory are activated in real time. In contrast to this type of retrieval, offline reactivation occurs after the retrieval event, typically during rest or sleep (Oudiette et al., 2013; Staresina et al., 2013; Tambini et al., 2010). During these periods, the brain continues to process and consolidate memories, even though the conscious mind may not be actively engaged. The transition from online to offline reactivation involves complex neural cascades, influencing the persistence and strength of the reactivated memory trace (Yagi et al., 2023). However, fundamental knowledge gaps remain about the role of online versus offline neural reactivation in post-retrieval dynamics of human memory in general, and its modification by stress in particular. Specifically, it remains elusive to what extent major stress mediators (noradrenaline, cortisol) affect subsequent memory, and whether such an effect is related to prior online or offline reinstatement dynamics. On this account it remains also unclear whether the original memory trace during (online reactivation) or after (offline reactivation) remembering is affected

by the stress intervention or whether the creation of a new trace is impaired, hampering future recall. As both options seem very well possible, the solution might be found in taking into account different brain areas, potentially performing the updating process, and being differently affected by stress.

It is well established that the hippocampus is the core of almost any memory process serving as a hub between diverse representation areas (i.e., parietal, occipital) implicated in learning and remembering (Battaglia et al., 2011). Its central role involves linking related pieces of information to form coherent memories (Eichenbaum, 2017; Schlichting & Preston, 2017). The hippocampus facilitates encoding, storage, and retrieval of these associations, enabling us to remember complex events and relationships (Davachi & DuBrow, 2015). Memory reactivation involves the hippocampus during conscious retrieval and during replaying activity patterns, that mirror those patterns from initial learning (Carr et al., 2011; Gillespie et al., 2021; Zielinski et al., 2020). Thus, the hippocampus not only helps create and store associative memories but also reinforces them through reactivation. On that behalf, the hippocampus has been suggested to serve as a crucial structure in creating indices that link different elements of a memory together, enabling efficient retrieval when needed (Teyler & DiScenna, 1986). At the core of this theory lies the idea that memories are not stored in a single location in the brain but are distributed across various neural networks, including specialized brain areas for i.e. visual processing (Teyler & Rudy, 2007). The VTC is specialized in visual recognition and categorization of objects and scenes (Grill-Spector et al., 2014), integral to our ability to identify and differentiate between various visual stimuli. On the other hand, the Posterior Cingulate Cortex (PCC), is pivotal for memory retrieval and the consolidation of memory traces (Bird et al., 2015; Thakral et al., 2015). It is involved in integrating sensory and mnemonic information, facilitating the recollection of past experiences by connecting contextual details with stored memories. The PCC further takes a central role within the Default Mode Network (DMN; Menon, 2023; Wang et al., 2020). The DMN becomes active when our minds wander, when we reflect on ourselves, or when we envision the future (Yeshurun et al., 2021). Besides the PCC, it includes areas like the medial prefrontal cortex (mPFC), medial temporal lobe (MTL) as well as the hippocampus. During tasks that demand our attention, like memory retrieval, the DMN's activity usually decreases, while regions associated with external focus become more active (Smallwood et al., 2021). However, certain parts of the DMN, particularly its posterior regions, remain engaged during retrieval tasks. Recent evidence has suggested a more specific role for the posterior DMN in memory retrieval ("not-so Default Mode Network"; Andrews-Hanna et al., 2010; Sestieri et al., 2011; Wang et al., 2020). This subnetwork after all seems to facilitate

the recall of specific events and details from the past, contributing to the reactivation of memories.

1.3.2 Changing the fate of memories

Once reactivated, memories are sensitive to various manipulations, ranging from new learning experiences (Agren, 2014; Hupbach et al., 2007; Monfils et al., 2009; Schwabe & Wolf, 2009) to pharmacological interventions (Kindt et al., 2009; Schwabe, Nader, et al., 2012) or electroconvulsive shock (Kroes et al., 2014). These observations are of major relevance as these results show that the updating process can be deliberately altered, thereby modifying future recall. Initial results from rodent studies implicated that stress and glucocorticoid administration after memory retrieval impair future recall (Cai et al., 2006; Maroun & Akirav, 2008). This was confirmed by human studies showing that post-retrieval stress impairs subsequent memory. However, due to the large diversity in designs and the timing of stress, there is also evidence for enhancing effects (e.g., Bos et al., 2014; Coccoz et al., 2011). Pharmacological studies have been conducted in humans and rodents in order to shed light on these contradictory findings. They demonstrated a significant impact of noradrenaline and glucocorticoids on post-retrieval memory processes, yet in turn revealed contradictions once more. Some studies suggested enhancing effects of post-retrieval glucocorticoids on subsequent memory (Antypa et al., 2019; Meir Drexler et al., 2015), while others report impairing effects of glucocorticoid receptor activation after retrieval (Antypa et al., 2021; Maroun & Akirav, 2008; Vafaei et al., 2023). For noradrenaline, several studies indicate that post-retrieval blockade of noradrenergic activity impairs putative reconsolidation or future memory accessibility (Kindt et al., 2009; Przybyslawski & Sara, 1997; Schramm et al., 2016; Schwabe, Nader, et al., 2012). However, this effect is also not consistently reported (Bos et al., 2014; Elsey et al., 2020; Muravieva & Alberini, 2010) and might depend on the arousal state of the individual (Maroun & Akirav, 2008) or the exact timing of drug administration (Otis et al., 2014; Thomas et al., 2017). This rather unclear picture of the underlying dynamics may exist for at least two reasons: Firstly, previous research predominantly focused on emotionally charged information or fear memories, which are at their core not comparable to non-emotional events as they are for example, inducing arousal themselves. Secondly, studies were not designed to record neuroimaging data across specific memory stages (encoding, reactivation, delayed retrieval). In light of the existing literature, this seems however to be of paramount importance, as extant studies suggest that brain regions implicated in initial memory formation, and consolidation,

such as the hippocampus, may also play a role in the modification of memories after their reactivation (Agren, 2014; Przybyslawski & Sara, 1997).

1.4 Research scope and aim

The overarching goal of the employed studies was to delineate how stress interacts with the neural signatures of both, the initial encoding of emotional memories, and the mechanisms involved in post-retrieval processing in regard of future memory retrieval. Illuminating the relationship between stress and memory processes has been a focal point of research over the past decades. Contrary to earlier beliefs, that acute stress universally impairs memory, contemporary studies have painted a more nuanced picture. Instead, it has become evident that stress has differential effects on memory processes, contingent upon factors such as timing and the emotional valence of the information being processed (Quaedflieg & Schwabe, 2018). There is strong evidence that stress during learning may enhance the formation of emotional stimuli (Domes et al., 2002; Schwabe et al., 2008; Smeets et al., 2008), yet the underlying oscillatory correlates, especially in the theta range, are missing. Theta oscillations are central to memory processes and emerge from the hippocampus (Herweg et al., 2020). As such, uncovering their interaction with stress during emotional encoding is vital. In sharp contrast to stress during encoding, stress post-encoding has been found to enhance the initial consolidation of non-emotional memories, filtering emotional memories, and hampering their consolidation (Ritchey et al., 2017). This mechanism is in turn contrary to post-retrieval stress effects, where subsequent memory for non-emotional stimuli seems to be impaired (Dongaonkar et al., 2013; Hupbach & Dorskind, 2014; Larrosa et al., 2017; Maroun & Akirav, 2008; Schwabe & Wolf, 2010). Based on animal studies implicating a central role of the original memory trace in the reactivation process, as well as the observed post-encoding effects of stress in humans, it is tempting to assume an equally important role of memory traces in post-retrieval memory processes. To this end, their role in memory updating under stress remains however unexplored in humans. Furthermore, the exact mechanism of neural reactivation (online and offline) are incompetently understood in general, but especially in light of stress. The hippocampus, PCC and VTC emerge as prime candidates within this process. Afterall, the cortico-hippocampal connectivity during memory reactivation may be critical to uncover underlying neural mechanisms during post-retrieval memory process under stress.

To enhance our understanding of post-retrieval memory updating under stress in light of these significant gaps, three independent studies were conducted. In study I, we set out to investigate the effects of acute stress during the encoding of negative and neutral pictures with

a specific focus on theta oscillations, given their crucial role in episodic memory. To this end, participants underwent a psychosocial stress induction procedure (Trier Social Stress Test; TSST; Kirschbaum et al., 1993) upon entering the MEG for a picture encoding task. Twenty-four hours later, a recognition test was conducted. We hypothesized a general emotional memory enhancement by stress, accompanied by increased theta oscillations in brain areas central to episodic memory formation (i.e., MTL). Study II was designed to investigate the behavioural and neural correlates of post-retrieval stress in the context of memory-updating processes. Through fMRI recordings across three days (encoding, reactivation, delayed retrieval), we probed the role of hippocampal memory trace reactivation for post-retrieval updating in healthy controls versus stressed participants. We hypothesized that stress after retrieval would generally impair memory of neutral information, contingent on the extent of memory reactivation prior to the TSST. Building upon the results of study II, study III served as a partial follow-up and extension, focusing on the neuromodulatory basis of stress effects in post-retrieval memory updating. Considering the prominent roles of cortisol and noradrenaline during the stress response, we here specifically probed their individual effects on post-retrieval memory processes. While also recording fMRI across three days this time also included resting-state scans before and after the critical memory reactivation. In summary, these three studies were designed to delineate how stress influences both, the initial encoding of memories, and the mechanisms involved in post-retrieval processing, thus shedding light on the differential effects stress may yield on the neural system across different stages of memory formation, and its effects on future remembering.

2 Experimental studies

2.1 Study I: The role of theta oscillations in emotional memory formation under stress

Stress enhances emotional memory-related theta oscillations in the medial temporal lobe. Heinbockel, H., Quaedflieg, C. W., Schneider, T. R., Engel, A. K., & Schwabe, L. (2021). *Neurobiology of Stress*, *15*, 100383.

2.1.1 Background

Stressful events affect memory formation (Quaedflieg et al., 2013; Wirz & Schwabe, 2020), especially for emotionally charged stimuli. While these stress-related effects on emotional memory formation could have significant consequences, the underlying neural mechanisms are not yet fully understood. In particular, the temporal processing aspects of the mechanisms involved in forming emotional memories under stress are still unclear. There is evidence suggesting that stress may modulate theta band activity (Gärtner et al., 2014), which is of strong relevance given its well established role in memory formation (Buzsáki & Moser, 2013; Nyhus & Curran, 2010; Sauseng et al., 2010). Additionally, rodent data suggest that stress might specifically impact theta activity in the MTL (Ghosh et al., 2013; Jacinto et al., 2013). We therefore hypothesized that acute stress would enhance subsequent memory, especially for emotionally arousing events, and that emotional memory formation under stress would be associated with increased theta activity in the MTL.

2.1.2 Methods

We recruited 67 healthy, right-handed adults. Testing spanned two days: Day 1 featured a behavioral stress induction via the TSST or a control tasks, followed by picture encoding in MEG. Participants here viewed emotionally negative and non-emotional (neutral) pictures while rating emotional intensity. Day 2 included a recognition memory test, including all images presented on Day 1 and an equal number of new foils. The successful stress induction was probed with repeated measurements of blood pressure, salivary cortisol, and mood. Besides subsequent memory performance, we also compared memory confidence between groups, for non-emotional and emotional images separately. Basic frequency analyses were conducted to confirm the role of theta oscillations in this process in general. Based on individually recorded anatomical MRI images, we conducted follow-up source reconstruction to localize theta power. Frequency and source level results were tested with cluster-corrected permutation t-tests.

2.1.3 Results

The TSST effectively induced stress, evidenced by significant increases in negative mood, blood pressure, and salivary cortisol. Furthermore, participants in the stress condition reported significantly higher stress ratings, unpleasantness, and difficulty compared to controls. 24 hours later, a recognition test was conducted. Memory performance was generally high, with overall increased recognition for emotional compared to non-emotional images, reflecting the expected general emotional memory enhancement (Figure 3A). We additionally observed a stress-related increase in confidence for negative images (Figure 3B). In line with our hypothesis, we observed a significant theta power increase in stressed compared to control participants during the encoding of emotional stimuli, particularly in medial temporal but also in occipito-parietal regions (Figure 3C). Importantly, stress did not influence theta activity associated with the encoding of non-emotional stimuli. Explorative analyses in the alpha and beta bands revealed differences in sensor-level power between negative and neutral stimuli but not on the source level, suggesting some degree of specificity for the theta range.

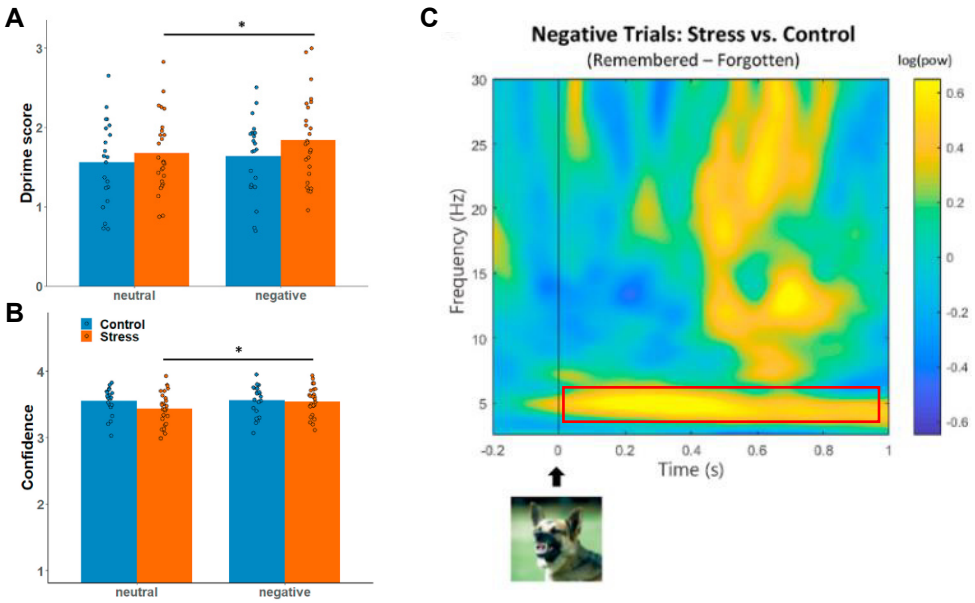

Figure 3. Stress effects on theta power during the encoding of negative trials. **A** Dprime scores confirmed the overall good memory performance and the expected emotional memory enhancement. **B** Memory confidence scores showed that whereas confidence was comparable for neutral and negative stimuli in control participants, negative items were recognized with higher confidence than neutral items when participants were stressed before encoding. **C** Averaged time-frequency representation (negative > neutral; stress > control) of occipito-parietal sensors, revealing a significant increase in the theta band (indicated by red frame); *p < .05

2.1.4 Conclusion

Using MEG, we probed how stress influences emotional memory formation at behavioural and neural levels. Our neural findings revealed stress-induced augmentation of memory-related theta activity, particularly in medial-temporal and occipito-parietal regions, which was specific for emotional pictures. This increase was localized in areas crucial for emotional memory processing, such as the hippocampus and amygdala. Despite observed neural changes, delayed recognition performance did not differ between stressed and control groups, possibly due to high overall performance and test sensitivity differences. However, stress did impact memory confidence, with stressed individuals showing heightened sensitivity to emotional stimuli. In summary, our findings show how stress shapes emotional memory formation via enhanced theta activity in key brain regions. This mechanism may prioritize storage of emotionally salient events, crucial for adaptive responses to stressors, implicated in disorders like PTSD.

2.2 Study II: Post-retrieval stress effects on memory updating

Heinbockel, H., Wagner, A. D., & Schwabe, L. (2024). Post-retrieval stress impairs subsequent memory depending on hippocampal memory trace reinstatement during reactivation. *Science Advances*, *10*(18).

2.2.1 Background

Memories are dynamic and can undergo alterations long after their initial consolidation (Dudai & Eisenberg, 2004; Nadel et al., 2012). Reactivated memories are sensitive to various interventions, including acute stress, impairing subsequent recall in humans (Dongaonkar et al., 2013; Hupbach & Dorskind, 2014; Larrosa et al., 2017; Maroun & Akirav, 2008; Schwabe & Wolf, 2010). However, the neural mechanisms underlying these effects remain unclear. In this study we hypothesized that post-retrieval stress would impair subsequent memory, especially for associations retrieved with a strong hippocampal memory trace reactivation. Furthermore, the PCC and VTC were expected to play pivotal roles, alongside their connectivity with the hippocampus, in memory reactivation and resulting stress effects.

2.2.2 Methods

A total of 89 healthy, right-handed adults were initially recruited for this three-day fMRI paradigm. On Day 1, participants encoded word-picture pairs and underwent immediate cued recall. On Day 2, half of the pairs were reactivated before they underwent a standardized stress or control manipulation (TSST). On Day 3, the final cued recall, and a functional localizer task (scenes vs. objects) were performed. Analyses focused on subsequent memory effects of word-picture associations comparing reactivated and not reactivated trials. Whole-brain contrasts (GLMs) within and between different experimental days were followed by Psychophysiological-Interaction-Analysis (PPI) to assess connectivity between seed and target regions during memory reactivation. MVPA was used to assess trial-wise cortical category reinstatement in the VTC. Finally, RSA was conducted to assess stress-related changes in neural patterns between reactivated and not reactivated trials, focusing on the PCC. Resulting estimates were employed in (Generalized) Linear Mixed Models (G/LMMs) in order to predict Day 3 memory performance.

2.2.3 Results

Participants successfully encoded and recalled word-picture associations on Day 2 and successfully reactivated these associations on Day 2. Importantly, post-retrieval stress induction on Day 2 led to increased negative mood, physiological arousal, and cortisol levels in the stress group compared to controls. On Day 3, both groups showed improved memory for reactivated compared to not-reactivated associations from Day 2, indicating effective memory reactivation. Stronger connectivity between the hippocampus and cortical representation areas during reactivation was associated with better memory performance on Day 3 in the control group but impaired memory performance in the stress group. Most critically, in controls, hippocampal reinstatement of the encoding representation during reactivation was predictive of Day 3 memory performance when accompanied by high hippocampal activity. However, this relation was significantly impaired in stressed participants (Figure 4A). Moreover, RSA indicated differences in pattern reconfiguration between stress and control groups from Day 1 to Day 3, particularly in the PCC. In the control group, subsequent memory was associated with increased pattern dissimilarity between Day 1 and Day 3 representations in the PCC (Figure 4B). Conversely, the stress group did not show such an increase in dissimilarity; instead, high similarity of neural patterns in the PCC from Day 1 to Day 3 was related to successful retrieval.

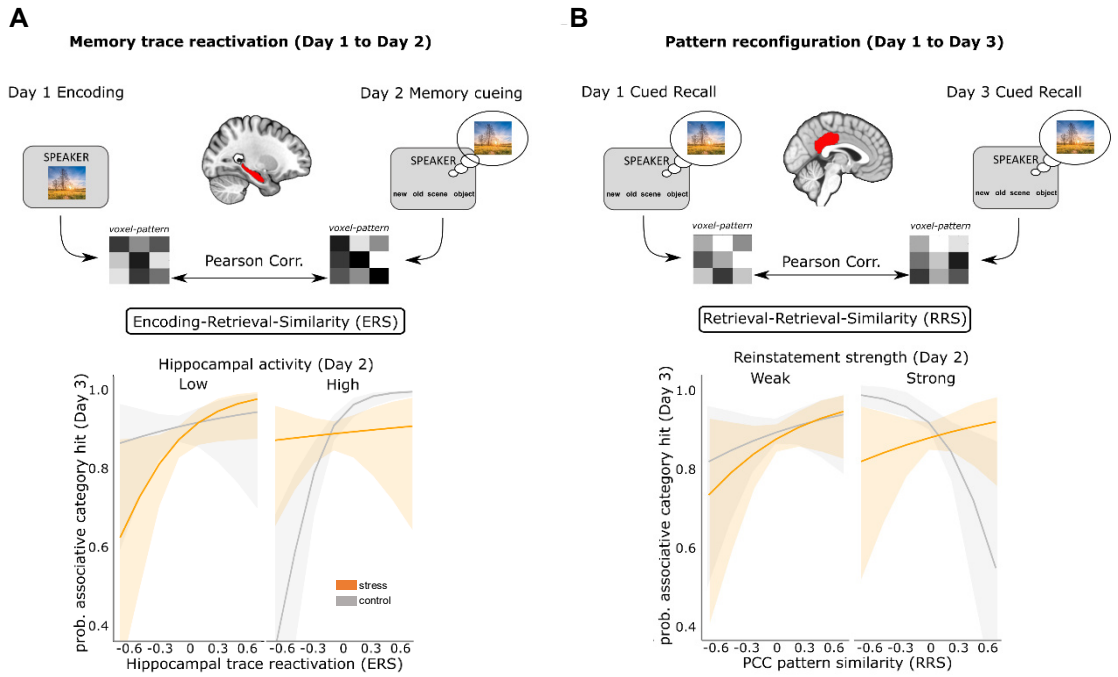

Figure 4. Post-retrieval effects of stress on memory linked to trace reactivation on day 2 and neural pattern reconfiguration from days 1 to 3. **A** Strong memory trace reactivation (Day 1-to-Day 2 ERS) together with high hippocampal activity during Day 2 increased Day 3 performance in controls. In the stress group, Day 3 performance was reduced when hippocampal activity and hippocampal ERS were high during reactivation. **B** In controls, strong VTC reinstatement together with low PCC pattern similarity (Day 1-to-Day 3) was related to successful retrieval. In the stress group, this effect was reversed resulting in lower memory.

2.2.4 Conclusion

This study demonstrates that the detrimental impact of post-retrieval stress on subsequent memory relies heavily on the reinstatement of hippocampal memory traces during reactivation, as well as cortico-hippocampal interactions. While this reactivation-dependent effect of post-retrieval stress aligns with the proposed reconsolidation mechanism, it is important to highlight that we found no evidence of a weakening of the original memory trace. Instead, following reactivation, memory in stressed individuals became more dependent on the original memory trace compared to control participants. This suggests that stress impedes the consolidation of a new memory trace based on retrieval, which would facilitate later recall, as observed in controls. Yielding evidence for both, reconsolidation theory and MTT, yet within different brain areas our findings also hold significant implications for efforts to address debilitating memories in anxiety disorders or PTSD.

2.3 Study III: The role of major stress mediators in post-retrieval memory updating

Heinbockel, H., Wagner, A, D., & Schwabe, L. (under review in *Elife*). Post-retrieval noradrenergic activation impairs subsequent memory depending on cortico-hippocampal reactivation.

2.3.1 Background

Recent evidence highlighted a detrimental impact of post-retrieval stress on subsequent memory, being bound to cortico-hippocampal interactions in general, and hippocampal memory trace reinstatement during reactivation in particular (Heinbockel et al., 2024). Stress triggers complex neurotransmitter and hormonal cascades (Joëls & Baram, 2009), including elevated levels of noradrenaline and glucocorticoids, strongly impacting memory processes (de Quervain et al., 1998; Roozendaal et al., 2009; Schwabe et al., 2022). The specific roles of either of these modulators during memory updating remains however unclear so far. Additionally, the potentially differential roles of online (during retrieval) and offline (during rest periods after retrieval) reactivation in interaction with elevated levels (post-retreival) of noradrenaline and glucocorticoids, and resulting effects on subsequent memory remain unknown.

2.3.2 Methods

68 healthy right-handed participants were recruited for this 3-day fMRI study, and randomly assigned to one of three groups: Placebeo, 20mg Yohimbine (α2-adrenoceptor antagonist; increased noradrenergic stimulation via indirect feedback mechanisms) or 20mg Hydrocortisone (cortisol). The study followed a fully crossed, double-blind design. Day 1 involved encoding word-picture pairs and immediate cued recall. Day 2 comprised drug administration and a memory reactivation task, where half of the encoded pairs were presented to prompt memory retrieval. Physiological measures (e.g., blood pressure, cortisol) confirmed drug action. Day 3 involved a final cued recall and an independent localizer task (scenes vs. objects). Analyses focused on comparing reactivated and non-reactivated trials. Single-trial beta estimates were computed for all days and tasks to provide detailed neural response characterization. MVPA assessed trial-wise cortical category reinstatement strength. Reactivation estimates were used in G/LMMs to predict Day 3 performance and estimate the trial-specific effect of stress based on the extent of reactivation prior to the intervention.

2.3.3 Results

On Day 1, participants effectively encoded and recalled word-picture pairs. Neural analysis on Day 2 showed no notable differences between cued and not reactivated pairs or among groups, suggesting similar memory retrieval processes. Participants performed well during the Reactivation task on Day 2, with significant brain activation in key memory regions like the hippocampus, VTC, and PCC indicating successful memory retrieval. Higher activity in hippocampal and PCC regions correlated with faster reaction times, suggesting their involvement in efficient memory reactivation. As expected, the Yohimbine (YOH) group showed noradrenergic arousal, and the Hydrocortisone (CORT) group displayed glucocorticoid activation post-memory reactivation, confirming drug action. On Day 3, memory performance was overall higher for cued associations, confirming reactivation efficacy. High confidence (Figure 5A), strong hippocampal activity (Figure 5B), as well as VTC reinstatement (Figure 5C) during reactivation, predicted subsequent memory in the PLAC and CORT groups. In the YOH group, stronger reactivation predicted poorer memory, particularly for high hippocampal activity trials. Offline reactivation patterns did not interact with noradrenergic or cortisol effects on subsequent memory.

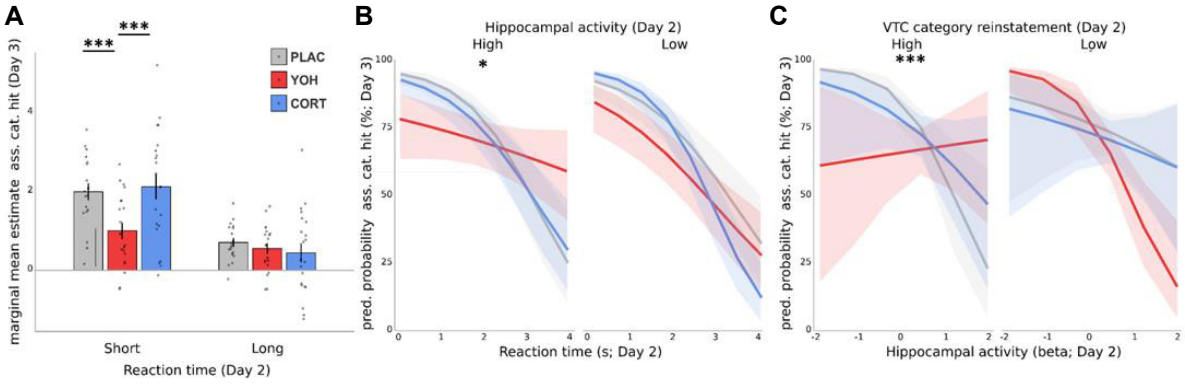

Figure 5. Subsequent memory impairment by noradrenergic activation depends on hippocampal and VTC online reactivation. **A** In all three groups, the probability of a later associative category hit on Day 3 was greater on trials for which there were shorter reaction times/higher confidence during recall on Day 2. However, trials which were reactivated more strongly prior to noradrenergic activation were affected most. **B** Reductions in the probability of later associative category hits on Day 3 were further related to high hippocampal activity during Day 2 memory reactivation, specifically for the YOH group. Notably, trials which were retrieved with low confidence during memory cueing were not affected by any drug. **C** Further reductions in the probability of later associative category hits on Day 3 were observed for strong category level reinstatement in the VTC in conjunction with strong hippocampal univariate activity in the YOH group on Day 2, which differed from the relationships seen in the PLAC and CORT groups.

2.3.4 Conclusion

In this study, we found that increasing noradrenergic activity, but not glucocorticoid activity, after memory retrieval impairs subsequent remembering. Importantly, this impairment was specific to items cued and correctly recalled before yohimbine administration, indicating that mere cueing was not enough to render memories vulnerable to modification. Our neural data revealed that yohimbine's negative effects on subsequent memory correlated with strong hippocampal reactivation and category-level representations in the VTC during memory cueing. Notably, noradrenaline's impact relied on online reactivation; no effects of offline reinstatement during rest periods were observed. Though patterns from online reactivation were also reinstated during post-retrieval rest, offline reinstatement did not interact with the drug's effects. Overall, these findings highlight the reliance of post-retrieval interventions on neural signals elicited during retrieval, and the specific role of noradrenaline in post-retrieval stress effects.

3 General discussion

The ability to learn and adapt under pressure shows how resilient and adaptive humans are. Intuitively, stress may be viewed as a hindrance to cognitive function (Arnsten, 2015; Kim & Diamond, 2002; McEwen & Sapolsky, 1995), yet it paradoxically seems to serve as a catalyst for fortifying memories of distressing experiences under certain conditions (Cheung et al., 2015; Christianson, 1992; Payne et al., 2006). While considerable attention has been devoted to exploring (emotional) memory formation under stress, these investigations have yielded mixed results, often accompanied by contradictions (Domes et al., 2002; Schwabe et al., 2008; Diamond et al., 2007; Elzinga et al., 2005; Kirschbaum et al., 1996). Especially how stress affects the precise spatiotemporal correlates within the MTL during emotional memory encoding remains elusive. Study I was specifically designed to close this gap, shedding light on the impact of acute stress on emotional memory encoding, with a specific focus on the underlying theta oscillations, which are critically implicated in episodic memory processes. Results revealed, for the first time, that increased theta activity in medial temporal and occipito-parietal areas during memory formation underlay the facilitating role of stress in emotional memory processing. Additionally, stressed individuals exhibited heightened memory confidence for emotional stimuli, indicating prioritization of emotionally salient memories. But stress does not only affect memory formation when we initially acquire information. Immediately after remembering an event, we might feel stressed, which subsequently impacts updating processes potentially impairing future remembering (Dongaonkar et al., 2013; Hupbach & Dorskind, 2014; Larrosa et al., 2017; Maroun & Akirav, 2008; Schwabe & Wolf, 2010). While it is established that post-retrieval memory updating hinges upon neural reactivation (Alvares et al., 2013; Lee et al., 2017), we lack a comprehensive understanding of how stress exactly interacts with this process. Recent evidence from animal models (Khalaf et al., 2018) but also human post-encoding studies (Ritchey et al., 2017) emphasized the central role of the memory trace formed during encoding for subsequent memory processing; yet little is known about whether stress impacts the stability or fidelity of this trace after retrieval. The hippocampus emerges as a prime candidate in this process, orchestrating episodic memory processes in general via its strong functional connections to cortical representation areas. Exploring the effects of stress on post-retrieval memory, study II showed that stress impaired subsequent memory, depending on cortico-hippocampal connectivity and most critically the reinstatement of the original memory trace within the hippocampus. These results confirmed the central role of the reactivation of the original memory trace formed during encoding for subsequent memory processes, and additionally, that the extent of reactivation indeed predicts

the impact of stress on future remembering. Stress effects on memory processes are strongly bound to physiological mediators, i.e. noradrenaline and cortisol. Disentangling the precise contributions of these mediators in post-retrieval stress effects poses another notable gap. To specifically delineate the role of major stress mediators within post-retrieval memory updating, study III focused on the specific roles of noradrenaline and cortisol within this process. Results revealed that pharmacologically increased levels of noradrenaline, but not cortisol, impaired subsequent memory. These effects were however strongly dependent on hippocampal and cortical online, but not offline, reactivation during retrieval, emphasizing the major importance of the reactivation event for post-retrieval interventions. Besides the specific vulnerability to noradrenaline, these findings suggest that memory updating, in general, relies primarily on online reactivation processes and that noradrenaline engages in retrieval, but not encoding related representations.

Overall, the results of studies I-III dovetail with existing evidence, supporting the facilitatory role of acute stress in memory processing for emotionally salient information during encoding (Domes et al., 2002; Schwabe et al., 2008), and impairing effects when occurring post-retrieval (Dongaonkar et al., 2013; Hupbach & Dorskind, 2014; Larrosa et al., 2017; Maroun & Akirav, 2008; Schwabe & Wolf, 2010). Especially the results from our neural data analyses provide a significant amount of novel findings, uncovering so far unknown oscillatory correlates of stress during emotional encoding and the effects and dependencies of memory reactivation in light of post-retrieval stress and the differential impact of major stress mediators. But what exact mechanisms might be at play in each of these studies, and what might be the overarching role of stress across the memory formation process?

3.1 Stress during encoding enhances memory for emotional events via prioritization

Results from study I revealed an improvement for emotional memory retention while non-emotional memory performance remained unaffected by stress. How and why did stress enhance the formation of emotional, but not non-emotional, memories during encoding? Emotionally negative events generally reflect potential threats. When acutely stressed, the fight-or-flight system is activated via the ANS, allowing us to defend ourselves or seek a safe place quickly. In order to be prepared for an additional encounter in the future, emotionally negative events are stored stronger than non-emotional events, which can be explained by the fact that stress boosts memory formation for details central to the stressor while reducing memory for

peripheral aspects (Payne et al., 2006; Rush et al., 2011; Wessel & Merckelbach, 1997). Mechanistically, the observed emotional memory improvement is likely facilitated by the influence of stress on brain prioritization processes that bolster the retention of emotional memories over non-emotional memories (Kensinger, 2009; Mather et al., 2016), which was behaviorally reflected in increased confidence for emotional event memory. This interpretation gains support from the observed interaction of stress and increased theta power in the MTL in the context of emotional images. Acute stress exposure triggers the release of various hormones, peptides, and neurotransmitters, many of which directly influence neuronal activity (Chen et al., 2012; Gulpinar & Yegen, 2004; Kovacs & Sawchenko, 1996). Animal studies suggest that cortisol exerts a non-genomic effect on neurons by inhibiting the release of cAMP, which is integral to synaptic transmission (Borski et al., 2002; Karst et al., 2005), and that way potentially influences brain oscillations. Consequently, major stress mediators, but cortisol in particular, may directly stimulate neurons generating theta-frequency oscillations inducing large-scale changes in neuronal activity. This interpretation aligns with prevailing models of memory formation under stress, which propose that stress enhances the processing of emotionally salient material (Payne et al., 2006; Weymar et al., 2012) depending on the MTL, including the amygdala and hippocampus, central regions in emotional memory formation under stress (Akirav & Richter-Levin, 2002; Kim et al., 2001). Besides the MTL, emotional images in study I also increased theta activity in occipital regions. Interestingly, there is evidence for a reciprocal functional connection between the amygdala and areas involved in early visual processing (Amaral et al., 2003; Furl et al., 2013; Morris et al., 2001; Tamietto et al., 2012). The stress-related increase in theta activity in the occipital cortex during emotional memory formation may thus be part of the same prioritization process, the MTL is involved in, which is particularly relevant during stressful encounters. Finally, memory-related theta activity was heightened in parietal areas, commonly associated with working memory and memory retrieval processes (Hebscher et al., 2019; Jacobs et al., 2006; Riddle et al., 2020; Sauseng et al., 2004). Speculatively, this increase in parietal theta might facilitate the retention of emotionally salient events in working memory for longer durations, aiding both coping strategies during stressful situations and the consolidation of these events into long-term memory. Overall, the stress-induced increases in emotional memory-related theta power in medial temporal and occipito-parietal areas likely promote the mnemonic binding of elements within and across representational areas. This enhanced processing of salient events and their prolonged availability in short-term memory potentially facilitates the storage of emotionally arousing events experienced during stress. Finally, beyond single brain areas, stress might have

led to a large-scale network reconfiguration favoring the salience network (Clemens et al., 2017). The salience network acts as a gatekeeper, determining the significance of incoming information from both external stimuli and internal mental states (Schimmelpfennig et al., 2023). It comprises key regions such as the anterior cingulate cortex (ACC) and the insula, which play pivotal roles in directing attention and prioritizing stimuli (Menon & Uddin, 2010; Vogt et al., 1992; Weissman et al., 2005). The salience network ensures that attention is directed toward relevant stimuli and coordinates appropriate responses. However, overactivity in this network has been linked to psychiatric and neurological conditions, including autism spectrum disorder, schizophrenia, and attention deficit hyperactivity disorder (ADHD), where individuals may struggle to filter irrelevant information or prioritize information effectively (Green et al., 2016; Schimmelpfennig et al., 2023; Yerys et al., 2019). As we however have not observed specific connectivity effects in study I, this explanation remains speculative.

3.2 Post-retrieval stress impairs subsequent memory – A specific role for noradrenaline?

At first glance, results from studies II and III might match those from study I, as neither post-retrieval stress, nor post-retrieval noradrenergic or glucocorticoid activation reduced the average subsequent memory performance of non-emotional stimuli. Yet the process of post-retrieval updating, and especially the effects of stress and major stress mediators, seems to be more nuanced. Results of studies II and III showed that post-retrieval stress, and noradrenaline specifically, can indeed impair subsequent memory depending on the extent to which event representations were reactivated during the intervening retrieval. Notably, this specificity of the neural reactivation effect was observed on the behavioral as well as neural level. All groups across studies II and III exhibited a robust enhancement in average memory performance 24 hours after reactivation, supporting the idea that event retrievals occurring between learning and future attempts to remember may influence future remembering (Antony et al., 2017; Dudukovic et al., 2009; Szapiro et al., 2002), and reflecting the well-established testing effect (McDaniel et al., 2007; Roediger III & Karpicke, 2006). This dynamic was confirmed by the neural data, as in both studies the hippocampus, VTC and PCC emerged as key players of neural reactivation during memory cueing. The hippocampal activity was not only correlated with participants' reaction times on successfully retrieved trials during memory reactivation, but also with the strength of category reinstatement within the VTC, implicating that the mere presentation of a reminder cue does not suffice to induce neural reactivation. As such, only

successfully retrieved (but not forgotten) associations showed the reactivation-enhancement in subsequent memory. Whole-brain fMRI results further revealed a network of cortical brain regions involved in successful memory reactivation, including core areas of the DMN (i.e. PCC). Traditionally associated with self-referential and internally focused mental processes (Yeshurun et al., 2021), the DMN's involvement in memory retrieval is by now well known (Andrews-Hanna et al., 2010; Sestieri et al., 2011; Wang et al., 2020). In non-stressed controls (within study II), category reinstatement in the VTC and hippocampal connectivity with this cortical network predicted subsequent memory performance. Contrary to controls, stressed participants did not benefit from category reinstatement in the VTC during reactivation for subsequent memory. Strikingly, subsequent memory performance was even impaired when cortico-hippocampal connectivity was strong during reactivation. This indicates that the same event reactivation that enhanced subsequent memory in controls was associated with impaired memory in stressed participants.

While the negative impact of post-retrieval stress on subsequent memory is consistent with previous studies suggesting stress impairs a proposed reconsolidation mechanism (Dongaonkar et al., 2013; Hupbach & Dorskind, 2014; Larrosa et al., 2017; Maroun & Akirav, 2008; Schwabe & Wolf, 2010), the specific decrease in memory performance due to noradrenergic activation appears to contradict existing evidence. Previous research suggested that administering the beta-blocker propranolol, which impairs noradrenergic activation, following memory reactivation can decrease subsequent memory formation, potentially disrupting the proposed reconsolidation process (Kindt et al., 2009; Przybyslawski et al., 1999; Schramm et al., 2016; Schwabe et al., 2012). However, this effect has not been consistently replicated (Bos et al., 2014; Elsey et al., 2020; Muravieva & Alberini, 2010), leading to the expectation that post-retrieval noradrenergic activation might in turn enhance memory. Study III, however, demonstrates that increased noradrenergic activity after memory retrieval actually diminishes subsequent memory performance. Notably, there are crucial distinctions between our investigation and previous propranolol studies. One key difference is that earlier research primarily focused on emotionally charged information or fear memories, operating on the assumption that post-retrieval propranolol might disrupt reconsolidation by reducing the emotional significance of these memories (Dębiec & LeDoux, 2004; Lee et al., 2006; Phelps et al., 2004), yielding mixed results. In contrast, our studies used emotionally neutral scene images, offering a novel perspective on the effects of noradrenergic activity on memory reconsolidation. Another significant difference lies in the pharmacological dynamics of the drugs used. Yohimbine, which blocks α2-receptors and significantly increases noradrenaline

levels, contrasts with propranolol, which significantly inhibits noradrenergic activation. Given the extreme effects of both drugs, our findings align with existing evidence suggesting an inverted U-shaped relationship between post-retrieval noradrenergic arousal and subsequent memory. Both propranolol-induced noradrenergic blockade and yohimbine-induced strong noradrenergic stimulation after reactivation seem to impair subsequent memory (Arnsten, 2015; Birnbaum et al., 1999; Hernaus et al., 2017). Importantly, in Study III, this effect was specifically related to hippocampal processing during reactivation. Excessive noradrenergic activation within the hippocampus may disrupt neurotransmission (Diamond et al., 2007). The hippocampus is highly sensitive to noradrenergic modulation, influencing long-term potentiation and depression (Katsuki et al., 1997), which could potentially impair subsequent memory following post-retrieval stress. Similarly, in Study II, the impact of post-retrieval stress appeared to hinge significantly on hippocampal reactivation dynamics, suggesting that initial noradrenergic activation played a pivotal role as part of the acute stress response.

Apart from noradrenaline, acute stress triggers a substantial increase in cortisol levels, which has been linked to potential impairments in memory reconsolidation after retrieval (Antypa et al., 2021; Maroun & Akirav, 2008; Vafaei et al., 2023; Wang et al., 2008). Interestingly, in Study III, the activation of glucocorticoids post-retrieval did not influence subsequent memory, as evidenced by similar performance between placebo and cortisol groups in the memory task following stress induction. This suggests that cortisol alone may not suffice in this context and likely requires collaboration with noradrenaline for its memory-modulating effects to fully manifest. Previous research has underscored that the impact of glucocorticoids on memory processes is particularly pronounced when accompanied by heightened noradrenergic arousal, which was observed during stressful circumstances (de Quervain et al., 2007; Roozendaal et al., 2006; Schwabe et al., 2022). Furthermore, it is noteworthy that the administration of hydrocortisone in Study III did not lead to increased arousal or negative mood. Stress induces a cascade of neurochemical changes where cortisol binds to receptors in limbic brain regions (Reul & Kloet, 1985), while noradrenaline indirectly activates the basolateral amygdala (Roozendaal et al., 2009). This coordinated action affects memory processes by modulating noradrenergic activity both before and after synaptic transmission (Krugers et al., 2012), influencing interconnected brain regions crucial for memory and emotion regulation, such as the hippocampus, prefrontal cortex, and dorsal striatum (Roozendaal et al., 2008; Barsegyan et al., 2010; Karst et al., 2005; Van Stegeren, 2008; De Quervain et al., 2007; Buchanan et al., 2006; Cahill et al., 2003). Thus, the findings from Study III suggest that while noradrenaline exerts specific effects in memory processing, cortisol alone may not be sufficient

to influence post-retrieval memory updating and may require concurrent noradrenergic arousal to fully manifest its memory-modulating effects (Maroun & Akirav, 2008; Roozendaal et al., 2006).

3.3 Post-retrieval stress prevents retrieval-related memory trace formation

Beyond the fundamental recruitment and coactivation of the hippocampus and neocortical areas, the role of memory traces in post-retrieval updating processes remains unexplored, particularly in light of stress. Generally, consolidation processes temper the neural signals from the encoding stage (Axmacher et al., 2009; Dudai et al., 2015), establishing memory traces (Miyashita et al., 2008). In line, study II showed that in non-stressed controls, the reinstatement of the hippocampal encoding representation during memory reactivation (i.e., ERS) was predictive of subsequent memory performance when accompanied by high hippocampal activity. This could mean that in controls, memory was enhanced via reconsolidation mechanisms, which strengthen the hippocampal memory traces from encoding. Yet it could also be the case that, during the reactivation process, new retrieval-related traces were formed, thereby enhancing future recall. While the formation of a new trace would favour MTT, the strengthening of an existing memory representation would be more in line with reconsolidation theory (Figure 6A). Interestingly, results from study II, comparing Day 1-to-Day 3 retrieval representations in the hippocampus, revealed that subsequent memory still relied on a high similarity, which would speak for a reconsolidation mechanism at play; not forming a new trace, but enhancing the original encoding trace. Generally, this underscores the pivotal role of the hippocampus in the post-retrieval modification of memory, aligning with recent evidence from rodents, which suggests a critical role of the original memory trace in post-retrieval memory changes (Khalaf et al., 2018). Our findings however extend the existing evidence, proposing reconsolidation as the critical mechanism of hippocampal memory trace updating.

Closely related, we discovered another intriguing dynamic in the PCC. That is, in the control group, subsequent memory was associated with increased pattern dissimilarity between the immediate and delayed cued recall (Day 1-to-Day 3) event representations, reflecting an opposite effect compared to the hippocampus. This reliance on dissimilarity can be interpreted as the development of a new, more specific, retrieval-related trace within the PCC, formed during reactivation. Although representing two contrary dynamics, both mechanisms (update of original trace, and creation of new retrieval-related trace) seem to work in parallel to facilitate subsequent memory in light of post-retrieval updating processes. While this would support the

view that reconsolidation and MTT are not mutually exclusive (Dudai et al., 2015), our findings suggest that both mechanisms might be part of a larger integrative process, which consists of both dynamics occurring in specialized, functionally heterogenic brain areas, recruited during reactivation (i.e., PCC, hippocampus).

The stress group on the other hand showed a markedly different pattern, as strong hippocampal trace reactivation prior to stress, impaired subsequent memory (Figure 6B). Thus, the same reactivation events that enhanced subsequent memory in controls were linked to diminished memory in participants exposed to stress after memory reactivation. Again, these findings are compatible with two possible interpretations. Based on reconsolidation theory, it could be argued that the stressor after memory reactivation interfered with the re-stabilization of the reactivated and hence labile memory representation, thus negatively affecting subsequent memory on Day 3. To look further into this question, Day 1-to-Day 3 retrieval representations within the hippocampus were compared and revealed that subsequent memory still relied on the original memory trace (high pattern similarity). This finding indicates that the original hippocampal memory trace was not changed by stress. From a MTT perspective, these observations are consistent with the possibility that stress disrupted the consolidation of newly formed retrieval-based memory traces. Interestingly, results from the PCC revealed a comparable pattern. Compared to controls, the stress group did not show such an increase in pattern-dissimilarity from Day 1-to-Day 3 in the PCC. Instead, high similarity of neural patterns in the PCC from immediate to delayed cued recall was related to successful retrieval, indicating reliance on the old/original memory trace. The pattern of results from study III partially supports this interaction. Here, effects of post-retrieval noradrenaline on subsequent remembering were also potentially owing to alterations in new hippocampal memory traces formed during retrieval, and not reconsolidation-related changes, as we did not observe interactions of any drug with the encoding-related hippocampal memory trace. In short, post-retrieval stress, and noradrenaline specifically, seem to impair memory updating processes in a twofold way. Post-retrieval stress may specifically impact the retrieval-related updating processes in the hippocampus, yet furthermore prevent retrieval-related memory trace formation in the PCC, rendering the updating process ineffective.

While these findings relate to the neural correlates derived from the retrieval tasks, memory updating may however also depend on offline neural reinstatement dynamics during rest (Oudiette et al., 2013; Staresina et al., 2013; Tambini et al., 2010); processes we did not specifically capture in study II. In an approach to tackle these so far unknown neural post-retrieval dynamics under stress, study III therefore included pre- and post-reactivation resting-

state scans to capture offline reactivation assays. Study III revealed that the neural patterns activated during memory retrieval were more frequently reactivated during the resting period after the task compared to before the task. This finding supports previous research on offline reactivation and replay in episodic memory (Káli & Dayan, 2004; Sara, 2010; Wimmer et al., 2020). Yet, it is surprising that this reactivation assay did not predict subsequent memory in any group, neither positively, nor negatively. Offline reactivation reflects repetitions of the neural patterns from online processing. So how can it be that the online reactivation correlates predict subsequent memory, but the offline correlates do not? To explain this deviation, it is important to differentiate between the estimated neural online compared to offline parameters. While offline reinstatement might seem like a simple repetition of the neural signals activated during retrieval, the two parameters we derived are not directly comparable. We studied offline reactivation in the brain by examining neural patterns using RSA (Representational Similarity Analysis) during rest periods before and after a memory reactivation task. We compared neural activity from the Reactivation task with resting-state fMRI scans taken before and after the task, focusing on the hippocampus, VTC, and PCC. The reported offline reinstatement events were in the end based on differences in correlations that exceeded a threshold, and do not reflect the direct strength of the underlying neural correlate (such as e.g. trial-wise hippocampal activity). Given that the observed impairments in subsequent memory in the YOH group were directly dependent on the trial-specific strength of online neural reactivation (i.e., hippocampal activity and reaction times) one would need to derive a comparable assay from the offline intervals. However, this is not directly possible for two reasons: Firstly, it is important to note that the reaction time (confidence) during memory cueing was the most powerful predictor of memory reactivation as well as post-retrieval dynamics, which could not be derived from resting state intervals. Secondly, offline reactivation processes are supposed to operate significantly faster than online processes, due to the absence of a cognitive task (Buch et al., 2021; Cousins et al., 2016; Ramanathan et al., 2015). This potential increase in processing speed poses a significant factor, as the rather slow fMRI cannot match this temporal resolution. In fact, it is possible that several specific events were indeed reactivated offline in the neural system, but these different representations would have been recorded in one single MRI image, removing any representational specificity from the observed patterns. One potential solution for this this challenge would be a concurrent recording of fMRI and EEG, combining the excellent spatial and temporal resolutions of these two methods.

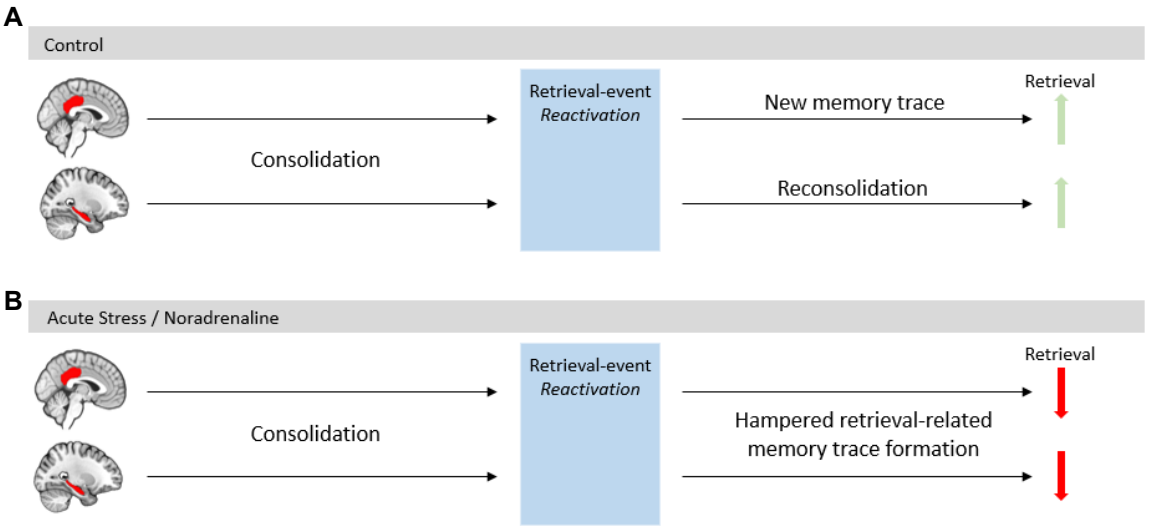

Figure 6. Dynamic development of memory traces and their role for delayed retrieval. **A** In the control group, successful recall on Day 3 was bound to high pattern dissimilarity in the PCC, indicating the formation of a new memory trace. In parallel, future remembering relied on high similarity of hippocampal patterns, indicating a reconsolidation mechanism. **B** Stress seemed to mainly interact with the reactivated neural signal during the intervening retrieval, as neither in the PCC nor in the hippocampus new memory traces were formed, in the end hampering subsequent recall.

3.4 Unpredictable stress triggers emotional prioritization in memory formation and updating

Across the conducted studies, stress had differential effects on subsequent memory. While storage of negative events was enhanced by stress during encoding, memory for non-emotional events was hampered by post-retrieval stress. Interestingly, these effects relied on a rather similar cortico-hippocampal network, posing a distinct target to acute stress across memory formation stages. While evidence suggests that brain regions implicated in initial memory formation may also play a role in the modification of memories during and after retrieval (Censor et al., 2010; Danker & Anderson, 2010; O'Neill et al., 2010), particularly the hippocampus has been suggested to serve as crucial structure, creating *indices* that link different elements of a memory together (Teyler & DiScenna, 1986). At the core of this theory is the idea that memories are not stored in a single location in the brain but are distributed across various neural networks, including specialized brain areas for i.e. visual processing (Teyler & Rudy, 2007). Across the three studies, the pattern of results aligns with this proposed 'index' function of the hippocampus, yet extends the existing theory by the possibility that it not only orchestrates stress-related encoding- and retrieval processes, but also post-retrieval modifications of memory.

With the hippocampus as the common key player of memory formation and updating, it is now central to identify an underlying mechanism of how exactly stress interacts with hippocampal processing. One powerful and potentially unifying modulator of emotional encoding and memory updating processes under stress is the Prediction Error (PE). PEs play a crucial role in memory processes in general (Ergo et al., 2020; Shing et al., 2023; Sinclair & Barense, 2019), as emotionally arousing events are characterized by unpredictability and are therefore linked to an expectancy violation (Trapp et al, 2018). This phenomenon ensures that emotionally charged experiences (and associated details), are particularly well-remembered. On that account, stressful encounters (such as the TSST) can be viewed as significant PEs themselves, being unpredictable in nature (De Berker et al., 2016; Kalbe et al., 2020; Trapp et al., 2018) as the physiological and psychological responses to stress often diverge from expectations of safety or predictability, marking a substantial deviation from normality. As such, not knowing any details about the stressful event has been reported to enhance memory encoding and subsequent memory of the event itself but also associated details/information (Kalbe et al., 2020). Transferring this dynamic to the results of study I, this discrepancy (surprise of sudden stressful encounter) cold have specifically intensified the encoding of emotional memories associated with the stressful event, contributing to their vividness and durability over time. Assuming that the control procedure in study I did not induce any PE would further explain why neither memory performance nor confidence differed between emotional and non-emotional events. Although in study II, the stressful event (TSST) occurred directly after the reactivation task, it is very well possible that it also induced a PE just like during the encoding in study I. As the TSST directly followed the reactivation procedure, one could assume that further processing/updating of the reactivated non-emotional event representations was hampered, or even discarded, in order to save resources, and focus on negative, more relevant events, central to the stressor. This could have led to a prioritization of emotional memories just like in study I. This explanation gets support by the results of study III, where noradrenaline also had a detrimental, yet overall less pronounced effect on subsequent memory, suggesting a more cognitive and less physiology-centered explanation (Trapp et al., 2018)) for the observed effects in study II. The critical difference between the first two studies and study III can be found in the fact that no behavioral stress-induction was conducted, as participants received either a pharmacological agent (YOH, CORT) or a placebo (double-blind design). As such, no stressful encounter occurred unexpectedly, and no stress-related PE was introduced, rendering the otherwise more detrimental effect less pronounced, compared to a behavioral stress procedure (i.e., TSST).

To sum up, the central role of the hippocampus across emotional memory formation and updating could in the end reflect a PE–dynamic. The stressful event (TSST) may induce an emotional prioritization of the hippocampus (and connected areas) onto emotional events, enhancing the encoding of emotional but suppressing the updating of non-emotional events. This theory gains support from fMRI studies that have shown increased hippocampal activity when subjects encounter unexpected outcomes, suggesting that the hippocampus is indeed responsive to PEs, particularly in spatial and contextual learning (Johnson & Redish, 2005; Schultz et al., 1997; Vinogradova, 2001).

3.5 Future directions

While the suggestion of a common role for a hippocampal-processed PE across memory formation and updating is rather speculative on the one hand, it also so far ignored one major difference among the applied studies: While study I utilized emotional and non-emotional images intermixed, studies II and III solely relied on non-emotional associations. So the first questions concerns how the TSST-induced PE would related to emotional versus non-emotional event representations in a memory-updating paradigm. As proclaimed, emotional events may get prioritized post-retrieval, yielding an emotional memory enhancement compared to non-emotional events, just like in study I. At the core, it remains open whether in study I the effect was observed only due to the parallel presentation, and therefore competition, of emotional and non-emotional events or not. This seems however reasonable, especially regarding the explanation of these effects relying on prioritization processes (negative > neutral). If this is the case, the hyperactivity of the hippocampal-parietal-occipital network in study I might be responsible for processing this competition and prioritization. As a similar network was active and subsequently affected in studies II and III, this could potentially reflect the exact same process (competition and prioritization) of emotionally negative events during memory updating. While emotionally negative events yield a high relevance for PTSD or anxiety disorders, great efforts have been made to weaken the underlying intrusive memories in order to alleviate symptoms. Evidence suggests that post-reactivation stress sufficiently impairs specific fear or phobia-related memories (de Quervain et al., 2017; Meir Drexler et al., 2015; Schwabe, et al., 2012; Vafaei et al., 2023), posing a potential conflict to the dynamic proclaimed above. Yet these studies utilized solely negative (fear, phobia) events and did not include non-emotional events. So in short, the role of emotional competition within the memory updating framework remains unknown so far, and to uncover such a dynamic, especially considering

neural reactivation assays, one would need to repeat studies II and III, using non-emotional and emotional associations intermixed.

Another open topic of discussion, which demands further investigation, concerns that we did not observe a significant interaction of stimulus valence and the stress manipulation on the behavioral level in study I. While within the stress group the associative dprime and confidence increased in emotional compared to non-emotional trials, this increase was not significantly greater compared to controls. The absence of behavioral effects can be explained by two reasons. First, a recognition test was conducted at the second day. Recognition tests are particularly effective in leveraging familiarity. Participants can identify previously encountered items based on a general sense of having seen them before, even if specific details are not recalled. This makes recognition tests highly sensitive to memories formed through exposure and repetition, capturing even those memories that are not deeply encoded but still familiar, rendering such tasks rather easy. In study I this is reflected in the overall very high confidence ratings across groups and emotionality, reflecting a ceiling effect, lowering sensitivity and interpretability. A possible solution could be found in the application of cued recall tests, focusing on active retrieval based on specific cues. Such tests can provide a more accurate measure of memory strength and depth, effectively managing similarity through detailed prompts. Yet, their success depends heavily on the quality and clarity of the cues provided. Secondly, when assessing memory performance, context plays a significant role. In study I, participants encoded the images within the MEG, yet 24 hours later the recognition test was conducted in a separate testing room. While this might look like a minor difference, research has shown that memory test performance often decreases when the test is applied in a different setting from where the learning originally occurred (Godden and Badeley, 1975; Smith, 1979; Smith and Vela, 2001). The overall subtle behavioural results of study I could therefore very well be bound to context-dependent memory effects. Future designs should (i) apply the memory test also within the same spatial learning context and (ii) potentially apply a cued recall and a subsequent recognition test in order to tackle trials with well-established memory traces.

3.6 Conclusion

Stress does not universally impair cognitive functions, as our findings revealed a nuanced reality where stress enhances the encoding of emotionally significant memories while impairing non-emotional post-retrieval memory processes. Using MEG and fMRI, we uncovered that acute stress increases memory-related theta activity in the MTL, enhancing the retention of emotionally negative events and increasing confidence for emotional images without affecting

overall recognition accuracy. Conversely, we found that post-retrieval stress disrupts memory-updating processes. Elevated noradrenaline levels post-retrieval here impaired subsequent memory, suggesting that stress interferes with retrieval-related memory trace formation of reactivated memories. Interestingly, cortisol alone did not influence post-retrieval memory, indicating that it requires concurrent noradrenergic activation to exert its effects. Although stress effects went in different directions at first sight, the underlying neural correlates and potential mechanism seem to be rather similar. Critically, results from all three studies emphasize the role of the initial memory trace, formed during encoding. Across all three studies, the hippocampus emerged as key player within the respective memory processes, being strongly connected to mainly visual representation areas. While in study I the subsequent memory effect was strongly related to theta power increases during encoding, sufficient memory reactivation in studies II and III critically depended on sufficient hippocampal memory trace reinstatement as well as cortico-hippocampal network activity. The observed hyperactivity of this cortico-hippocampal network could reflect an induced PE in context of the behavioral-stress manipulation, leading to an emotional prioritization during encoding and updating. This effect underscores the complexity of stress-related memory processes and provides valuable insights for addressing debilitating memories associated with anxiety disorders or PTSD. Future research should delve deeper into the interactions between stress mediators like noradrenaline and cortisol and their combined impact on memory updating, utilizing magneto- or electrophysiological imaging techniques to capture the spatial and temporal dynamics of neural activity utilizing emotional and non-emotional event associations.

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Appendix A: Study I

Stress enhances emotional memory-related theta oscillations in the medial temporal lobe. Heinbockel, H., Quaedflieg, C. W., Schneider, T. R., Engel, A. K., & Schwabe, L. (2021). Neurobiology of Stress, 15, 100383.

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Stress enhances emotional memory-related theta oscillations in the medial temporal lobe

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ABSTRACT

Stressful events impact memory formation, in particular for emotionally arousing stimuli. Although these stress effects on emotional memory formation have potentially far-reaching implications, the underlying neural mechanisms are not fully understood. Specifically, the temporal processing dimension of the mechanisms involved in emotional memory formation under stress remains elusive. Here, we used magnetoencephalography (MEG) to examine the neural processes underlying stress effects on emotional memory formation with high temporal and spatial resolution and a particular focus on theta oscillations previously implicated in mnemonic binding. Healthy participants (n = 53) underwent a stress or control procedure before encoding emotionally neutral and negative pictures, while MEG was recorded. Memory for the pictures was probed in a recognition test 24 h after encoding. In this recognition test, stress did not modulate the emotional memory enhancement but led to significantly higher confidence in memory for negative compared to neutral stimuli. Our neural data revealed that stress increased memory-related theta oscillations specifically in medial temporal and occipito-parietal regions. Further, this stress-related increase in theta power emerged during memory formation for emotionally negative but not for neutral stimuli. These findings indicate that acute stress can enhance, in the medial temporal lobe, oscillations at a frequency that is ideally suited to bind the elements of an ongoing emotional episode, which may represent a mechanism to facilitate the storage of emotionally salient events that occurred in the context of a stressful encounter.

1. Introduction

Stress has a major impact on our memory. Research over the past decades showed that stress around the time of encoding can enhance memory formation whereas stress before retention testing impairs memory retrieval (Schwabe et al., 2012; Roozendaal and McGaugh, 2011; Joëls et al., 2011; De Quervain et al., 1998). Interestingly, both the enhancing effects of stress on memory formation and the detrimental effects on memory retrieval appear to be most pronounced for emotionally arousing information (Shields et al., 2017; Buchanan et al., 2006; Cahill et al., 2003). In particular, the enhanced (emotional) memory formation under stress may have important implications for our understanding of stress-related mental disorders, such as anxiety disorders or posttraumatic stress disorder (PTSD; De Quervain et al., 2017; Pitman et al., 2012; Hyman, 2005; Dalgleish and Watts, 1990).

Given these important implications, a plethora of studies aimed at elucidating the brain mechanisms involved in the impact of stress on emotional memory formation. It is well known that the hormones and neurotransmitters that are released in response to a stressful event, such as noradrenaline and glucocorticoids, act directly on brain regions critical for memory formation, such as the prefrontal cortex or medial temporal lobe, including the hippocampus (Qin et al., 2012; Lovallo et al., 2010; Arnsten, 2009; Pruessner et al., 2008; Kim and Diamond, 2002). Moreover, noradrenaline has been suggested to initiate a large-scale network reconfiguration, resulting in a bias towards the so-called 'salience network' (Hermans et al., 2011, 2014), which prioritizes emotionally salient information and may thus promote emotional memory formation. Compelling research in rodents further led to a model according to which the enhanced (emotional) memory formation under stress is due to the interactive interplay of

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noradrenaline and glucocorticoids in the basolateral part of the amygdala, which then modulates memory storage processes in other brain areas, such as the hippocampus or the dorsal striatum (Roozendaal et al., 2006, 2009; McGaugh and Roozendall, 2002). Although this model was initially based on studies in rodents, there is also evidence from humans in line with the predictions of this model (Van Stegeren, 2008; De Quervain et al., 2007; Buchanan et al., 2006; Cahill et al., 2003).

Most human research on the processes underlying memory formation under stress used functional magnetic resonance imaging (fMRI), which has an excellent spatial but limited temporal resolution. Accordingly, the temporal processing dimension of the mechanisms through which stress alters memory remains less well understood. Initial evidence from studies using electroencephalography (EEG) shows that stress modulates event-related potentials implicated in memory formation (Wirz et al., 2017; Quaedflieg et al., 2013; Wirkner et al., 2013) and at least some of these effects appeared to be specific for emotionally arousing material (Weymar et al., 2012). Importantly, there is also initial evidence suggesting that stress may modulate activity in the theta band (Gärtner et al., 2014). Theta oscillations may be of particular interest for stress effects on memory given their assumed role in memory formation (Sauseng et al., 2010; Buzsáki and Moser, 2013; Nyhus and Curran, 2010). Interestingly, rodent data suggest that stress may affect theta activity specifically in the medial temporal lobe (Ghosh et al., 2013; Jacinto et al., 2013). EEG studies in humans lack this degree of spatial resolution, accordingly the spatio-temporal correlates through which (emotional) memories are built under stress remain elusive. At this point it is important to note that neuroimaging methods, such as EEG or MEG, are correlative in nature and therefore do not allow causal inferences on the relationship between brain activity and the studied cognitive process. In order to probe the causal role of theta activity in memory, studies utilizing brain stimulation techniques directly modulating theta activity are required. Such evidence comes from a recent study showing that tACS, but not sham stimulation, in the theta range (6 HZ) applied over the right fusiform region increased associative memory performance (Lang et al., 2019). These results indicate that an increase in theta power might indeed be mechanistically related to memory processes.

In the present experiment, we leveraged magnetoencephalography (MEG) which enables the measurement of neural activity with high temporal and spatial resolution to elucidate the underlying neural signature of emotional memory formation shortly after a stressful event, with a particular focus on potential changes in medial temporal theta activity. To this end, healthy participants underwent a psychosocial stress or control procedure before they encoded a series of neutral and emotionally arousing pictures while MEG was recorded. Memory was tested in a recognition test 24 h later. To probe the neural underpinnings of (emotional) memory formation after stress, we used a subsequent memory analysis contrasting the neural activity during encoding of subsequently remembered and forgotten stimuli. We predicted that acute stress would enhance memory specifically for emotionally arousing events and that emotional memory formation under stress would be linked to increased theta activity in the hippocampus.

2. Materials and methods

2.1. Participants and experimental design

We recruited 67 healthy, right-handed adults with normal or corrected-to-normal vision (35 women, 32 men; age = 19–35 years, mean = 25.05 years, SD = 3.72 years). Exclusion criteria were checked in a standardized interview and comprised a history of any neurological or psychiatric disease, smoking, drug abuse, intake of any prescribed medication, previous participation in the stress protocol. Women were only included if they did not use hormonal contraception and were not tested during their menses because these factors may affect the endocrine stress response (Kudielka and Kirschbaum, 2005). Participants were asked not to drink coffee or other caffeinated beverages and not to do any exercise on the day of the experiment. Additionally, they were requested not to eat or drink anything except water 2 h before the experiment. Participants were pseudo-randomly assigned to the stress or control group, to achieve a comparable number of men and women per group. All participants gave written informed consent and received monetary compensation for participation. The study protocol was approved by the local ethics committee of the Faculty for Psychology and Human Movements Science at the Universität Hamburg.

Fourteen participants were excluded from analyses due to excessive head movement during MEG (mean displacement >20 mm, $n = 3$), not showing up on day 2 ($n = 4$) or technical issues ($n = 7$), thus leaving a final sample of 53 participants (27 men and 26 women, age 19–35, mean = 24.6, SD = 3.74, no age difference between groups, $t_{(52)} = 0.675$, $p = .502$, $d = 0.085$). An a priori power calculation with G*Power (Faul et al., 2007) indicated that a sample size of $N = 46$ is required to detect a *group* × *valence* interaction effect with a size of $f = 0.25$ ($\alpha = 0.05$; $1\text{-}\beta = 0.90$).

2.2. Experimental procedure

Testing was conducted on two consecutive days, with an interval of about 24 h: Day 1 included the experimental stress induction and a picture encoding task in the MEG followed by an unrelated task that is reported elsewhere (Quaedflieg et al., 2020). In brief, this task involved a think/no-think paradigm (Anderson and Green, 2001), in which participants were asked to learn and subsequently recall word-face pairs, which were clearly distinct from the stimulus materials used in the encoding task and did not include an emotional component, thus making interference (Lechner et al., 1999) or behavioural tagging effects (Vishnoi et al., 2016) rather unlikely. Day 2 included the recognition memory test. In addition, a structural MRI image was acquired from all participants in a separate session. In order to control for the diurnal rhythm of the stress hormone cortisol, all testing took place in the afternoon and early evening. To control for potential group differences in depressive mood and anxiety, participants completed the Beck Depression Inventory (BDI; Beck et al., 1961) and the State Trait Anxiety Inventory (STAI; Spielberger, 1983) prior to the experiment.

2.2.1. Experimental Day 1: stress and control manipulation

In order to induce acute psychosocial stress, participants in the stress condition were exposed to the Trier Social Stress Test (TSST; Kirschbaum et al., 1993), a standardized paradigm in experimental stress research. Participants were first asked to indicate a desired job position and after a 3-min preparation period they were requested to give a 5-min free speech about their qualification for the desired job. Thereafter, participants had to perform a 5-min mental arithmetic task (counting backwards from 2043 in steps of 17). Both tasks were performed in front of a panel of two non-reinforcing committee members (1 man, 1 woman), dressed in white lab coats. The panel was introduced as experts in behavioural analysis and supposed to act rather cold, non-reinforcing and non-responding to questions from the participants. In addition, participants were video-taped during the TSST, and the recording was shown on a TV screen placed behind the TSST panel.

In the control condition, participants engaged in two tasks of the same duration. The first task included a free speech about the last book they read, a movie they saw or holiday destination they went to. In the second task, participants counted forward in steps of 15. Importantly, there was no panel present, and no video recordings were taken.

In order to assess the successful stress induction, we took subjective ratings, blood pressure, heartrate, and saliva samples at several time points before and after the experimental manipulation. We measured mood changes using the negative affect subscale of the state positive and negative affect schedule (PANAS; Watson et al., 1988). In addition, participants' rating of the stressfulness, unpleasantness and difficulty of the experimental manipulation was measured on a visual analogue

(VAS) scale from 0 (not at all) to 100 (extremely) directly after the experimental manipulation. Blood pressure and heartrate (arm cuff: Omron Healthcare Europe BV) were measured at baseline, before, during, and immediately after the experimental manipulation, and when participants left the MEG (i.e., −25, −1, +10, +15, +90 min relative to TSST onset). Saliva samples were obtained, before and immediately after the experimental manipulation, before the encoding task, after the encoding task as well as well at the end of day 1 (i.e., −1, +15, +30, +70, +105 min relative to the onset of the experimental manipulation). At the end of data collection, cortisol was analysed from saliva samples with a luminescence assay (IBL International, Hamburg, Germany).

2.2.2. Experimental Day 1: picture encoding task

Stimulus materials for the memory tasks consisted of 300 emotionally negative and 300 emotionally neutral pictures taken from the International Affective Picture System (IAPS; Lang and Bradley, 2007). One hundred and fifty pictures of each valence were used as stimuli during encoding on day 1, the remaining 300 pictures (150 negative, 150 neutral) were used for the Recognition Test on day 2, representing *new* Items.

About 20 min after the experimental manipulation, participants performed the picture encoding task in the MEG. In this task, 150 neutral and 150 negative pictures were presented in pseudorandomized order (not more than three emotional or neutral pictures in a row) on a computer screen using MatLab (version R2017b; The MathWorks). Each picture was presented for 2 s in the middle of the screen. Afterwards a scale appeared at the lower part of the screen asking participants to rate the intensity (1–4; anchors: 1 = not intense at all, 4 = very intense) of the presented picture. Between stimuli, a fixation cross was presented for a random interval between 2 and 3 s. Participants were instructed to memorize all presented pictures. This encoding session took about 30 min.

2.2.3. Experimental Day 2: recognition test

In order to control for potential group differences in stress levels before the memory test, blood pressure and heart rate were measured, and another saliva sample was collected at the beginning of day 2. To assess memory performance of the pictures encoded on day 1, a recognition test programmed in MatLab (version R2017b; The MathWorks) was presented on a computer screen. This recognition test included the 300 pictures that were encoded on day 1 as well as 300 new pictures. Old and new pictures were again presented in pseudorandomized order (not more than three new or old pictures in a row). Each item was presented for 4 s, and participants were instructed to indicate whether the picture was presented on day 1 ('old') or not ('new') via button press. If a picture was classifieded as 'old', participants were further asked to rate the confidence of their decision (1–4; anchors: 1 = very unconfident, 4 = very confident; Yonelinas et al., 2005). Each trial was followed by a fixation cross of 2 s.

2.3. Statistical analyses

To test the successful stress induction, data on subjective ratings, vital signs, and salivary cortisol were analysed using 2 × 2 repeated-measures ANOVAs (Type III) with the between-subjects factor *group* (stress/control) and the within-subject factor *time*. During the encoding task on day 1, participants rated the intensity of the presented pictures. We tested potential differences in the expressed intensity using a 2 × 2 repeated-measures ANOVA (Type III) with the between-subjects factor *group* (stress/control) and the within-subject factor *valence* (negative/neutral). In order to analyse the performance in the recognition task, we calculated hits and false alarms as well as the sensitivity index *dprime,* based on signal detection theory (Wickens, 2002), separately for stimuli of neutral and negative valence. Each of these measures was analysed using 2 × 2 repeated-measures ANOVAs (Type III) with the between-subjects factor *group* (stress/control) and the within-subject factor *valence* (negative/neutral). Furthermore, we tested potential differences in recognition confidence with a 2 × 2 repeated-measures ANOVA (Type III) including the between-subjects factor group (stress/control) and the within-subject factor valence (negative/neutral). In an additional, explorative analysis of potential sex differences, we added the factor sex (male vs. female) to this model. In order to relate memory performance, memory confidence and theta power to subjective and objective stress-parameters, pearson correlations were used utilizing changes in *cortisol*, *systolic blood pressure* and *scores of the negative PANAS scale* (pre-to post-stress). Cortisol values were log-transformed, and the area-under-the-curve increase from pre-stress to peak (+30 min relative to TSST onset) was used. For systolic blood pressure the absolute change between pre-stress and peak (during TSST) was used. To counteract the problem of multiple comparisons, holm correction (Holm, 1979) was applied. Accordingly, corrected p-values are reported.

All data analyses were performed with R version 3.3.6 (R Core Team, 2017). All reported *p*-values are two-tailed and Greenhouse-Geisser correction was applied if required. Significant ANOVA results were followed up by appropriate post-hoc tests. Prior to inference statistical procedures, data were checked for normal distribution (Shapiro-Wilk Test), homogeneity of variance (Levene-Test) as well as outliers.

2.4. Structural MRI acquisition

MRI measurements were obtained on a 3 T Siemens Magnetom Prisma scanner, equipped with a 32-channel head coil. A high-resolution T1-weighted anatomical image (voxel size = 1 × 1 × 1 mm) was acquired for later source-analysis of the MEG data.

2.5. MEG data acquisition

MEG was acquired at a rate of 1200 Hz, with a 275-channel whole-head system (Omega 2000, CTF Systems Inc.), housed in an electrically and magnetically shielded room. Additional Ag/AgCl-electrodes were applied to measure horizontal and vertical electrooculogram (EOG) and electrocardiogram (ECG). The head position relative to MEG sensors was monitored online during the whole recording and corrected as soon as the movement exceeded 5 mm using three fiducial points (nasion, left and right external ear canal).

2.6. MEG data processing

All analyses of the MEG data were conducted in MatLab (version R2017b; The MathWorks) using either custom made scripts or functions from the FieldTrip toolbox (Oostenveld et al., 2011).

2.6.1. Preprocessing

Data were imported to MatLab and filtered between 0.5 and 120 Hz (BUT Filter, Low-pass filter 4th order, high-pass filter 3rd order), and specifically filtered for line-noise using band-stop filters for relevant frequency intervals (49.5–50.5 Hz, 99.5–100.5 Hz). Signals were subsequently resampled to 400 Hz. Raw data were then divided into 6 s epochs (−2 to +4 s relative so stimulus onset). All Epochs were further demeaned based on the average signal of the whole trial. In order to remove artifacts related to SQUID jumps, muscle artifacts or external noise, we utilized semi-automatic detection based predefined thresholds (Quaedflieg et al., 2020). Following this procedure, on average 85% of all trials (SD = 10%) were retained in each dataset. In the next step, we calculated an extended infomax independent component analysis using the 'runica' command (ICA, stop criterion: weight change $<10^{-7}$) in order to identify and reject components related to eye-blinks or heartbeat. These components were identified by visual inspection of time courses and corresponding brain topographies. On average 5 (±SD: 1.6; range 2–10) components reflecting either cardiac or electro-ocular activity were removed before back-projecting the signals into

sensor-space.

2.6.2. Frequency analysis

Spectral decomposition of MEG data was performed using sliding Hanning windows (2–30 Hz, 1-Hz steps, five-cycle window, interval: −2 to 4 s relative to stimulus onset). The single trials were log-transformed (Grandchamp and Delorme, 2011; Smulders et al., 2018) and baseline corrected (absolute baseline correction −1 to 0 s relative to stimulus onset). The spectral data was then averaged per stimulus type (negative and neutral valence; remembered and not remembered) across participants of the experimental and control group, respectively.

2.6.3. Source analysis

Localization of frequency specific source activity was performed with the dynamic imaging of coherent sources (DICS; Gross et al., 2001) beamforming technique utilizing all 275 sensors (magnetometer and gradiometer). Volume conduction models were created using a single-shell volume conductor model (Nolte, 2003), based on the T1-weighted structural magnetic resonance image (MRI; Siemens Magnetom Prisma) from each participant. For three participants no T1 MR image was available, and consequentially the standard MNI 152 brain template was used. Individual MEG sensor positions were aligned to the MR images based on three fiducials (left and right acoustic meatus, nasion) using rigid body transformation. Segmentation of brain tissue was performed using the SPM12 software. Head models were derived from individual MR images using a single-shell volume conductor model (Nolte, 2003). A template grid of source positions was used (6 mm spacing). Following, leadfield matrices were calculated for each participant using the individual MEG sensor positions aligned to the individual head model and the source grid. Cross-spectral density matrices of the MEG data were computed for the time window and frequency which revealed a significant difference in the frequency data. The regularization parameter was set to $\lambda = 0.05$. Common spatial filters were computed by averaging the cross-spectral density matrices across all stimulus types and conditions. Power estimates in each source were estimated by multiplying the common filters with the cross-spectral density matrix of each stimulus type.

2.6.4. MEG analysis

All following statistical analyses of MEG data were centred around spectral and source power differences during immediate encoding (0–1 s). Contrast specific effects at whole-brain sensor and source level were tested with cluster-based permutation tests (10.000 permutations to correct for multiple comparisons; Maris and Oostenveld, 2007). This approach allows testing for statistical differences in large-scale data sets without the need for prior assumptions about the location of effects, while controlling for multiple comparisons. The samples were clustered at a level of $\alpha = 0.05$. Clusters with a Monte Carlo *p*-value of .05 and less are reported as significant. Prior to the statistical tests on source level, we parcellated the brain space using an anatomical mask (AAL; Tzourio-Mazoyer et al., 2002) to reduce computational effort and increase interpretability.

In a first step, we compared spectral power differences between negative and neutral trials independent of group and memory performance in theta frequency range (4–7 Hz) using a dependent sample cluster-based permutation *t*-test. This way we were able to identify the exact time-windows of where a significant difference between both stimulus categories was present, and could simultaneously probe the distinct role of theta oscillations during emotional memory formation (Hsieh and Ranganath, 2014; Lega et al., 2012). Thereafter, data windows corresponding to significant frequency clusters were projected to the source level and averaged over Regions of Interest using the AAL Atlas. Source data was next compared with dependent sample cluster-based permutation t-tests.

In a next step, we performed a subsequent memory analysis, in order to relate the neural signature of picture encoding on day 1 to the actual memory performance on day 2. We therefore divided the data of the day 2 recognition task for valence, and whether pictures were correctly recognized or not. The MEG data were afterwards divided accordingly, in order to organize the MEG data of each participant in the following categories: Negative_remembered, Negative_forgotten, Neutral_remembered and Neutral_forgotten. As the initial analysis revealed a significant difference of spectral theta power between negative and neutral trials, further analyses were also primarily focussed on the theta frequency range (4–7 Hz). We subtracted the theta power of forgotten trials from remembered trials in order to retain brain activity associated with remembering. Next, we extended the analysis by adding the factor *group* (stress vs. control), and subsequently compared spectral power differences of negative (remembered-forgotten) and neutral (remembered-forgotten) trials separately between stress and control groups. Independent sample cluster-based permutation t-tests were calculated to find the exact time-window of were a significant difference between both stimulus categories was present. Data windows corresponding to significant frequency clusters were projected to the source level and averaged over Regions of Interest using the AAL Atlas. Source data was next compared with cluster-based permutation t-tests on the source level.

3. Results

3.1. Successful stress induction

Shortly before the picture encoding in the MEG on day 1, participants underwent either the TSST ($n = 28$) or a non-stressful control manipulation ($n = 25$). Significant increases in subjective stress ratings, blood pressure, and salivary cortisol confirmed the successful stress induction through the TSST. Participants in the stress condition experienced the experimental manipulation as significantly more stressful ($t_{(51)} = -6.893$, $p < .001$, $d = 1.896$), unpleasant ($t_{(51)} = -6.275$, $p < .001$, $d = 1.726$), and difficult ($t_{(51)} = -10.476$. $p < .001$, $d = 2.883$) than participants in the control condition (Table 2). Negative mood state, as measured with the negative affect subscale of the PANAS, increased significantly in response to the TSST but not after the control manipulation (*time* × *group* interaction: $F_{(1,77)} = 12.45$, $p < .001$, $\eta^2_p = .203$; Table 1). Post-hoc tests revealed significantly higher negative affect ratings in the stress group compared to the control group after the experimental manipulation ($t_{(49)} = -5.676$, $p < .001$, $d = 1.597$), whereas groups did not differ in their negative affect score at baseline ($t_{(51)} = -1.779$, $p = .081$, $d = 0.489$).

Systolic and diastolic blood pressure increased significantly in the stress group compared to controls, as reflected in a significant *time* × *group* interaction (systolic: $F_{(3,182)} = 19.68$, $p < .001$, $\eta^2_p = .282$; diastolic: ($F_{(3,182)} = 8.92$, $p < .001$, $\eta^2_p = .151$; Fig. 1A and B)). Post-hoc tests revealed that participants exposed to the TSST had significantly higher blood pressure than participants in the control group during the experimental manipulation (systolic: $t_{(51)} = -5.011$, $p < .001$, $d =$

Table 1
Subjective stress ratings.

	Stress	Control
Stressfulness	62.25 (23.53)***	23.08 (16.83)
Unpleasantness	57.64 (25.06)***	19.40 (18.29)
Difficulty	61.42 (17.24)***	16.40 (13.56)
Baseline NA	12.78 (3.08)	11.52 (1.87)
Pre-stress NA	11.75 (2.11)	10.64 (0.99)
Post-stress NA	15.07 (3.60)***	10.65 (1.02)

Subjective stress ratings reflected by the items 'stressfulness', 'unpleasantness' and 'painfulness' were rated on a scale from 0 ('not at all') to 100 ('very much') immediately after the TSST/Control procedure.
NA: Negative Affect was measured with the PANAS questionnaire for positive and negative mood states. Data represent means (±SD); *$p < .05$, **$p < .01$, ***$p < .001$.

Table 2
Negative affect and physiological stress parameters on day 2.

	Stress	Control
Heart rate (beats per minute)	80.53 (13.79)	86.40 (12.55)
Systolic blood pressure (mmHg)	120.85 (14.11)	118.50 (15.00)
Diastolic blood pressure (mmHg)	81.07 (7.37)	81.64 (8.44)
Cortisol (nmol/l)	4.34 (2.84)	4.69 (3.77)
Negative affect	11.00 (1.58)	10.72 (1.54)

Subjective and physiological parameters of participants on day 2. All parameters were taken at the beginning of day 2 and revealed no significant difference in either subjective or physiological stress parameters between stress and control groups. Data represent means (±SD).

1.379; diastolic: $t_{(51)} = -3.801$, $p < .001$, $d = 1.046$) and directly after the experimental manipulation (systolic: $t_{(51)} = -3.603$, $p < .001$, $d = 0.991$; diastolic: $t_{(51)} = -3.239$, $p = .002$, $d = 0.891$), whereas groups did not at baseline (systolic: $t_{(51)} = -0.921$, $p = .361$, d = 0.253; diastolic: $t_{(51)} = -0.841$, $p = .404$, $d = 0.231$). Furthermore, there was a significant *time* × *group* interaction for heart rate ($F_{(4,182)} = 5.89$, $p = .001$, $\eta^2_p = .105$; Fig. 1C). Post hoc tests indicated that the heart rate increased significantly from baseline to post-treatment in the stress group ($t_{(27)} = 3.357$, $p = .002$, $d = 0.597$), whereas there was no such increase in control participants ($t_{(24)} = -0.911$, $p = .371$, $d = 0.102$).

Finally, salivary cortisol increased in response to the TSST but not after the control procedure (*time* × *group* interaction: $F_{(2,96)} = 10.67$, $p < .001$, $\eta^2_p = .179$; Fig. 1D). The stress group had significantly higher cortisol concentrations than controls immediately before the encoding task started (i.e., 20 min after TSST onset: $t_{(51)} = -3.046$, $p = .004$, $d =$

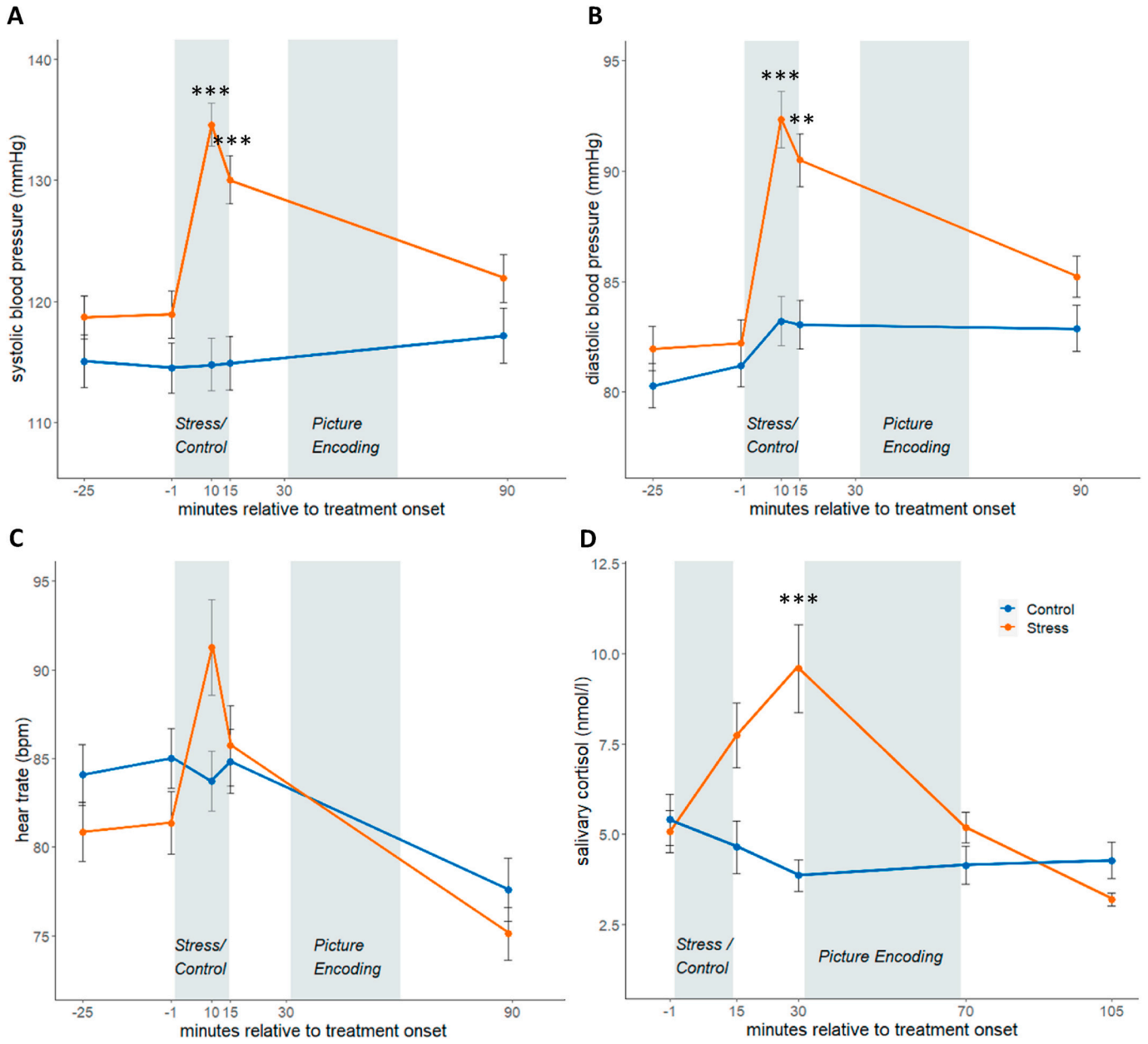

Fig. 1. Physiological stress response to the TSST/Control procedure. ***A***, Significant increases in systolic and ***B,*** diastolic blood pressure as well as ***C,*** heart rate. ***D***, The stress group further showed a significant increase in concentrations of salivary cortisol prior to the picture encoding task. Grey shades indicate the periods of the TSST/Control procedure as well as the picture encoding task. Data represent means (±SE); *$p < .05$, **$p < .01$, ***$p < .001$. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

0.838). Groups did not differ in cortisol concentrations before the experimental manipulation ($t_{(51)} = 0.250$, $p = .803$, $d = 0.068$), immediately after the experimental manipulation ($t_{(51)} = -1.900$, $p = .063$, $d = 0.522$), and 55 min after the experimental manipulation ($t_{(48)} = -1.482$, $p = .144$, $d = 0.304$).

3.2. Emotional memory enhancement

To assess stress-related changes in emotional memory and its neural underpinnings, participants encoded 150 neutral and 150 negative items in the MEG scanner. On day 1, during the picture encoding task, participants were asked to rate the intensity of each presented stimulus. As expected, negative pictures were experienced as significantly more intense (stress: 2.13 ± 0.36, control: 2.24 ± 0.43) than neutral pictures (stress: 0.42 ± 0.26, control: 0.37 ± 0.20; main effect emotionality: $F_{(1,50)} = 1389.35$, $p < .001$, $\eta^2_p = .965$). Importantly, the stress and control groups did not differ in the emotional intensity ratings (all main and interaction effects including the factor *group*: all $F < 1.10$, all $p > .313$, all $\eta^2_p < .020$).

About 24 h after encoding, participants returned to the lab for a surprise recognition test. Importantly, groups did not differ in negative affect levels, autonomic measures, or salivary cortisol before this memory test (all $t < 1.613$, all $p > .112$, all $d < 0.440$; Table 2). Overall, participants recognized 68.25 percent of the pictures encoded on day 1 correctly as 'old' (hits), whereas only 10.25 percent of the new pictures were classified as 'old' (false alarms), thus indicating very good memory performance. Accordingly, the signal detection theory-based sensitivity measure *dprime* yielded on average a high score of 1.71.

Memory was overall significantly better for negative than for neutral items, as reflected in an increased hit rate (main effect *valence*: $F_{(1,45)} = 87.82$, $p < .001$, $\eta^2_p = .661$; Fig. 2A) and a significantly higher *dprime* (main effect *valence*: $F_{(1,48)} = 10.24$, $p = .002$, $\eta^2_p = .176$; Fig. 2C),

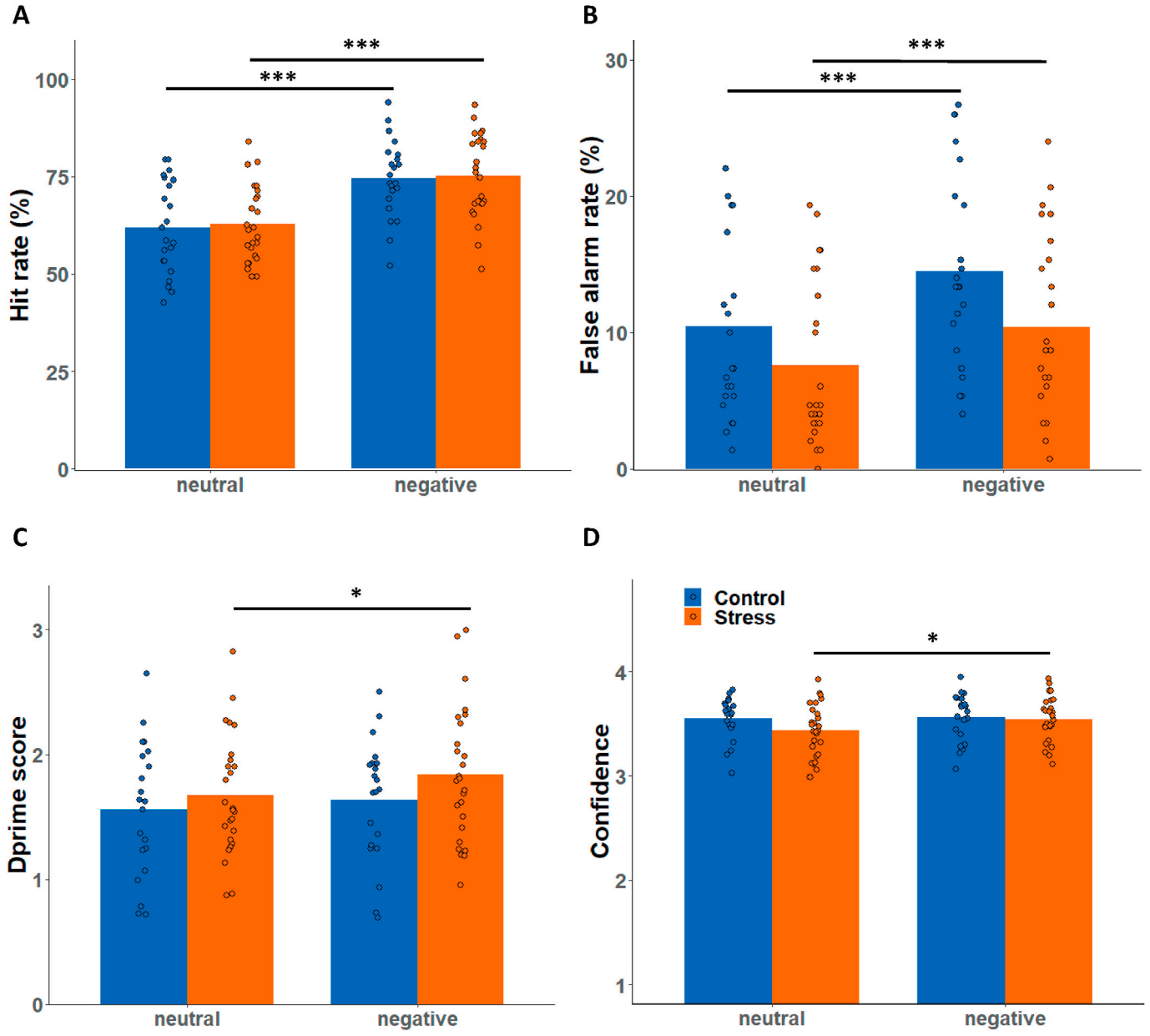

Fig. 2. Memory performance on day 2. ***A***, The hit rate reflected a high memory performance, with significantly better memory for negative than for neutral stimuli. ***B***, False alarm rates were also higher for negative than for neutral pictures. ***C***, Dprime scores further confirmed the overall good memory performance and the emotional memory enhancement. ***D,*** Memory confidence scores showed that whereas confidence was comparable for neutral and negative stimuli in control participants, negative items were recognized with higher confidence than neutral items when participants were stressed before encoding; *$p < .05$, ***$p < .001$.

although the false alarm rate was also elevated for negative compared to neutral items (main effect *valence*: $F_{(1,45)} = 36.95$ $p < .001$, $\eta^2_p = .451$; Fig. 2B). Results from the 2 × 2 ANOVA indicated that the stress and control groups did not significantly differ in recognition memory performance expressed as *dprime* (all main and interaction effects including the factor *group*: all $F < 0.50$, all $p > .485$, all $\eta^2_p < .010$; for hits and false alarms: all $F < 3.52$, all $p > .067$, all $\eta^2_p < .073$). Finally, we compared the relative differences in recognition performance between negative and neutral stimuli within each group. Results from paired t-tests revealed a significantly increased hit rate for emotional compared to neutral items (stress: $t_{(24)} = 8.022$, $p < .001$, $d = 1.210$; control: $t_{(21)} = 5.621$, $p < .001$, $d = 1.147$) and more false alarms for negative compared to neutral stimuli in both groups (stress: $t_{(23)} = 4.187$, $p < .001$, $d = 0.442$; control: $t_{(22)} = 4.419$, $p < .001$, $d = 0.593$). For the sensitivity parameter *dprime,* only the stress group showed a significantly higher performance for negative compared to neutral stimuli ($t_{(25)} = 2.590$, $p = .015$, $d = 0.331$), whereas this difference was not significant in the control group ($t_{(23)} = 1.953$, $p = .063$, $d = 0.247$). This difference, however, needs to be interpreted with great caution given the non-significant interaction effects reported above. Explorative analyses of the correlations of memory performance (*hits*, *false alarms*, *dprime*) with changes in cortisol (AUCi), systolic blood pressure (peak-baseline), and negative PANAS scale (post-pre) did not reveal a significant association (all $r < 0.359$, all $p_{corrected} > .160$).

If participants classified a picture as 'old', they further had to indicate the confidence of their decision. Overall, participants were very confident in their choices as reflected by an average confidence rating of 3.52 (±0.21). Negative pictures were overall remembered with higher confidence than neutral pictures (main effect *emotionality*: $F_{(1,46)} = 8.49$, $p < .006$, $\eta^2_p = .156$). Interestingly, whereas the confidence ratings were comparable for neutral and negative items in controls ($t_{(20)} = 0.233$, $p = .818$, $d = 0.034$), participants in the stress group recognized negative items with significantly higher confidence than neutral items ($t_{(26)} = 4.552$, $p < .001$, $d = 0.455$; *group* × *valence* interaction: $F_{(1,46)} = 6.39$, $p = .015$, $\eta^2_p = .122$; main effect *group*: $F_{(1,46)} = 0.99$, $p < .236$, $\eta^2_p = .021$; Fig. 2D).

Explorative analyses of the correlations of memory confidence with changes in cortisol (AUCi), systolic blood pressure (peak-baseline), and negative PANAS scale (post-pre) did not reveal significant direct associations (all $r < 0.329$, all $p_{corrected} > .560$).

3.3. Explorative analyses of sex differences

Although the present study did not focus on potential sex differences and was therefore not sufficiently powered to detect such effects, we ran an explorative analysis testing for potential differences in the impact of stress on emotional memory in men and women. While the sensitivity parameter *dprime* indicated an overall increase in memory performance in women compared to men (main effect *sex*: $F_{(1,46)} = 10.774$, $p = .002$, $\eta^2_p = .190$; $t_{(90)} = 4.205$, $p < .001$, $d = 0.854$), participants' sex did not modulate the influence of stress on memory for neutral and negative events, neither for *dprime*, nor for *hits*, *false alarms* or *confidence* (*group* × *valence* × *sex* interactions: *all* $F < 1.576$, all $p > .211$, all $\eta^2_p < .033$), thus suggesting that the impact of stress on emotional memory formation did not differ between men and women.

3.4. Stress increases theta power in medial temporal and occipito-parietal regions during emotional memory formation

In a next step, we asked whether stress affected the neural processes through which emotional memories are formed. In a first step, we analysed spectral power associated with the encoding of negative and neutral stimuli on sensor level, contrasting sensor level theta power (4–7 Hz) during negative and neutral trials. The cluster-based permutation *t*-test revealed a positive cluster of sensors, in which theta power was significantly increased in negative relative to neutral stimuli. From 0 to 0.9 s after stimulus onset, theta power was increased in frontal sensors ($p = .001$; *ci*-range = 0.001; std <0.001; Fig. 3A). Following source analysis, spectral data was averaged over ROIs of the AAL atlas and the subsequent cluster based permutation t-tests on ROI level revealed that the observed theta power difference related to the encoding of negative vs. neutral pictures originated from a cluster centred around frontal and temporoparietal brain regions ($p < .001$; *ci*-range < 0.001; std <0.001; Fig. 3B). These changes in source level theta power did not differ between the stress and control groups (no cluster-$p < 0.05$), suggesting that these changes may reflect general mechanisms of emotional processing that were not influenced by stress.

Next, we specifically focussed on the key question of our study, whether stress affected the mechanisms of emotional memory formation. To this end, we ran subsequent memory analyses (i.e. contrasted subsequently remembered vs. forgotten trials) for neutral and negative items, and investigated, whether the stress and control groups differed in the neural underpinnings of memory formation for negative relative to neutral stimuli. Cluster-based permutation tests on sensor level revealed that theta power was significantly increased during the encoding of negative stimuli (remembered – forgotten) in the stress group compared to controls ($p = .038$; *ci*-range = 0.004; *std* = 0.002; Fig. 4A and B; see supplementary Fig. S1 for a depiction separately in stressed and control participants) from 0 to 0.9 s relative to stimulus onset. Follow-up source analyses using cluster-based permutation tests on ROI level revealed that the observed theta power difference originated from a cluster of medial temporal lobe and occipito-parietal regions ($p = .026$; *ci*-range = 0.003, *std* = 0.002; Fig. 4C).

While stress impacted theta activity related to emotional memory formation in occipito-parietal and medial-temporal regions, theta power involved in the remembering of neutral stimuli did not differ between groups (sensor-level: no cluster-$p < .05$). Even when a more lenient threshold was used ($\alpha = 0.1$), there was no group difference in theta activity associated with the encoding of neutral stimuli. Explorative analyses of the correlations of theta activity with changes in cortisol (AUCi), systolic blood pressure (peak-baseline), and negative PANAS scale (post-pre) did not reveal significant direct associations (all $r < .447$, all $p_{corrected} > 0.156$).

3.5. Explorative analyses in additional frequency bands

In addition to our main analysis focussing on stress-induced changes in theta oscillation s related to emotional memory formation, we performed explorative analyses in the alpha (8–12 Hz) and beta (13–30 Hz) bands. In the alpha band, a signficant sensor cluster could be found, reflecting a decrease in alpha activity for negative compared to neutral stimuli, ranging from 0.6 to 1 s after stimulus onset ($p = .031$; *ci*-range = 0.065; std = 0.033). The subsequent cluster based permutation test on source level did however not reveal a significant cluster of alpha activity (no cluster-$p < .05$). In the beta band, a signficant cluster of sensors was detected, ranging from 0.6 to 1 s after stimulus onset. Here, beta power was significantly decreased for negative compared to neutral stimuli ($p = .015$; *ci*-range = 0.044; std = 0.023). Source analysis revealed that the observed beta power difference associated with negative vs. neutral pictures originated from a wide-spread occipito-parietal cluster of brain regions ($p < .001$; *ci*-range < 0.001; std <0.001).

To further uncover potential stress effects on the neural underpinnings of emotional memory formation, we exploratively compared spectral power of the alpha (8–12 Hz) and beta (13–30 Hz) bands during encoding of emotional stimuli between groups. We therefore again compared subsequent memory-related brain activity for negative and neutral items between groups. For negative trials, cluster-based permutation tests on sensor level revealed no difference in alpha power (no cluster-$p < .05$), yet a non-significant trend for a positive (stress > control) sensor cluster in the beta band from 0.4 to 0.8 s ($p = .063$; *ci*-range = 0.005; *std* = 0.002). Subsequent source analysis did however not reveal a significant cluster of activity (no cluster $p < .05$).

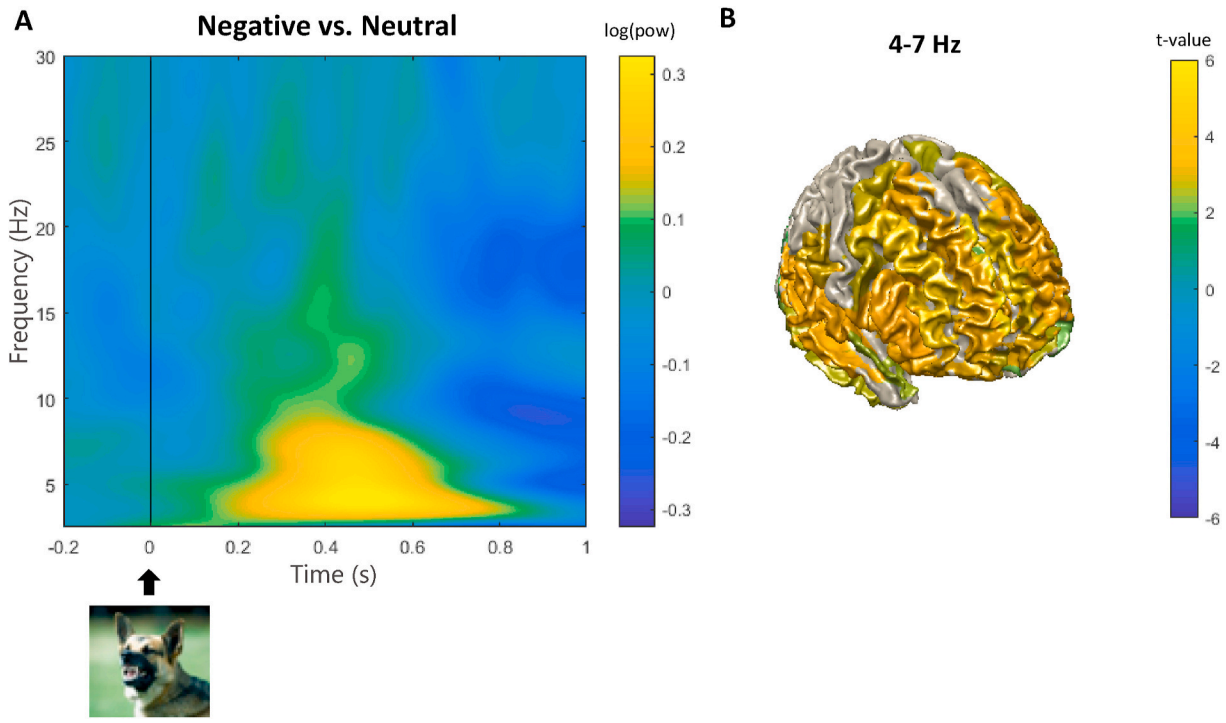

Fig. 3. Differences in spectral and source level data decompositions for negative versus neutral trials, independent of stress. ***A***, Time-Frequency representation, averaged over all sensors for illustrative purposes. ***B***, Regions with significant differences in the theta range (4–7 Hz, 0–0.9 s) resulting from the cluster-based permutation *t*-test (Negative > Neutral) on source level.

Alpha and Beta power involved in the remembering of neutral stimuli did also not differ between groups (sensor-level: no cluster-$p < .05$).

3.6. Control variables

We controlled for potential group differences in depressive mood as well as state and trait anxiety at the beginning of day 1 (Table 3). Importantly, the stress and control groups did not differ in any of these variables (depressive mood: $t_{(51)} = -0.345$, $p = .730$, $d = 0.095$, state anxiety: $t_{(51)} = -1.098$, $p = .277$, $d = 0.302$; trait anxiety: $t_{(51)} = -0.848$, $p = .399$, $d = 0.233$).

4. Discussion

Stress-induced changes in emotional memory formation are highly relevant for many contexts, including eyewitness testimony (Marr et al., 2021; Sauerland et al., 2016), educational settings (Vogel and Schwabe, 2016), or stress-related mental disorders (De Quervain et al., 2017; Pitman et al., 2012). Nevertheless, the neural mechanisms underlying changes in emotional memory formation under stress are not yet fully understood and, in particular, the temporal changes in mnemonic processing under stress remained elusive. Here, we used MEG to study the neural underpinnings of emotional memory formation under stress with high temporal and spatial resolution. At the behavioural level, we did not find a significant influence of stress on overall recognition performance but found that stress increased the influence of emotion on memory confidence. Even more importantly, our neural data revealed that stress increased memory-related theta activity in medial-temporal and occipito-parietal areas specifically for emotionally relevant material.

Theta activity is thought to act as 'glue' in memory formation and to bind brain regions during memory encoding through an increase in oscillatory power (Hanslmayr and Staudigl, 2014; Buzsáki and Moser, 2013; Nyhus and Curran, 2010). Specifically, episodic memories are comprised of multiple elements that are processed in distinct areas, which need to be integrated during memory formation (and during later retrieval). This binding relies on the precise timing of neural activity, which is assumed to be orchestrated through hippocampal theta activity (Clouter et al., 2017; Berens and Horner, 2017). From a neurophysiological perspective, theta oscillations are thought to act as a driving force in hippocampal neuronal plasticity, facilitating memory formation processes (Jutras et al., 2013; Huerta and Lisman, 1995). Our findings show that acute stress is accompanied by enhanced theta activity during memory formation, which may point to an improved binding of the separate elements of an episode under stress.

Importantly, the increase of theta power during memory formation was specific to negative stimuli and specifically present in medial temporal regions and occipito-parietal areas. This pattern of results is generally in line with prominent models of memory formation under stress, which assume that stress facilitates specifically the processing of emotionally-arousing, salient material closely linked to noradrenergic activation as well as the role of the medial temporal regions, the amygdala and the hippocampus in emotional memory formation under stress (Schwabe et al., 2012; Joëls et al., 2011; Roozendaal et al., 2009). Moreover, it is specifically hippocampal theta that has been linked to mnemonic binding (Lega et al., 2012; Tesche and Karhu, 2000). Beyond the hippocampus, however, there is also evidence that emotionally arousing stimuli lead to increased occipital activity (Phan et al., 2002; Herrmann et al., 2008), suggesting that emotional stimuli are prioritized already during early visual processing. Furthermore, there is evidence for a functional connection between the amygdala and areas involved in early visual processing (Tamietto, 2012; Amaral et al., 2003) and the effect of emotional stimuli on visual cortex activation is closely related to the amygdala's response (Furl et al., 2013; Morris et al., 2001). The stress-related increase in theta activity in the occipital cortex during emotional memory formation may, thus, further enhance the prioritization of emotionally salient information, as well as the binding of visual representations which may be particularly relevant during stressful threatening encounters. In addition to occipital cortex, memory-related theta activity was also significantly increased in parietal areas. Parietal

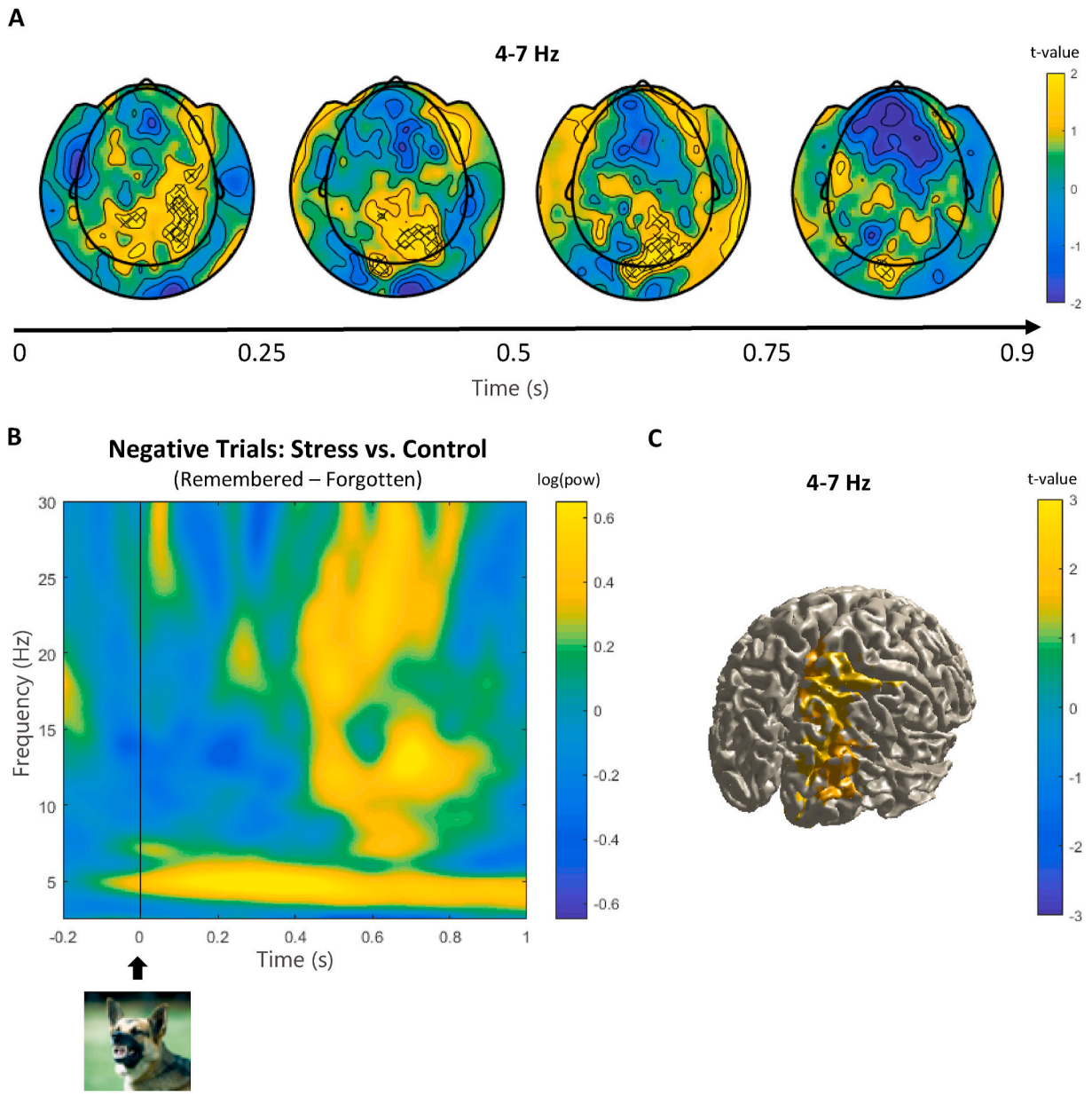

Fig. 4. Stress effects on theta power during the encoding of negative trials (remembered-forgotten). ***A***, Topography of theta activity differences (stress > control). Crosses indicate a significant cluster of sensors returned by the cluster-based permutation *t*-test. For illustrative purposes, data has been binned into four time-segments, ranging from 0 to 0.9 s relative to stimulus onset. ***B***, Averaged time-frequency representation (stress > control) of parieto-occipital sensors which were included in the significant sensor-cluster presented in A. ***C***, Brain regions with significantly higher theta activity during encoding of negative items in the stress (vs. control) group on source level.

Table 3
Participants state, and trait anxiety and depression scores.

	Stress	Control
State Anxiety	35.35 (4.93)	33.72 (5.91)
Trait Anxiety	35.21 (5.85)	33.52 (8.55)
Depression Score	3.96 (3.54)	3.60 (4.12)

State and Trait anxiety scores were measured with the State-Trait Anxiety Inventory. Depression Scores were determined utilizing the Beck Depression Inventory. Participants conducted both questionnaires at Baseline on day 1. Data represent means (±SD).

theta activity has been most commonly related to working memory (Riddle et al., 2020; Sauseng et al., 2004) and memory retrieval processes (Jacobs et al., 2006; Hebscher et al., 2019). Thus, the stress-related increase in parietal theta might represent a mechanism through which emotionally salient events are kept for longer in working memory, which may promote both the coping with the ongoing situation and the storage of the specific event in long-term memory. In sum, the stress-related increases of emotional memory-related theta power in medial temporal and occipito-parietal areas that we observed here might represent a mechanism that facilitates the mnemonic binding of elements of an episode within and across representational areas. The enhanced visual processing of salient events as well as their longer availability in short-term memory, may foster the prioritized storage of emotionally arousing events experienced in the context of a stressful encounter. Although there is evidence suggesting a causal link between theta and memory (Lang et al., 2019), it is at this point important to note that MEG studies are correlative in nature and that based on the present data as such the conclusion that changes in theta are a causal mechanism

underlying memory formation under stress may not be warranted.

How may stress have induced the observed increases in memory-related theta? Theta power reflects the strength of a specific oscillation of neuronal populations. In particular, theta oscillations are believed to be critical for formation of active neuronal ensembles and the modification of synaptic weights (Buzsáki, 2002). It thus seems reasonable that a modification of theta oscillations is directly linked to changes in synaptic plasticity. The exposure to acute stress triggers the release of a cocktail of hormones, peptides, and neurotransmitters, many of which exert a direct effect on neuronal activity (Joëls and Baram, 2009; Kim and Diamond, 2002). For instance, results from animal studies indicate that cortisol exerts a non-genomic effect on neurons by blocking the release of cAMP (Cyclic Adenosine Monophosphate; Vijayan et al., 2010), which plays a central role in mediating synaptic transmission (Duman and Nestler, 1999). Thus, stress mediators such as cortisol might have directly stimulated the activity of neurons generating theta-frequency oscillations. At the systems level, in particular concurrent glucocorticoid and noradrenergic activity is known to enhance amygdala activity which then modulates activity in other memory-related regions such as the hippocampus (Kim et al., 2015; Richter-Levin and Akirav, 2000). Further, stress mediators may induce a large-scale network reconfiguration in favour of a 'salience network' (Hermans et al., 2011, 2014), including, for instance, the amygdala which is closely connected to other medial temporal regions as well as to visual representation areas (Meier et al., 2021; Wendt et al., 2011; Sabatinelli et al., 2009). Thus, the orchestrated action of a multitude of different stress mediators may enhance activity in brain areas specialized in emotional memory formation and further promote the communication via a specific frequency band (i.e. theta) that appears to be particularly well suited for mnemonic binding of the elements of an episode. In line with the idea that multiple stress mediators drive neural and behavioural changes after stress in interaction, single stress mediators, such as cortisol or autonomic activity did not correlate significantly with changes in memory performance, confidence, or theta activity.

Although our imaging data show a significant effect of stress on the spatio-temporal neural underpinnings of emotional memory formation, it is important to note that 24 h-delayed recognition performance did not differ between the stress and control groups. One potential explanation for the latter may relate to the overall recognition performance in the present study. Participants' performance was overall high, particularly for emotionally negative pictures, which may have resulted in a ceiling effect, leaving not much space for an additional stress-related enhancement. Moreover, in contrast to a free recall test, which involves an active search process in memory, recognition tests require only a comparison process, which might be less sensitive to stress effects. At least, there are also several previous studies that did not find a significant effect of stress on recognition memory (Meier et al., 2020; Hidalgo et al., 2015; Li et al., 2014; Quaedflieg et al., 2013). Finally, the discrete old-new responses in the recognition test are considerably less fine-grained than our neural measures and may hence be less sensitive to stress effects. Indeed, when we analysed participants' confidence ratings, which did provide a more fine-grained analysis of memory performance, we observed that the influence of stimulus emotionality on memory confidence was significantly higher in stressed participants than in controls. Interestingly, this influence of stress was manifested in reduced confidence for neutral stimuli rather than in increased confidence in memory for emotional events. This finding suggests a stronger priorization of memory based on emotional salience after stress, which is generally in line with earlier findings suggesting that stress or arousal may not only enhance memory for central features of an episode but also reduce memory for more peripheral information (Kalbe et al., 2020; Kensinger et al., 2007).

Together, our data provide novel insights into the neural underpinnings through which stress may impact emotional memory formation. Specifically, we show that stress is accompanied by an increase in memory-related theta activity in medial temporal and occipito-parietal areas. Importantly, this effect was specifically observed during the encoding of emotionally arousing, but not neutral, stimuli. The present findings suggest that stress enhances neuronal oscillations that appear to be ideally suited for binding elements of an episode, in areas known to play a prominent role in emotional memory formation. Through this process, stress may facilitate the long-term storage of emotionally salient events encoded in the context of a stressful encounter, which may be highly adaptive for coping with similar future events, but could also contribute to the painful memory for aversive experiences in disorders such as PTSD.

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CRediT authorship contribution statement

Hendrik Heinbockel: Formal analysis, Methodology, Visualization, Writing – original draft. **Conny W.E.M. Quaedflieg:** Data curation, Writing – review & editing. **Till R. Schneider:** Methodology, Writing – review & editing. **Andreas K. Engel:** Resources, Validation, Funding acquisition, Writing – review & editing. **Lars Schwabe:** Conceptualization, Project administration, Writing – original draft, Writing – review & editing, Supervision.

Declaration of competing interest

None.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ynstr.2021.100383.

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Supplementary material

Stress enhances emotional memory-related theta oscillations in the medial temporal lobe

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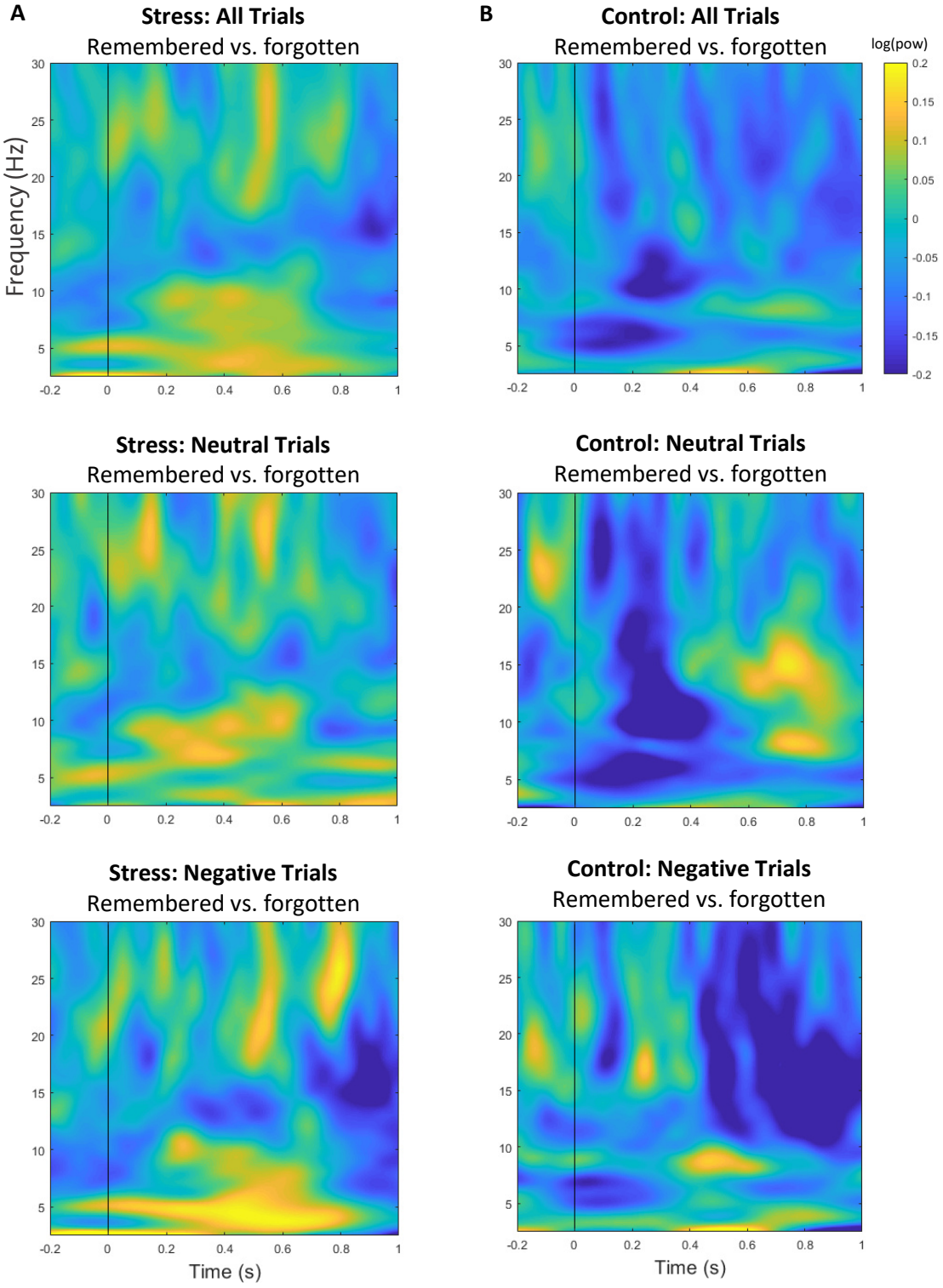

Figure S1: Neural activity in the time-frequency domain of remembered vs. forgotten trials, for each group and valence respectively ***A***, Time-Frequency representations of remembered vs. forgotten trials in the stress group. ***B***, Time-Frequency representations of remembered vs. forgotten trials in the control group.

Appendix B: Study II

Heinbockel, H., Wagner, A. D., & Schwabe, L. (2024). Post-retrieval stress impairs subsequent memory depending on hippocampal memory trace reinstatement during reactivation. Science Advances, 10(18).

COGNITIVE NEUROSCIENCE

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

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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

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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

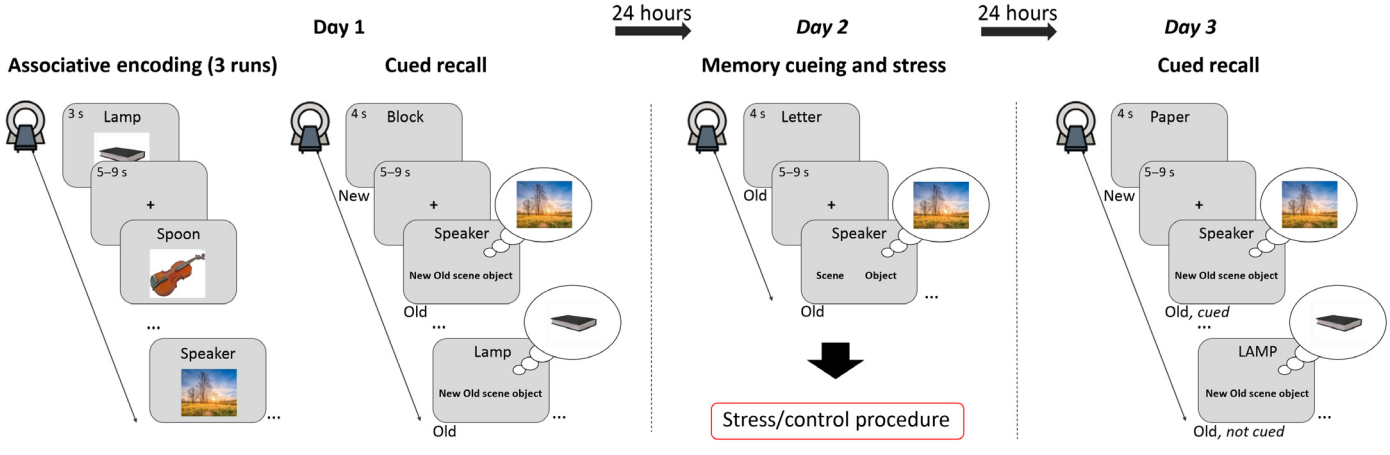

Fig. 1. Experimental task. Stress effects on memory reconsolidation were probed in a 3-day paradigm, with fMRI measurements on all 3 days. On day 1, participants encoded word-picture pairs across three runs and underwent an immediate 4AFC cued recall test including both previously presented and new words. 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

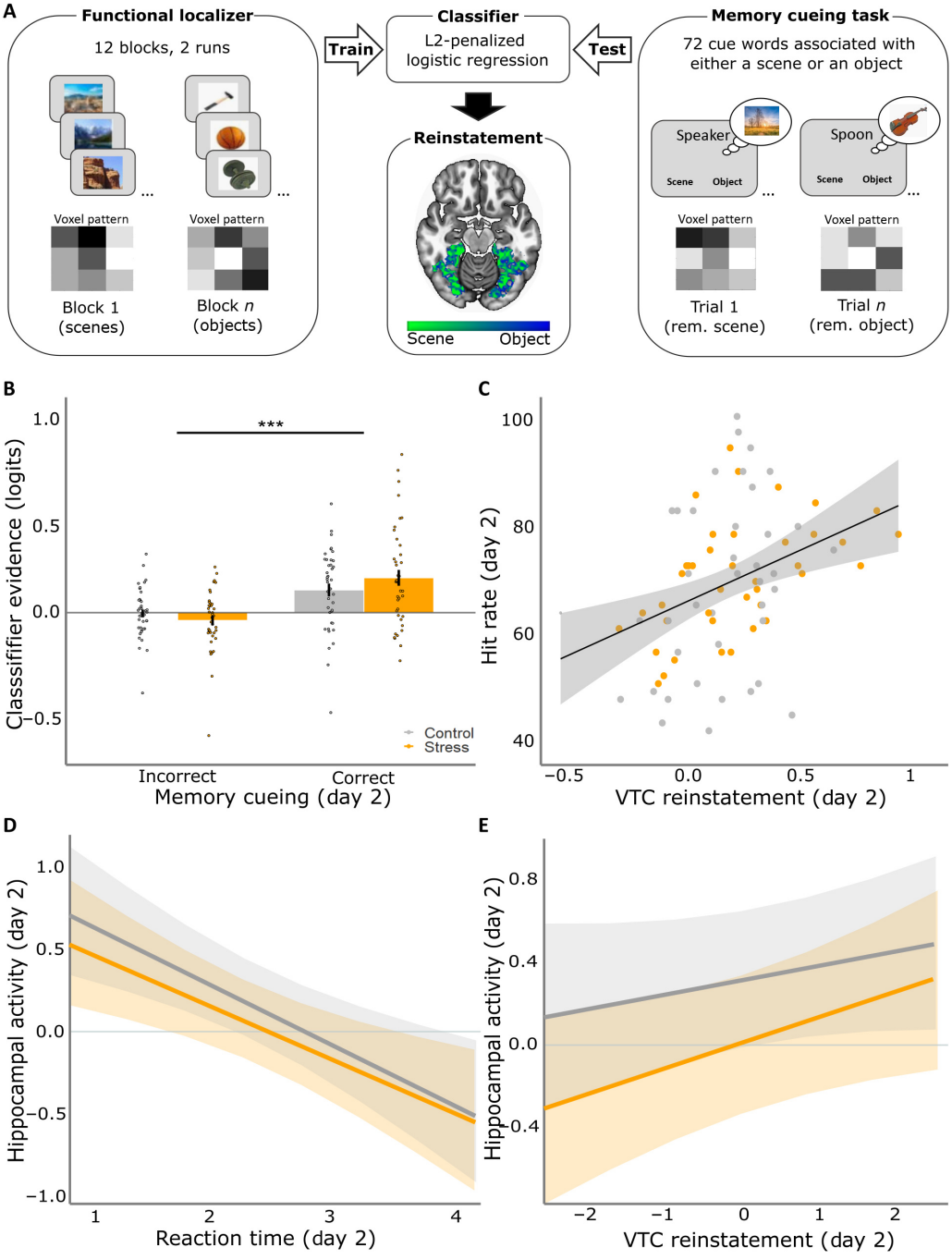

Fig. 2. Tracking memory reactivation by hippocampal activity and category pattern reinstatement in the ventral temporal cortex (VTC). (**A**) Trial-wise category pattern reinstatement was derived from multivariate voxel pattern analysis in the VTC. The logistic classifier (L2 penalized logistic regression) 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

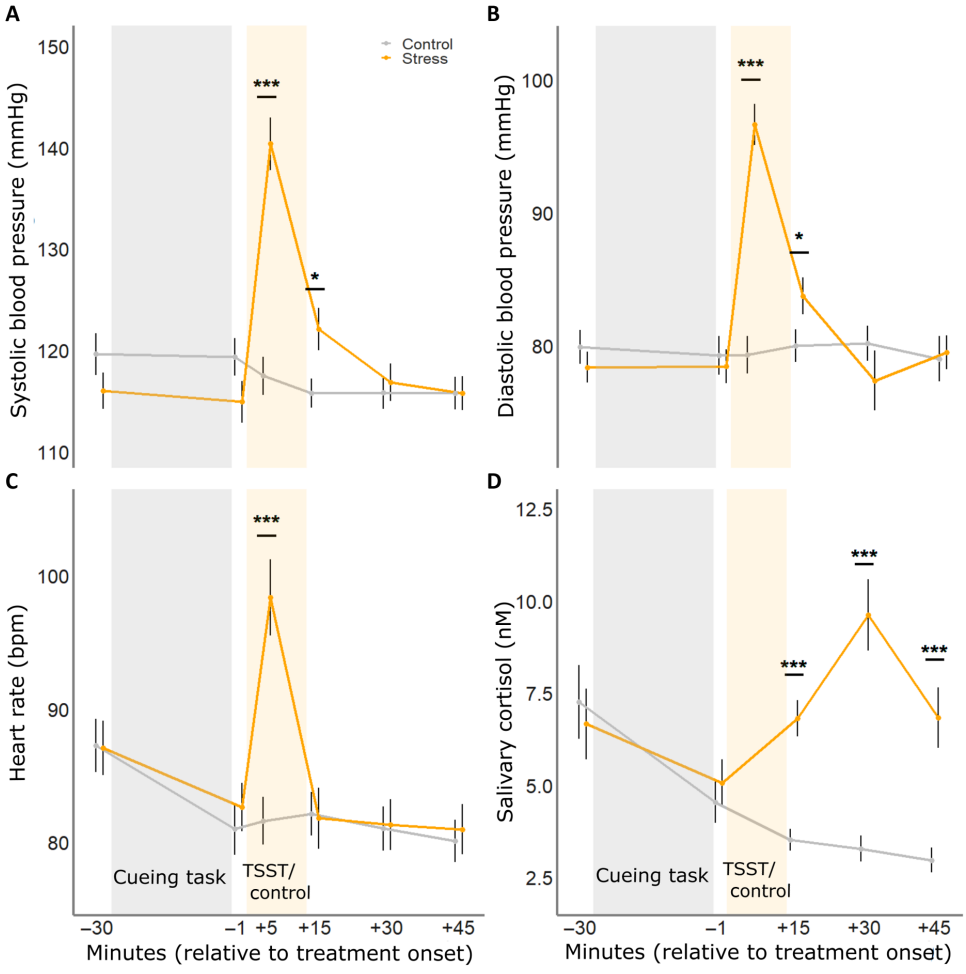

Fig. 3. Physiological stress response to the TSST and control procedurerespectively. Significant increases in (**A**) systolic and (**B**) diastolic blood pressure as well as (**C**) heart rate in response to the TSST but not in response to the control manipulation. (**D**) The stress group further showed 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

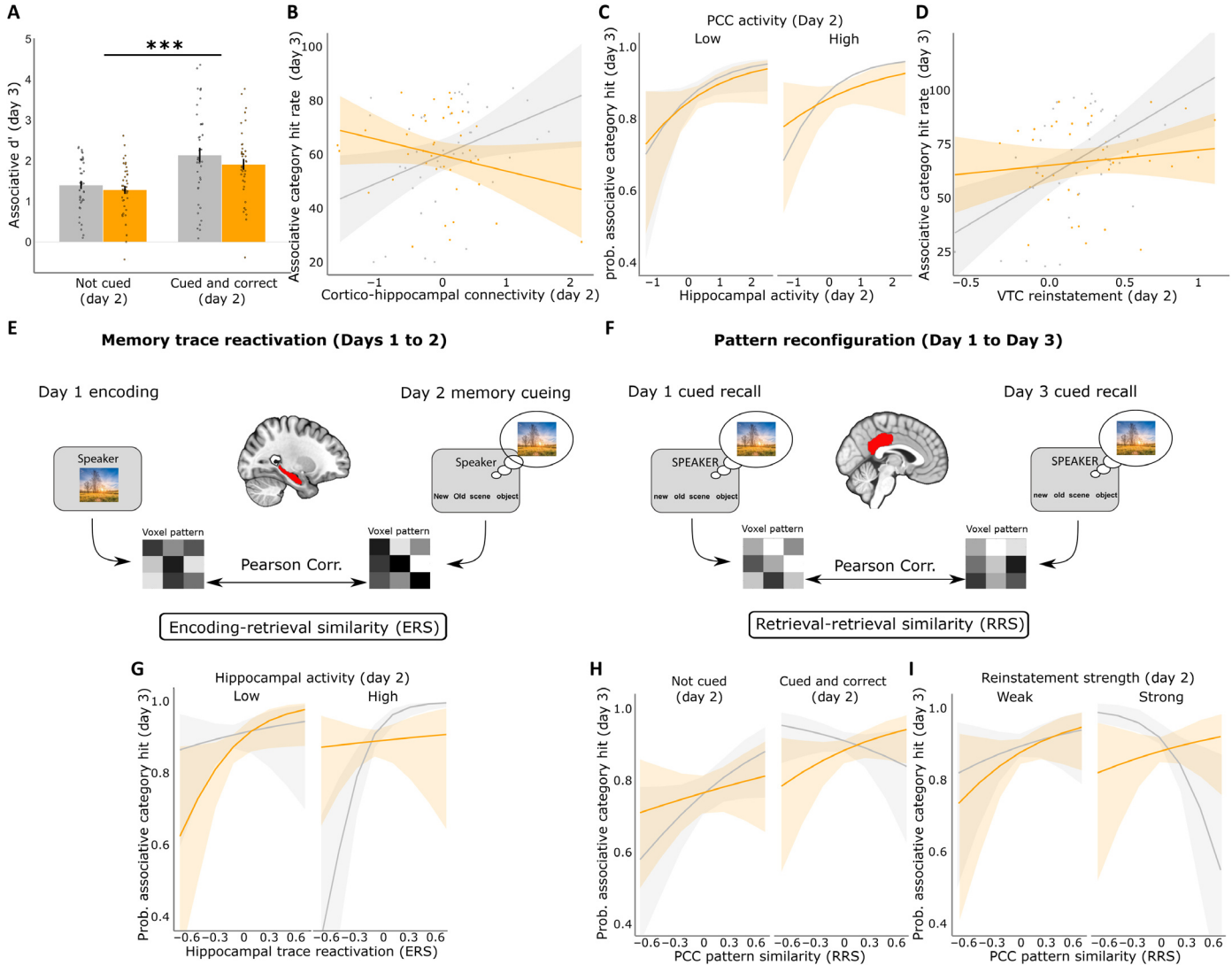

Fig. 4. Post-retrieval effects of stress on memory linked to trace reactivation on day 2 and neural pattern reconfiguration from days 1 to 3. (**A**) On day 3, memory (associative *d'*) was significantly better for pairs that were successfully retrieved on day 2 compared to those that were not successfully 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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Supplementary Materials for

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

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Results

S1: Localizer Training Performance

Using data from the independent localizer, we assessed the discriminability of category-related beta patterns in the ventral temporal cortex (VTC) while participants viewed scenes, faces, and objects. Employing a leave-one-run-out cross-validated L2-regularized logistic regression analysis, we classified scenes versus objects and evaluated classifier performance based on accuracy. The average accuracy scores were high (M±SD: 0.87 ±0.02) indicative of a highly reliable model. Importantly, there were no significant group differences in classification accuracy ($t(71.50) = 0.37$, $P = .709$, $d = 0.08$).

S2: Control variables

We controlled for potential group differences in depressive mood, chronic stress as well as state and trait anxiety. Importantly, the stress and control groups did not differ in any of these variables (depressive mood: $t(67.42) = -0.53$, $P = .594$, $d = 0.13$, state anxiety: $t(67.37) = -0.62$, $P = .534$, $d = 0.15$; trait anxiety: $t(69.58) = -0.46$, $P = .648$, $d = 0.11$, chronic stress: $t(69.01) = 0.01$, $P = .994$, $d = 0.01$).

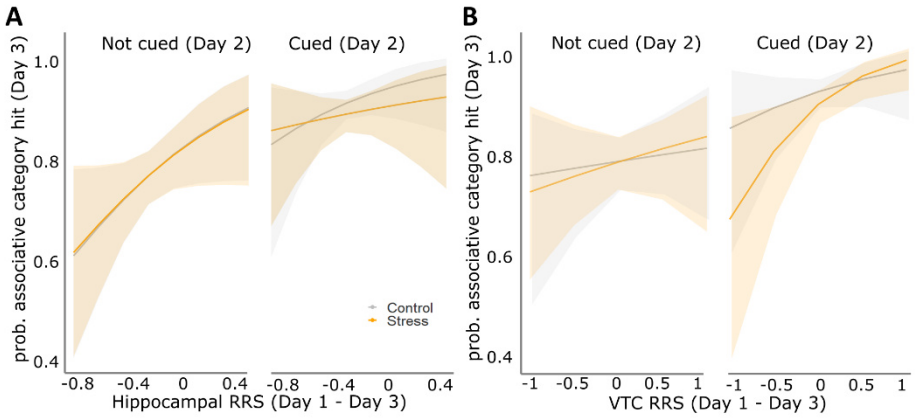

Fig S1. Day 3 Performance predicted by hippocampal and VTC representational change. Successful retrieval of cued (Day 2) trials on Day 3 relied on increased (A) hippocampal and (B) VTC pattern similarity from Day 1 to Day 3. This relation was unaffected by post-retrieval stress.

Table S1. Memory performance (in %) across the three experimental days.

	All	Stress	Control
Day 1			
Item hit rate (Cued Day 2)	75.54 (1.49)	75.19 (1.90)	75.90 (2.31)
Item hit rate (Not cued Day 2)	74.97 (1.37)	74.04 (1.78)	75.90 (2.11)
Item miss rate (Cued Day 2)	24.46 (1.49)	24.81 (1.90)	24.10 (2.31)
Item miss rate (Not cued Day 2)	25.03 (1.37)	25.96 (1.78)	24.10 (2.11)
Associative category hit rate (Cued Day 2)	51.67 (2.09)	50.55 (2.53)	52.79 (3.35)
Associative category hit rate (Not cued Day 2)	51.49 (2.15)	49.73 (2.65)	53.24 (3.38)
Associative miss rate (Cued Day 2)	48.33 (2.09)	49.45 (2.53)	47.21 (3.35)
Associative miss rate (Not cued Day 2)	48.51 (2.15)	50.27 (2.65)	46.76 (3.38)
Associative category error rate (Cued Day 2)	14.88 (1.03)	13.76 (2.62)	15.99 (1.28)
Associative category error rate (Not cued Day 2)	14.49 (0.93)	14.26 (1.36)	14.71 (1.29)
Day 2			
Associative hit rate	70.81 (1.44)	71.40 (1.62)	70.23 (2.39)
Associative miss rate	29.19 (1.44)	28.60 (1.62)	29.77 (2.39)
Day 3			
Item hit rate (Cued and correct Day 2)	90.05 (1.08)	91.27 (1.08)	88.84 (1.86)
Item hit rate (Not cued Day 2)	74.39 (1.45)	74.11 (1.77)	74.65 (2.31)
Item miss rate (Cued and correct Day 2)	9.95 (1.08)	8.73 (1.08)	11.16 (1.86)
Item miss rate (Not cued Day 2)	25.61 (1.44)	25.89 (1.77)	25.35 (2.31)
Associative category hit rate (Cued and correct Day 2)	69.99 (2.18)	69.55 (2.80)	70.44 (3.38)
Associative category hit rate (Not cued Day 2)	45.27 (2.15)	44.24 (2.84)	46.31 (3.26)
Associative miss rate (Cued and correct Day 2)	30.01 (2.18)	30.45 (2.80)	29.56 (3.38)
Associative miss rate (Not cued Day 2)	54.73 (2.15)	55.76 (2.84)	53.69 (3.26)
Associative category error rate (Cued and correct Day 2)	10.38 (1.02)	11.37 (1.55)	9.39 (1.32)
Associative category error rate (Not cued Day 2)	15.23 (1.06)	15.12 (1.62)	15.34 (1.38)

Data represent mean percentage values (±SE).

Table S2. Trial counts for univariate retrieval success analyses of Day 1 data, memory outcome analyses for Day 2 data, and Day 3 outcomes as a function of Day 2 cueing and memory outcome.

	All	Stress	Control
Day 1			
Item hit (Cued and correct Day 2)	39.80 (1.36)	40.20 (1.49)	39.40 (2.29)
Item hit (Not cued Day 2)	53.03 (0.99)	52.38 (1.24)	53.68 (1.55)
Item miss (Cued and correct Day 2)	9.15 (0.59)	9.40 (0.80)	8.90 (0.88)
Item miss (Not cued Day 2)	17.70 (0.98)	18.40 (1.27)	17.00 (1.50)
Associative category hit (Cued and correct Day 2)	30.40 (1.61)	30.28 (1.90)	30.53 (2.63)
Associative category hit (Not cued Day 2)	36.45 (1.53)	35.18 (1.87)	37.73 (2.44)
Associative miss (Cued and correct Day 2)	18.55 (0.79)	19.33 (1.08)	17.78 (1.16)
Associative miss (Not cued Day 2)	34.28 (1.52)	35.60 (1.89)	32.95 (2.38)
Associative category error (Cued and correct Day 2)	5.73 (0.37)	5.23 (0.58)	6.23 (0.45)
Associative category error (Not cued Day 2)	10.24 (0.66)	10.10 (0.96)	10.38 (0.91)
Day 2			
Associative hit	49.85 (1.04)	50.45 (1.13)	49.25 (1.76)
Associative miss	20.51 (1.01)	20.25 (1.16)	20.77 (1.67)
Day 3			
Item hit (Cued and correct Day 2)	44.25 (1.38)	45.7 (1.42)	42.80 (2.35)
Item hit (Not cued Day 2)	51.71 (1.16)	52.53 (1.27)	53.59 (1.80)
Item miss (Cued and correct Day 2)	4.34 (0.43)	4.15 (0.50)	4.53 (0.71)
Item miss (Not cued Day 2)	17.71 (1.00)	18.35 (1.26)	17.08 (1.55)
Associative category hit (Cued and correct Day 2)	35.34 (1.71)	35.35 (1.98)	35.33 (2.80)
Associative category hit (Not cued Day 2)	31.66 (1.56)	31.35 (2.03)	31.98 (2.41)
Associative miss (Cued and correct Day 2)	13.25 (0.85)	14.5 (1.23)	12.00 (1.14)
Associative miss (Not cued Day 2)	37.76 (1.49)	39.53 (2.03)	36.00 (2.17)
Associative category error (Cued and correct Day 2)	4.55 (0.40)	5.25 (0.62)	3.85 (0.49)
Associative category error (Not cued Day 2)	10.59 (0.75)	10.70 (1.14)	10.48 (0.99)

Data represent means (±SE).

Table S3. Memory Performance expressed as associative d' during Day 1 cued recall

	Stress	Control
Cued and correct Day 2	1.25 (0.12)	1.15 (0.14)
Not Cued	1.13 (0.11)	1.21 (0.14)

Groups did not differ in associative d' values during the immediate cued recall task at Day 1, suggesting a comparable acquisition of word-picture pairs. Data represent means (±SE).

Table S4. Physiological stress parameters and mood on Days 1 and 3.

		Stress	Control
Day 1	Heart rate (bpm)	85.58 (1.93)	86.60 (2.25)
	Systolic blood pressure (mmHg)	116.45 (2.09)	120.45 (1.68)
	Diastolic blood pressure (mmHg)	78.66 (1.43)	80.33 (1.65)
	Cortisol (nmol/l)	10.10 (1.08)	10.93 (1.50)
	Mood (good/bad)	35.02 (0.51)	34.10 (0.74)
	Tiredness (energized/tired)	31.17 (0.82)	30.52 (0.88)
	Calmity (calm/restless)	32.97 (0.68)	32.17 (0.90)
Day 3	Heart rate (bpm)	88.35 (2.41)	88.20 (2.44)
	Systolic blood pressure (mmHg)	116.76 (1.93)	118.78 (1.62)
	Diastolic blood pressure (mmHg)	78.12 (1.09)	80.17 (1.38)
	Cortisol (nmol/l)	8.98 (1.10)	7.56 (1.06)
	Mood (good/bad)	34.57 (0.59)	34.02 (0.73)
	Tiredness (energized/tired)	31.67 (0.75)	30.67 (0.79)
	Calmity (calm/restless)	33.52 (0.81)	33.35 (0.70)

Subjective and physiological parameters of participants on days 1 and 3. All parameters were taken at the beginning of Days 1 and 3 and revealed no significant difference in either subjective or physiological stress parameters between stress and control groups. Data represent means (±SE).

Table S5. Subjective mood scores and VAS ratings after the stress/control procedure on Day 2.

		Stress	Control
MDBF *Pre*	Mood (good/bad)	33.57 (0.62)	33.94 (0.74)
	Tiredness (energized/tired)	31.57 (0.67)	30.55 (0.80)
	Calmness (calm/restless)	31.62 (0.65)	30.56 (0.81)
MDBF *Post*	Mood (good/bad)	30.55 (0.72)	33.55 (0.79) ***
	Tiredness (energized/tired)	31.65 (0.61)	31.60 (0.75)
	Calmness (calm/restless)	29.37 (0.78)	32.20 (0.87) ***
VAS	Stressful	7.25 (0.41)	3.95 (0.37) ***
	Unpleasant	6.52 (0.50)	3.67 (0.37) ***
	Difficult	6.55 (0.46)	3.67 (0.38) ***

Stressed subjects increased (Pre to Post) in bad mood and restlessness compared to control participants (MDBF), and rated the TSST as significantly more stressful, unpleasant and difficult (VAS ratings 1-10). Data represent means (±SE); ***P < .001.

Table S6. Significant clusters in the whole-brain univariate analyses of Day 2 memory performance (associative hit – associative miss).

Region	Central coordinates (x,y,z; MNI)	Cluster-T	Cluster-P(FWE 0.05)
PCC,angular, sup parietal, MPFC	-8, -36, -42	9.93	< .001
Mid Temp Gyrus posterior left	-54, -26, -8	6.89	< .001
Mid Temp Gyrus posterior right	48, -22, -8	6.09	.002
Temporal Occipital Fusiform left	-26, -52, -18	7.20	< .001
Temporal Occipital Fusiform right	-32, -40, -12	6.19	.001
Frontal Pole left	14, 54, 20	6.28	.001
Frontal Pole right	-38, 46, 14	6.19	.002
Mid Temporal Gyrus temporo-occipital left	52, -56, -2	6.67	< .001
DLPFC right	32, 34, 44	6.74	< .001
Inferior Frontal Gyrus right	46, 42, 4	6.89	< .001
Inferior Frontal Gyrus, pars opercularis right	56, 14, 8	6.83	< .001
Orbito-Frontal Cortex /	-14, 4, -16	7.49	< .001
Parahippocampal gyrus anterior left			
Orbito-Frontal Cortex right	20, 28, -20	6.67	< .001
Hippocampus /	-30, -30, -14	6.66	< .001
Parahippocampal gyrus posterior left			
Precentral gyrus right	26, -8, 68	7.42	< .001
Precentral gyrus left	-54, 2, 34	6.94	< .001
Occipital Pole	-8, -88, 20	6.16	.002
Precuneus	-20, -62, 30	6.00	.003
Insular left	-38, 4, 0	5.95	.004
Nucleus accumbens right	14, 6, -16	9.29	< .001
Putamen left	-20, 8, 14	6.39	.001
Putamen right	30, 4, 4	7.03	< .001

Table S7. Participants' state, trait anxiety, chronic stress and depression scores.

	Stress	Control
Depression score	5.75 (0.86)	6.52 (1.09)
State anxiety	46.18 (0.55)	45.61 (0.69)
Trait anxiety	41.75 (0.74)	41.22 (0.80)
Chronic stress	15.95 (0.68)	15.96 (0.59)

State and Trait anxiety scores were measured with the State-Trait Anxiety Inventory. Depression Scores were determined utilizing the Beck Depression Inventory. Chronic stress was measured with the Trier Inventory of Chronic Stress. Participants conducted the three questionnaires at home before the actual experiment started. Data represent means (±SE).

Appendix C: Study III

Heinbockel, H., Wagner, A, D., & Schwabe, L. (under review in Elife). Post-retrieval noradrenergic activation impairs subsequent memory depending on cortico-hippocampal reactivation.

Title

Post-retrieval noradrenergic activation impairs subsequent memory depending on cortico-hippocampal reactivation

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Impact Statement

We show that pharmacological elevations of noradrenergic but not glucocorticoid activity after retrieval impair subsequent remembering. These impairments were bound to strong hippocampal and cortical neural reactivation before drug action.

Abstract

When retrieved, seemingly stable memories can become sensitive to modification through significant events, such as acute stress. While memory dynamics after retrieval have profound implications, for instance, in eyewitness testimony or aberrant memory in mental disorders, the mechanisms underlying these dynamics remain poorly understood. Here, we show in healthy humans that increases in noradrenaline after memory retrieval impairs subsequent remembering, depending on hippocampal and cortical reactivation during retrieval. In a three-day fMRI study, we measured brain activity during initial encoding (Day 1), 24h-delayed memory cueing accompanied by administration of placebo, hydrocortisone, or the α2-adrenoceptor antagonist yohimbine (Day 2), and final recall, 24h later (Day 3). While post-retrieval hydrocortisone did not affect subsequent memory (i.e., final recall), the impairing effect of yohimbine on final recall depended on the strength of hippocampal reactivation and category-level reinstatement in ventral temporal cortex during Day 2 retrieval. Notably, the effect of yohimbine on subsequent memory was contingent specifically on the neural reactivation during retrieval. While patterns from online reactivation were also reinstated in the post-retrieval rest-period, this offline reinstatement did not interact with the pharmacological manipulation. Additionally, the original memory trace from encoding was not significantly reactivated during retrieval and not reinstated offline during rest, further supporting the critical dependency of post-retrieval manipulations on the neural signal emerging during retrieval-related reactivation. Our findings demonstrate that, depending on the neural reactivation of memories, noradrenergic arousal after retrieval can alter the future accessibility of consolidated memories.

Introduction

Memories are not stable entities but can undergo changes long after initial consolidation (Dudai and Eisenberg 2004; Nadel et al. 2012). The updating of existing memories in light of new information or experiences is a key feature of adaptive memory. A potential mechanism underlying such updating is memory reconsolidation. According to reconsolidation theory, memories become labile again upon their reactivation, requiring another period of stabilization (i.e. reconsolidation; Lee, Nader, and Schiller 2017; Nader and Einarsson 2010; Schwabe, Nader, and Pruessner 2014). During the reconsolidation window, memories are assumed to be modifiable (Galarza Vallejo et al. 2019; Kroes et al. 2014). Alternative views posit that post-reactivation changes in memory are due to the emergence of new traces during retrieval, potentially interfering with the retrieval of the original memory (Nadel et al. 2000; Polyn, Norman, and Kahana 2009; Sederberg et al. 2011). The dynamics of memory after retrieval, whether through reconsolidation of the original trace or interference with retrieval-related traces, have fundamental implications for educational settings, eyewitness testimony, or mental disorders (Clem and Schiller 2016; Schacter and Loftus 2013; Schwabe et al. 2014). In clinical contexts, post-retrieval changes of memory might offer a unique opportunity to retrospectively modify or render less accessible unwanted memories, such as those associated with posttraumatic stress disorder (PTSD) or anxiety disorders (Björkstrand et al. 2016; Walsh et al. 2018; Xue et al. 2012). Given these far reaching implications, understanding the mechanisms underlying post-retrieval dynamics of memory is essential.

Stress has a major impact on memory (de Quervain, Roozendaal, and McGaugh 1998; Roozendaal, McEwen, and Chattarji 2009; Schwabe et al. 2022). While most studies have focused on stress effects on memory formation or retrieval, accumulating evidence suggests that stress may also alter the dynamics of memory after retrieval. The majority of studies suggest a disruptive influence of post-retrieval stress on subsequent remembering (Dongaonkar et al. 2013; Hupbach and Dorskind 2014; Larrosa et al. 2017; Maroun and Akirav 2008; Schwabe and Wolf 2010), but see (Bos et al. 2014; Coccoz, Maldonado, and Delorenzi 2011) for an opposite effect). Although post-retrieval stress-induced changes in putative memory reconsolidation or accessibility are highly relevant in legal or clinical contexts, the mechanisms involved in these effects remain poorly understood. Exposure to stressful events triggers the release of various hormones, peptides, and neurotransmitters (Joëls and Baram 2009). Among these, noradrenaline and glucocorticoids appear to be of particular relevance for stress-induced changes in memory (de Quervain et al. 1998; Roozendaal et al. 2006; Strange and Dolan 2004). Pharmacological studies in humans and rodents demonstrate a significant impact of noradrenaline and glucocorticoids on the posited reconsolidation or mnemonic interference processes after retrieval. However, their exact roles remain elusive. Some studies suggest enhancing effects of post-retrieval glucocorticoids on subsequent memory (Antypa et al. 2019; Meir Drexler et al. 2015), while others report impairing effects of glucocorticoid receptor activation after retrieval (Antypa et al. 2021; Maroun and Akirav 2008; Vafaei et al. 2023; Wang et al. 2008). For noradrenaline, several studies indicate that post-retrieval blockade of noradrenergic activity impairs putative reconsolidation or future memory accessibility (Kindt, Soeter, and Vervliet 2009; Przybyslawski, Roullet, and Sara 1999; Schramm, Everitt, and Milton 2016; Schwabe, Joëls, et al. 2012). However, this effect is not consistently found (Bos et al. 2014; Elsey et al. 2020; Muravieva and Alberini 2010; Wood et al. 2015) and

might depend on the arousal state of the individual (Maroun and Akirav 2008) or the exact timing of drug administration(Otis, Fitzgerald, and Mueller 2014; Thomas et al. 2017). The brain mechanisms underlying the potential effects of post-retrieval glucocorticoids or noradrenergic arousal on subsequent remembering are largely unknown, especially in humans.

Extant studies suggest that brain regions implicated in initial memory formation, such as the hippocampus, may also play a role in the modification of memories after their reactivation (Nader, Schafe, and Le Doux 2000; Przybyslawski and Sara 1997; Schwabe, Nader, et al. 2012). Research in transgenic mice indicates that effective post-reactivation interventions require the reactivation of specific neuronal subsets within the engram, underscoring the significant contribution of the original memory trace to changes during the proposed reconsolidation window (Khalaf et al. 2018). While human neuroimaging studies cannot assess the reactivation of individual neurons within an engram, multivariate pattern analysis (MVPA) enables the assessment of neural pattern reinstatement at the stimulus category or event level (Kuhl et al. 2011; Polyn et al. 2005; Staresina et al. 2012; Thakral, Wang, and Rugg 2015; Wing, Ritchey, and Cabeza 2015). Notably, memory reactivation occurs not only during goal-directed retrieval (online) but also offline during post-retrieval rest periods. Online reactivation reflects the immediate impact of memory retrieval on neural networks and may involve modifications of the existing memory trace and/or the encoding of a new memory trace in response to retrieval demands (Johnson and Rugg 2007; Tanaka et al. 2014). Offline reactivation offers a pivotal window for the consolidation and stabilization of these memory alterations (Oudiette and Paller 2013; Staresina et al. 2013; Tambini, Ketz, and Davachi 2010). The transition from online to offline reactivation involves complex neural cascades, influencing the persistence and strength of the reactivated memory trace (Yagi et al. 2023). Fundamental knowledge gaps remain about the role of online and offline neural reactivation in post-retrieval dynamics of human memory in general, and its modulation by stress mediators in particular.

This pre-registered study aimed to elucidate the brain mechanisms underlying the impact of post-retrieval glucocorticoids and noradrenaline on subsequent remembering in humans, with a specific focus on whether the effects of post-retrieval stress are contingent on online or offline neural reinstatement. To this end, healthy participants underwent a three-day experiment. On Day 1, participants encoded a series of word-picture pairs and subsequently completed an immediate cued recall test. On Day 2 (24 hours later), half of the learned words were presented again during a Memory Cueing task, prompting participants to consciously retrieve the associated pictures and thereby reactivate their underlying neural representations. Notably, according to both reconsolidation and interference accounts of post-retrieval changes in memory (Nader and Einarsson 2010; Sederberg et al. 2011), only cued items that were reinstated should be susceptible to post-retrieval manipulations. The remaining words served as non-reactivated controls. Importantly, shortly before the Memory Cueing task, participants received orally either a Placebo (N=20), 20mg Hydrocortisone (N=21), or 20mg of the α2-adrenoceptor antagonist yohimbine (N=21) leading to increased noradrenergic stimulation. This timing of drug administration was chosen to result in significant elevations of glucocorticoid or noradrenergic activity after completion of the Memory Cueing task, during the proposed post-retrieval consolidation or reconsolidation window. The action of the drugs was assessed by arousal and salivary cortisol measured before and after drug intake. On Day 3 (another 24 hours later), participants underwent a final cued

recall memory test, enabling assessment of the impact of post-retrieval noradrenergic and glucocorticoid activation on subsequent memory performance.

Critically, brain activity was recorded using fMRI throughout all stages of the memory paradigm, on all three days. On Day 2, we also included resting-state scans before and after the Memory Cueing task to assess offline memory reactivation. Given that associative memories rely on the hippocampus and cortical representation areas (Kim 2010; Ranganath et al. 2004), such as the ventral temporal cortex (VTC), which represents stimulus categories (scenes, objects) encountered during encoding (Bracci, Ritchie, and de Beeck 2017; Grill-Spector and Weiner 2014), and the posterior cingulate cortex (PCC), which is assumed to represent memory traces formed during retrieval (Bird et al. 2015; Thakral et al. 2015), we focused our analysis on these key regions. Building on recent findings in rodents (Khalaf et al. 2018), we hypothesized that the effects of post-retrieval noradrenergic and glucocorticoid activation would critically depend on the reinstatement of the neural event representation during retrieval. To investigate memory reinstatement, we employed multivariate pattern analysis (MVPA) and representational similarity analysis (RSA) across experimental days.

Results

Day 1: Successful Memory Encoding

After completing an associative encoding task comprising 164 word-picture pairs (Fig. 1), participants engaged in an immediate cued recall task in which 144 previously presented 'old' word cues (plus eight catch trials) were presented intermixed with 152 'new' foils. On each trial, participants could respond with one of four options: 'old/scene', 'old/object', 'old', or 'new' (4AFC decision; Fig. 1). Participants successfully distinguished between old words and new words, with a 74.4% hit rate (response 'old', 'old/scene', 'old/object' to an old word) and a 16.8% false alarm rate (response 'old', 'old/scene, 'old/object' to a new word). Participants recognized the word and correctly identified the associated image category in 47.3% of trials (associative category hit rate) with an associative error rate of 13.1%. Signal detection theory-based analysis revealed an average associative d' of 1.13 (SE = 0.09).

Because the critical stress system manipulations were implemented only on Day 2 (hydrocortisone, yohimbine, placebo groups), we confirmed that immediate cued recall performance on Day 1 did not differ between pairs later cued and uncued on Day 2 ($F(1,58) = 1.25$, $P = .267$, $\eta^2 < 0.01$), nor between groups (all main or interaction effects; all Ps > .481; see Supplemental Table S1). Moreover, groups did not differ in mood, arousal, or cortisol levels before encoding on Day 1 (all Ps > .564; see Supplementary Table S2). Whole-brain fMRI analyses on immediate cued recall data (associative category hits > associative misses), considering the within-subject factor *Cued* and the between-subjects factor *Group,* revealed no significant main or interaction effects (all Ps > .564; see Supplementary Table S2). These outcomes suggest comparable neural underpinnings of immediate (Day 1) memory retrieval for pairs that, on Day 2, were subsequently cued and correctly remembered and pairs subsequently uncued, as well as across experimental groups on Day 1.

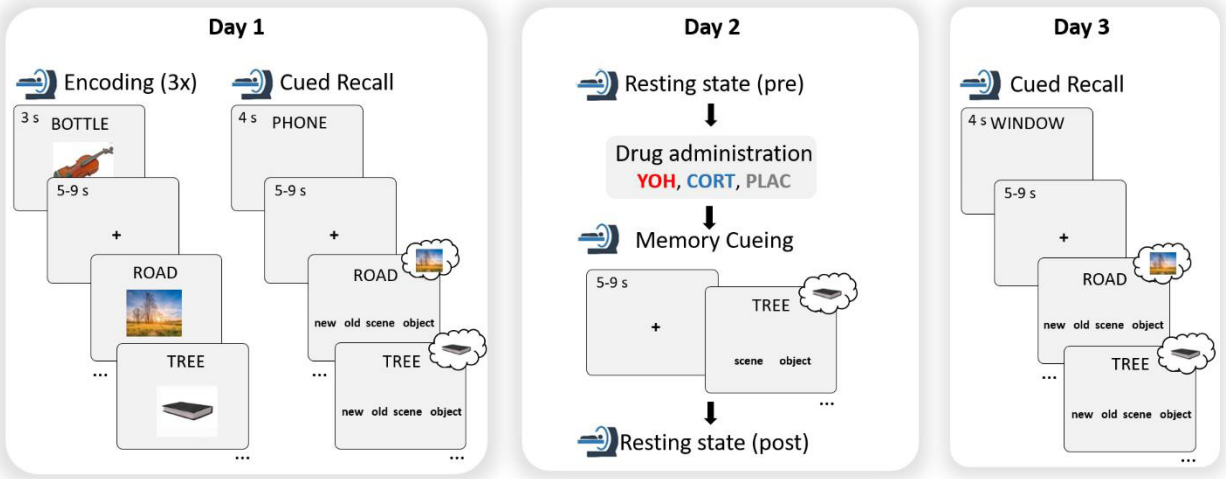

Fig. 1. Experimental task. The impact of post-retrieval yohimbine and hydrocortisone on subsequent memory was tested in a 3-day paradigm, recording fMRI data on all days. On Day 1, participants encoded word-picture pairs across three runs and then underwent an immediate cued recall test. On Day 2, 24 hours later, participants started with a 10-minute resting-state fMRI scan, followed by the oral administration of 20 mg yohimbine (YOH), 20 mg hydrocortisone (CORT), or a placebo (PLAC). Thereafter, in the Memory Cueing task, half of the word-picture pairs were cued by presenting the corresponding word; Day 2 ended with another 10-minute resting-state scan. On Day 3, again 24 hours later, participants completed a final cued recall test including word cues for all 144 pairs from Day 1 encoding, half of which had been cued and half of which had not been cued on Day 2, along with 152 new foils.

Day 2: Neural Signatures of Successful Memory Reactivation

Successful Memory Cueing

On Day 2, participants returned to the MRI scanner for a Memory Cueing task (cued recall; 2AFC; Fig. 1) in which half of the word-picture associations encoded on Day 1 were cued. Before the Memory Cueing task, there were no significant differences between groups in subjective mood, autonomic arousal, or salivary cortisol (all Ps > .096, Supplemental Table 2). During this task, participants were presented 76 old cue words (36 previously paired with scenes, 36 previously paired with objects, and four catch trials). Participants were instructed to recall the picture associated with the word cue in as much detail as possible and to indicate whether the picture depicted an object or a scene. Due to the absence of new foils in this task, memory outcomes were restricted to associative hits (i.e., correct trials) and associative misses (i.e., incorrect trials). Overall, participants performed well, accurately identifying the correct picture category in 67.5% of trials (SE = 2.6%; chance = 50%), and the three groups did not differ in performance ($F(2,58) = 1.53$, $P = .224$, $\eta^2 = 0.05$).

Neural Reactivation in Hippocampus and Cortical Areas during Memory Cueing

Drawing upon recent discoveries in rodent studies (Khalaf et al. 2018), we hypothesized that the impact of post-retrieval noradrenergic and glucocorticoid activation would hinge significantly on the reactivation of neural event representations during and after retrieval. To

initially elucidate the neural underpinnings of successful memory retrieval (i.e., retrieval success), we examined univariate brain activity on associative hits vs. associative misses in the Memory Cueing task. A whole-brain fMRI analysis revealed significant activation in bilateral hippocampi (Left: [-26, -32, -10], t = 7.93, P(FWE) < .001; Right: [32, -40, -12], t = 7.89, P(FWE) < .001), ventral temporal cortex (VTC; Left: [-30, -40, -12], t = 7.75, P(FWE) < .001; Right: [52, -50, -14], t = 7.26, P(FWE) < .001), and PCC ([4, -42, 38], t = 8.10, P(FWE) < .001), along with other regions central for episodic memory retrieval (e.g., medial prefrontal cortex; see Supplemental Table S3). Importantly, there were no group differences in univariate brain activity related to successful retrieval during the Memory Cueing task (all *Retrieval success* × *Group* interaction Ps > .420).

A linear mixed-effects model (LMM) using participants' reaction times as a proxy for memory confidence/memory strength revealed that higher hippocampal as well as PCC activity was associated with faster 2AFC reaction times (Left hippocampus: $\beta = -0.51 \pm 0.18$, $t = -2.88$, $P = .018$, $R^2_{conditional} = 0.08$; Right hippocampus: $\beta = -0.47 \pm 0.18$, $t = -2.60$, $P = .033$, $R^2_{conditional} = 0.11$; PCC: $\beta = -0.75 \pm 0.20$, $t = -3.67$, $P < .001$, $R^2_{conditional} = 0.09$), while no such relation was observed in the VTC ($P = .282$). Importantly, LMMs did not reveal main or interaction effects including the factor *Group* (all Ps > .131). Thus, while these four regions were generally more active during successful vs. unsuccessful memory cueing, activity in the hippocampus and PCC also tracked memory confidence/memory strength (also shown in (Gordon et al. 2014).

Category-Level Pattern Reinstatement in Hippocampus and Cortical Areas during Memory Cueing

In an independent localizer task, we assessed the discriminability of category-related beta patterns in the VTC, hippocampus, and PCC while participants viewed scenes, faces, and objects (Fig. 2A). Employing a leave-one-run-out cross-validated L2-regularized logistic regression analysis, we classified scenes versus objects and evaluated classifier performance based on accuracy. For the VTC, the average classifier accuracy was high (M±SD: 90.0% ± 0.1%); $t(60) = 25.99$, $P < .001$, $d = 3.83$) indicative of reliable category-level processing in the VTC. Importantly, there were no significant group differences in classification accuracy ($F(1,59) = 2.56$, $P = .115$, $\eta^2 = 0.04$). Further probing VTC category processing, we next tested the localizer-trained classifier on the Day 1 Encoding task (Fig. 2B), in which objects and scenes were presented. Average accuracy was again high (M±SD: 77.9% ± 0.9%, $t(60) = 29.88$, $P < .001$, $d = 3.80$), further supporting category-level processing in the VTC, again without significant group differences in classification accuracy ($F(2,58) = 0.44$, $P = .643$, $\eta^2 = 0.01$).

Next, we quantified the reinstatement of visual category-level representations during successful memory cueing on Day 2 in the VTC. Using the localizer-trained logistic classifier, testing on all trials of the Memory Cueing task (in which only words but not associated images were presented) confirmed that associative hits were accompanied by stronger visual category pattern reinstatement in VTC, compared to associative misses (main effect *Retrieval Success*: $F(1,58) = 12.45$, $P < .001$, $\eta^2 = 0.13$). Importantly, there were no significant differences between groups in VTC reinstatement during the Memory Cueing task (all main and interaction effects, Ps > .504). Subsequently, we tested whether the strength of single-trial category-level reinstatement (logits) in VTC was predicted by Day 2 memory performance. A generalized

linear mixed model revealed a main effect of *Retrieval success* ($F(1,58) = 12.61$, $P = .003$, $\eta^2 = 0.13$)., but no effect of *Group* and no *Group* × *Retrieval success* interaction (both Ps =1), showing that successful memory cueing on Day 2 was associated with greater trial-wise category-level reinstatement in the VTC, without differences between groups. Finally, we tested the VTC-trained classifier selectively on associative hit trials, corresponding to remembered scenes and objects, during the Memory Cueing task. Overall, the classifier distinguished remembered scenes from remembered objects, performing significantly above chance-level (50%; M±SE = 54.4% ± 1.0%; $t(60) = 4.44$, $P < .001$, $d = 1.14$), without a difference between scenes and objects ($P = .092$). By contrast, when tested on associative miss trials, the classifier failed to differentiate forgotten scenes from forgotten objects (M±SE = 50.1% ± 1.7%; $P = 1$). Again, classifier accuracy on remembered trials in VTC did not differ between groups ($F(2,58) = 0.86$, $P = 1$, $\eta^2 = 0.03$).

We also examined scene vs. object classification accuracy in the left and right hippocampus, using data from the independent localizer. The average accuracy scores did not significantly differ from chance (50%; Left: M±SD: 53.3% ± 1.8%, $t(60) = 1.72$, $P = .501$, $d = 0.22$; Right: M±SD: 52.9% ± 1.5%, $t(60) = 1.50$, $P = .520$, $d = 0.18$), indicating poor category-coding in the hippocampus (Liang, Wagner, and Preston 2013). We also trained the classifier on the localizer runs (scenes vs. objects) and tested it on the Day 1 Encoding task data, in which objects and scenes were presented. The average accuracy scores were above chance-level (50%; Left: M±SD: 53.8% ± 0.9%, $t(60) = 3.29$, $P = .006$, $d = 0.42$; Right: M±SD: 53.4% ± 0.9%, $t(60) = 3.71$, $P <. 001$, $d = 0.93$) indicating category-coding in the hippocampus during visual encoding, without significant group differences in classification accuracy (Left: $F(1,59) = 0.02$, $P = .874$, $\eta^2 < .01$; Right: $F(1,59) = 0.03$, $P = .784$, $\eta^2 < 0.01$). However, in contrast to VTC, classifiers trained on localizer activation patterns in the left and right hippocampus were neither able to distinguish remembered scenes and remembered objects (Left: M±SE = 50.71% ± 1.0%; $t(60) = 0.69$, $P = 1$, $d = 0.09$; Right: M±SE = 51.82% ± 0.9%; $t(60) = 2.10$, $P = .156$, $d = 0.23$), nor forgotten scenes and forgotten objects (Left: M±SE = 47.95% ± 1.6%; $t(60) = -1.31$, $P = 1$, $d = 0.17$; Right: M±SE = 49.61% ± 1.3%; $t(60) = -0.27$, $P = 1$, $d = 0.09$) when tested on Day 2 Memory Cueing task data.

Finally, we examined scene vs. object classification accuracy in the PCC using localizer task data. The average accuracy scores significantly exceeded chance level (50%; M±SD: 62.4% ± 2.24%, $t(60) = 5.39$, $P < .001$, $d = 0.69$), indicating category-coding in PCC, without group differences ($F(1,59) = 0.81$, $P = .370$, $\eta^2 = 0.01$). We also trained the classifier on the localizer runs (scenes vs. objects) and tested it on the Day 1 Encoding task data. The average accuracy scores were above chance (50%; M±SD: 54.6% ± 1.0%, $t(60) = 4.43$, $P < .001$, $d = 0.57$), indicating category-coding in the PCC during visual encoding, with no significant group differences in classification accuracy ($F(1,59) = 0.45$, $P = 1$, $\eta^2 < 0.01$). The classifier trained on localizer activation patterns in the PCC was neither able to distinguish remembered scenes and remembered objects during the Day 2 Memory Cueing task (M±SE = 52.3% ± 0.98%; $P = .092$), nor forgotten scenes and forgotten objects (M±SE = 49.5% ± 1.70%; $t(60) = -0.27$, $P = 1$, $d = 0.03$).

Contrasting within-localizer classifier accuracies revealed a main-effect of *Region* ($F(2,174) = 101.74$, $P < .001$, $\eta^2 = .054$). Post-hoc tests revealed significantly higher accuracy for the VTC compared to PCC ($t(60) = -12.00$, $P < .001$, $d = 1.54$) and hippocampus ($t(60) = -17.40$, $P < .001$, $d = 2.24$), and for the PCC compared to hippocampus ($t(60) = -3.90$, $P < .001$,

d = 0.50). Moreover, while we found evidence for category-level reinstatement during Day 1 Encoding in the VTC, PCC and hippocampus, a main-effect of *Region* ($F(2,174) = 192.32$, $P < .001$, $\eta^2 = 0.69$) revealed significantly higher accuracy for the VTC compared to PCC ($t(60) = -16.90$, $P < .001$, $d = 2.18$) and hippocampus ($t(60) = -19.01$, $P < .001$, $d = 2.45$). Classifier accuracy of PCC and hippocampus did not differ during the Encoding task ($t(60) = 0.94$, $P = 1$, $d = 0.12$). Finally, significant category-level reinstatement of remembered trials during the Day 2 Memory Cueing task was observed in cortical areas (VTC, PCC), but not in the hippocampus. Comparing corresponding accuracy estimates revealed a main-effect of *Region* ($F(2,174) = 3.45$, $P = .034$, $\eta^2 = 0.04$). Post-hoc tests showed no difference between VTC and PCC ($t(60) = -1.69$, $P = .283$, $d = 0.22$) nor PCC and hippocampus ($t(60) = 1.24$, $P = .660$, $d = 0.16$), whereas VTC accuracy was significantly higher than hippocampal accuracy ($t(60) = -2.61$, $P = .034$, $d = 0.34$).

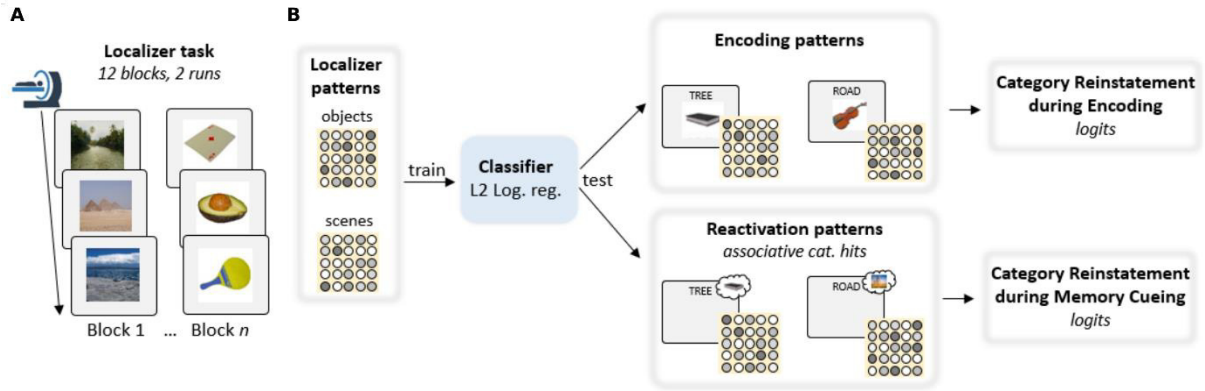

Fig. 2. Trial-wise pattern reinstatement during Encoding and the Day 2 Memory Cueing task. A To derive an index of visual category reinstatement in the VTC, an independent localizer task was conducted at the end of Day 3. During this task, pictures of scenes and objects were presented block-wise to participants. **B** The resulting neural patterns of both categories were then used to train an L2-regularized logistic regression. This function served to classify trial-wise patterns during the Day 1 Encoding task as well as the Day 2 Memory Cueing task, while also providing the strength of category-level online reinstatement (quantified as logits).

No Evidence for Event-level Online Reinstatement

Beyond category-level reinstatement, we assessed event-level memory trace reinstatement from initial encoding (Day 1) to memory cueing (Day 2), via RSA, correlating neural patterns in each region (hippocampus, VTC, and PCC) across days. To test for evidence that associative hits during memory cueing entailed the reinstatement of representations established at encoding, we compared the average event-level Day 1 (encoding) to Day 2 (memory cueing) similarity of the associative hits against 0. In PCC and hippocampus, we did not obtain evidence for event-level memory trace reinstatement (t-test against 0; both Ps > .296). By contrast, for the VTC, average similarity was significantly negative, suggesting that from Day 1 (encoding) to Day 2 (memory cueing), neural patterns became more dissimilar ($t(60) = -7.87$, $P < .001$, $d = 1.01$). As the VTC is implicated in category-level processing, we next compared trial-wise event- vs category-level similarities. Results revealed that memory trace reinstatement during successful memory cueing on Day 2 (i.e., associative hits) was characterized by significantly

higher category-level representations compared to event-level representations in all three regions (hippocampus: $t(60) = 5.51$, $P < .001$, $d = 0.71$; VTC: $t(60) = -11.83$, $P < .001$, $d = 1.51$; PCC: $t(60) = 8.25$, $P < .001$, $d = 1.06$). This outcome is consistent with the above MVPA outcomes demonstrating that associative hits on Day 2 are accompanied by category-level reinstatement (as quantified by the localizer-trained classifier). Given this finding, all subsequent analyses focused on category-level, rather than event-level, patterns.

Day 2: Noradrenergic Activity and Glucocorticoid Concentrations

Shortly before the Memory Cueing task, participants were administered either 20 mg YOH (n = 21), 20 mg CORT (n = 21), or a PLAC (n = 20). Given the known pharmacodynamics of YOH and CORT, we expected the drugs to be effective after the Memory Cueing task and subsequent resting-state interval (Kluen et al. 2017; Krenz et al. 2021), exerting their influence during the putative post-retrieval (re)consolidation window. To confirm successful noradrenergic and glucocorticoid activation, and to verify that their effects occurred only after (but not during) the Memory Cueing task, we assessed autonomic arousal (blood pressure, heart rate, and skin conductance), salivary cortisol, and subjective mood throughout Day 2.

Analysis of autonomic measures revealed a significant *Time* × *Group* interaction in systolic blood pressure ($F(8.71, 256.99) = 5.87$, $P < .001$, $\eta^2 = .03$; Fig. 3A), but not in diastolic blood pressure or heart rate (both Ps > .120; Supplemental Table S4). Post-hoc t-tests showed significantly higher systolic blood pressure in the YOH group compared to the PLAC group 70 minutes ($t(29.77) = -3.31$, $P = .014$, $d = 1.02$), 85 minutes ($t(34.15) = -3.33$, $P = .012$, $d = 1.03$), and 100 minutes after pill intake ($t(36.94) = -3.98$, $P < .001$, $d = 1.23$). The CORT group did not significantly differ from the PLAC group in systolic blood pressure (all Ps > .229). Importantly, systolic blood pressure in the YOH and CORT groups did not differ from the PLAC group immediately before or after the MRI session, suggesting that the drug was not yet effective during the Memory Cueing task and the post-reactivation resting-state scan (both Ps > .485).

We also recorded skin conductance, a continuous indicator of autonomic arousal, during the MRI scans (i.e., during the Memory Cueing task and the resting-state scans), when the drug should not have been active yet. Skin conductance response analysis during the Memory Cueing task and pre- and post-reactivation resting-state scans showed no *Time* × *Group* interaction ($F(3.30, 97.44) = 0.33$, $P = .819$, $\eta^2 < 0.01$) and no main effect of *Group* ($F(2,59) = 2.60$, $P = .083$, $\eta^2 = 0.07$), suggesting that groups did not reliably differ in autonomic arousal during the MRI scans.

In contrast to systolic blood pressure, salivary cortisol increased, as expected, in the CORT group but not in the YOH or PLAC groups (*Time* × *Group* interaction: $F(5.33, 157.17) = 43.80$, $P < .001$, $\eta^2 = .472$). Post-hoc t-tests indicated a significant cortisol increase in the CORT group compared to the PLAC group at 40 minutes ($t(27.91) = 2.30$, $P = .020$, $d = 0.99$), 70 minutes ($t(20.64) = -11.23$, $P < .001$, $d = 3.42$), and 100 minutes after pill intake ($t(20.19) = -10.36$, $P < .001$, $d = 3.15$; Fig. 3B), whereas salivary cortisol of PLAC and YOH groups revealed no significant difference at any timepoint (all Ps > .350). Importantly, salivary cortisol concentrations did not differ between groups immediately before or during the MRI session, suggesting that CORT was not yet effective during the Memory Cueing task or post-reactivation resting-state scan (both Ps > .162). Finally, subjective mood analyses across Day 2 revealed no

significant *Time* × *Group* interaction on any scale (all interaction Ps > .460; Supplemental Table S5).

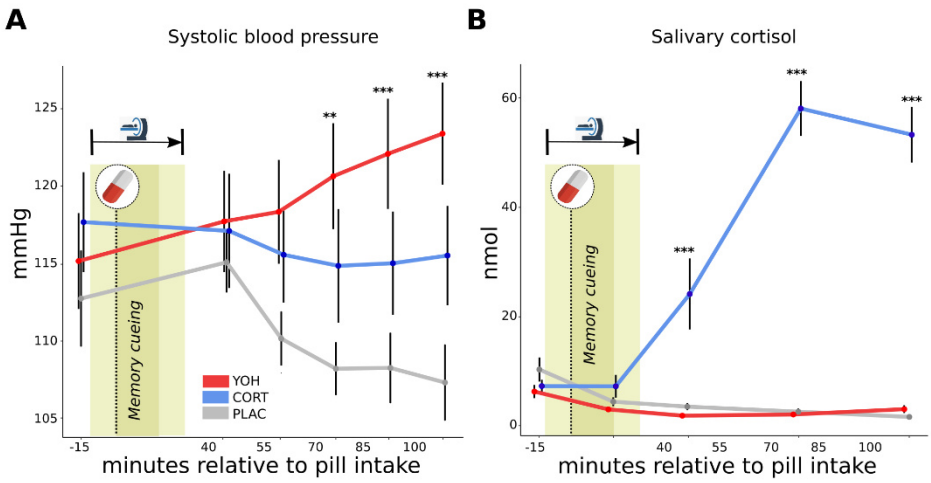

Fig. 3. Effective noradrenergic and glucocorticoid action after Day 2 memory cueing. Systolic blood pressure **(A)** and salivary cortisol **(B)** did not differ between groups before or immediately after the Memory Cueing task. However, 70 minutes after pill intake, systolic blood pressure was significantly higher in the YOH group relative to the PLAC group. Conversely, salivary cortisol was significantly higher in the CORT group relative to PLAC starting 40 min after pill intake. Light yellow shades indicate the pre- and post-memory cueing resting-state fMRI scan periods. Data represent means (± SE). ***P< .001, **P< .01.

Day 3: Memory Cueing Increases Subsequent Memory Performance

On Day 3, 24 hours after memory cueing and drug administration, participants returned to the MRI scanner for a final cued recall task. Groups did not differ in subjective mood, autonomic arousal, or salivary cortisol before this final memory test (all Ps > .158, see Supplemental Table S2). The Day 3 cued recall task was identical to that on Day 1, except that it contained novel lures. Participants successfully distinguished between old words and new words, with an 81.1% hit rate (response 'old', 'old/scene', 'old/object' to an old word) and a 21.75% false alarm rate (response 'old', 'old/scene, 'old/object' to a new word). Participants recognized the word and correctly identified the associated image category in 50.1% of trials (associative category hit rate) with an associative error rate of 11.6%. Day 3 associative d' was 1.14 (SE = 0.15). Importantly, across groups, memory was significantly enhanced for associations that were cued and successfully retrieved on Day 2 (M = 2.05; SE = 0.21) compared to uncued associations (M±SE = 1.14 ±0 .15; $F(1,58) = 143.51$, $P < .001$, $\eta^2 = 0.29$; Fig. 4), in line with the established testing effect (Karpicke and Roediger 2008; Roediger and Karpicke 2006), and confirming the efficacy of the selective, association-specific cueing manipulation.

According to both memory reconsolidation and mnemonic interference accounts, drugs should selectively affect subsequent memory for associations cued and reactivated before the effective action of the drugs on Day 2 but not for uncued items. When collapsing

across all cued associations (i.e., not considering whether the memory was indeed reactivated), a mixed-design ANOVA on associative d' scores revealed neither a significant *Cued* × *Group* interaction nor a main effect of *Group* (all Fs < 2.08, all Ps > .134), suggesting that the mere presentation of the word cue on Day 2 was insufficient to induce post-retrieval stress hormone effects that change future memory performance. Furthermore, univariate analyses showed no *Cued* × *Group* interactions in whole-brain or ROI activity.

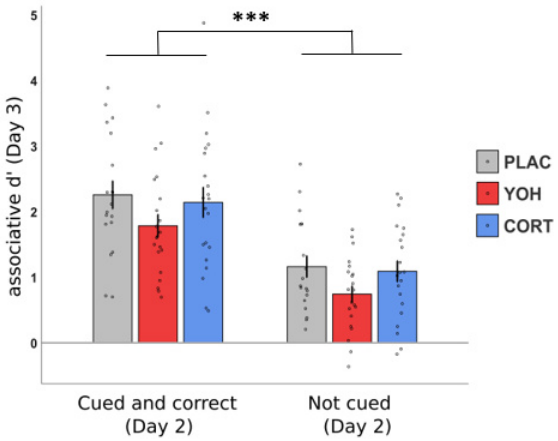

Fig. 4. Subsequent memory performance on Day 3, split for cued and correct (Day 2) and uncued trials. Average memory performance (associative d') was significantly increased for cued and correct (Day 2) trials compared to uncued trials. This effect was, however, unaffected by the pharmacological manipulation. Data represent means +- SE. ***P< .001.

Day 3: Effects of Post-retrieval Noradrenergic Stimulation on Subsequent Memory Depend on Prior Online Hippocampal and Cortical Reactivation

We hypothesized that the post-retrieval effects of noradrenergic arousal and cortisol on subsequent memory depend on robust neural memory reactivation shortly before the action of the drugs on Day 2. We therefore tested whether the strength of neural reinstatement during successful memory cueing (Day 2) predicted the impact of post-retrieval noradrenergic and glucocorticoid activation on subsequent memory (Day 3). Overall, univariate activity on cued and correct trials (Day 2 associative hits) in hippocampus, PCC and VTC did not reveal any interaction with *Group* on subsequent memory (Day 3 associative d'), suggesting that the average activation across trials and voxels within a single brain area may not suffice to predict post-retrieval effects of noradrenaline or cortisol (all interaction Ps > .711).

Reaction times from the Day 2 Memory cueing task, revealed a trial-specific gradient in reactivation strength. Thus, we turned to single-trial analyses, differentiating (median splitting) Day 3 trials by short and long reaction times during memory cueing on Day 2, putatively indicative of high/low underlying memory reactivation. A GLMM was employed to predict associative category hits on Day 3 by *Group* and *Day 2 Reaction time (short, long).* A significant interaction (*Group* × *Reaction time (Day 2)* interaction: β = 0.79 ± 0.30, z = 2.61, P = .008, $R^2_{conditional}$ = 0.27 ; Figure 5A) revealed that the relationship between Day 2 reactivation and the probability of an associative hit on Day 3 varied across groups. Post-hoc marginal means tests revealed a differential decrease in the probability of associative hits on Day 3 in light of short Day 2 reaction times when comparing YOH vs. CORT (β = 2.55 ± 0.94, z-ratio = 2.55, P =

.031) and YOH vs. PLAC (β = 0.34 ± 0.14, z-ratio = -2.55, P = .032). By contrast, comparing CORT vs. PLAC revealed no such difference (β = 0.88 ± 0.37, z-ratio = -0.29, P = 1), suggesting that noradrenergic arousal specifically interacts with strongly reactivated representations after retrieval.

As hippocampal and PCC activity scaled with Reaction times from the Day 2 Memory cueing task, we next differentiated trials according to the strength of their neural reactivation. To relate Day 2 reactivation strength to subsequent memory (Day 3), we fit GLMMs, predicting Day 3 associative category hits by *ROI activity* (Day 2), *Reaction time* (Day 2) and *Group*. Strikingly, shorter reaction times and stronger hippocampal activity on Day 2 predicted an increased probability of an associative category hit on Day 3 memory in the PLAC group, whereas these measures of stronger reactivation on Day 2 predicted a lower probability of an associative category hit on Day 3 in the YOH group (*Group* × *Hippocampal activity (Day 2)* × *Reaction time (Day 2)* interaction: β = 0.90 ± 0.36, z = 2.45, P = .038, $R^2_{conditional}$ = 0.27) but not in the CORT group (β = 0.89 ± 0.39, z = 2.28, P = .068). Post-hoc comparisons confirmed significant differences in strongly reinstated trials between YOH and PLAC groups (β = -1.12 ± 0.35, z-ratio = -3.13, P = .005) and between YOH and CORT groups (β = 0.88 ± 0.34, z-ratio = 2.58, P = .029), but not between PLAC and CORT groups (β = -0.23 ± 0.36, z-ratio = -0.63, P = 1; Fig. 5A). Parallel models with univariate PCC and right hippocampal activity did not yield a significant interaction with *Group* (all Ps > .081), suggesting that cued memories specifically accompanied by left hippocampal reactivation during Day 2 was associated with increased vulnerability to the influence of post-retrieval YOH, disrupting post-retrieval processing and subsequent memory on Day 3.

We further hypothesized that the post-retrieval effects of noradrenergic arousal and cortisol on subsequent memory would depend on the reinstatement of the original memory trace (as assayed by the similarity of neural patterns during Encoding and Memory Cueing). We therefore tested whether the strength of memory trace reinstatement in the hippocampus, VTC and PCC during successful memory cueing (Day 2) predicted the impact of post-retrieval noradrenergic and glucocorticoid activation on subsequent memory (Day 3). In contrast to our prediction, none of these regions showed a significant effect that included the factor *Group* (all Ps > .257). These results suggest that the previously observed post-retrieval noradrenergic subsequent memory impairment may be associated with retrieval-related univariate activity but not the reinstatement of encoding-related neural patterns.

Building on our observation that category-level pattern reinstatement during Day 2 memory cueing (assessed by MVPA) in the VTC was linked to successful memory retrieval, we next classified cued and correct (Day 2) trials as strongly or weakly reactivated based on a median-split on the strength of VTC category-level pattern reinstatement (assayed by logits), allowing us to include the uncued trials in further analyses. Testing whether *Reactivation strength (uncued, low VTC reinstatement, high VTC reinstatement)* interacted with *Group* and *Hippocampal activity (Day 2)* to predict Day 3 (24-hour-delayed) memory performance yielded a significant interaction (β = -0.21±0.07, z = -3.08, P = .002, $R^2_{conditional}$ = 0.18; Fig. 5B). Post-hoc slope tests confirmed that noradrenergic activation significantly affected Day 3 memory for the trials associated with stronger trial-wise VTC category-level pattern reinstatement and hippocampal univariate activity on Day 2, resulting in an impairment of subsequent retrieval on Day 3 (YOH vs. PLAC: β = 0.14±0.05, z-ratio = 2.57, P = .030; YOH vs. CORT: β = 0.13±0.05, z-ratio = 1.31, P = .708; Fig. 5C). By contrast, neither drug affected Day 3 memory for the trials

associated with weaker trial-wise VTC category-level pattern reinstatement and hippocampal univariate activity on Day 2 (all Ps > .210). Notably, when directly comparing the slopes of weak and strong category-level VTC reinstatement in interaction with hippocampal activity, only the YOH group showed a significant decrease related to Day 3 performance (YOH: β = 0.12±0.05, z-ratio = 2.72, P = .018; CORT: β =- 0.02±0.05, z-ratio = -0.42, P = 1; PLAC: β =- 0.09±0.05, z-ratio = -1.68 , P = .274).

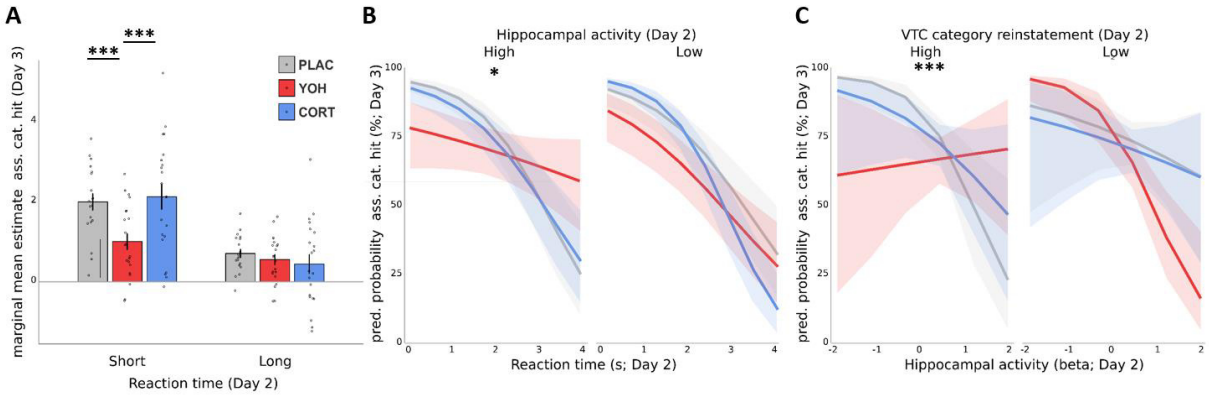

Fig. 5. Subsequent memory impairment by noradrenergic activation depends on hippocampal and VTC online reactivation. A Reactivation strength was initially indexed using trial-wise reaction times (memory confidence) during the Day 2 Memory Cueing task. In all three groups, the probability of a later associative category hit on Day 3 was greater on trials for which there was shorter reaction times/higher confidence during recall on Day 2. However, post-retrieval adrenergic activation (YOH group) differentially impaired subsequent memory following high confidence Day 2 retrieval, suggesting that trials which are reactivated more strongly prior to noradrenergic activation are affected most by the intervention. **B** Such reductions in the probability of later associative category hits on Day 3 was further related to high hippocampal activity during Day 2 memory cueing specifically for the YOH group. Notably, trials which were retrieved with low confidence during memory cueing were not affected by any drug. **C** Further reductions in the probability of later associative category hits on Day 3 were observed for strong category level reinstatement in the VTC in conjunction with strong hippocampal univariate activity in YOH group on Day 2, which differed from the relationships seen in the PLAC and CORT groups. As such, post-retrieval adrenergic activation (YOH group) impaired subsequent memory as a function of the strength of memory reactivation prior to drug efficacy. *P<.05,***P<.001.

Offline Reinstatement Analyses

Aside from examining neural activity related to retrieval during the Memory Cueing task, we also investigated offline reactivation, which is manifested in neural reinstatement observed during the resting-state scans conducted both pre and post memory cueing (Supplemental Methods S2). Neural representations from the Memory Cueing task were reinstated significantly offline (i.e., post > pre resting state) in the hippocampus, PCC, and VTC. Moreover, the initial patterns from encoding were reinstated offline in the VTC (Supplemental Results S2). However, in contrast to the above reported online reactivation × drug effects, none of these factors interacted with *Group* when considering Day 3 subsequent memory performance (Supplemental Results S3).

Discussion

Upon their retrieval, memories can become sensitive to modification (Dudai and Eisenberg 2004; Nadel et al. 2012). Such post-retrieval changes in memory may be fundamental for adaptation to volatile environments, yet the brain mechanisms involved in the dynamics of memory after retrieval are largely unknown, especially in humans. Here, we aimed to shed light on the neural mechanisms underlying the impact of post-retrieval elevations in the major stress mediators noradrenaline and cortisol on subsequent remembering. Our results revealed that post-retrieval noradrenergic activation led to an impairment in subsequent memory, depending on memory strength/confidence, hippocampal activation, and VTC pattern reinstatement during memory reactivation. By contrast, post-retrieval glucocorticoid activation did not influence subsequent memory in any way.

Previous research showed that administering the beta-blocker propranolol after memory reactivation reduces subsequent memory, potentially interfering with the putative reconsolidation process (Kindt et al. 2009; Przybyslawski et al. 1999; Schramm et al. 2016; Schwabe, Joëls, et al. 2012). While this impairing influence has not been consistently replicated (Bos et al. 2014; Elsey et al. 2020; Muravieva and Alberini 2010; Wood et al. 2015), these results suggest that post-retrieval noradrenaline may facilitate subsequent remembering. In contrast to this idea, our results demonstrate that increased noradrenergic stimulation after memory retrieval impairs subsequent memory. However, a key distinction between our study and prior research using propranolol lies in the emotional nature of the memory task. Previous studies predominantly focused on emotionally arousing information or fear memories (Dębiec and LeDoux 2004; Lee, Milton, and Everitt 2006; Phelps et al. 2004), assuming that post-retrieval propranolol may weaken reconsolidation by attenuating the emotional salience of memories, making them more comparable to neutral ones (Schwabe, Nader, et al. 2012). In our study, we employed emotionally neutral scene images, offering a novel context to explore noradrenergic effects on memory (re)consolidation or mnemonic interference. Furthermore, our findings suggest a potential inverted u-shaped relationship between post-retrieval noradrenergic arousal and subsequent memory, where both noradrenergic blockade by propranolol and strong noradrenergic stimulation induced by yohimbine result in a subsequent memory impairment. This idea is in line with previous reports of inverted u-shaped relationships between noradrenergic arousal and memory processes(Arnsten 2011; Birnbaum et al. 1999; Hernaus et al. 2017; Li and Mei 1994). Most importantly, our results suggest that the yohimbine-induced memory impairment critically depended on hippocampal reactivation during memory cueing. The hippocampus, crucial for episodic memory formation and retrieval, is highly sensitive to noradrenergic modulation, which can impact hippocampal long-term potentiation and depression (Katsuki, Izumi, and Zorumski 1997; Strange et al. 2014). Excessive noradrenergic activity in the hippocampus may further have disrupted neurotransmission (Diamond et al. 2007; Kim and Kim 2023). This disruption may have manifested as deficits in consolidating new retrieval-related memory traces or reconsolidating existing memories. Furthermore, the subsequent memory impairment in the YOH group was additionally dependent on robust activation of the VTC during memory cueing. These effects could relate to an impeding of the (re)consolidation of visual memory contents, given the VTC's role in processing complex visual stimuli and encoding categorical information, such as scenes (Bracci et al. 2017; Grill-Spector and Weiner 2014).

In addition to noradrenergic activation, acute stress is accompanied by a significant increase in cortisol levels, which has been associated with impairments in putative memory reconsolidation after retrieval (Antypa et al. 2021; Maroun and Akirav 2008; Vafaei et al. 2023; Wang et al. 2008). Our results revealed that post-retrieval glucocorticoid activation did not influence subsequent memory, as the placebo and cortisol groups performed similarly in the subsequent memory task. Acute stress triggers a series of neurochemical changes, and it has been shown that noradrenergic and glucocorticoid activation are strongly intertwined. Accordingly, previous studies have highlighted that the effects of glucocorticoids on memory processes are particularly pronounced when accompanied by high noradrenergic arousal, commonly observed during stressful situations (de Quervain, Aerni, and Roozendaal 2007; Roozendaal et al. 2006; Schwabe et al. 2022). Notably, in the current study, the administration of hydrocortisone was not associated with an increase in arousal or negative mood. As such, our findings may imply that cortisol alone is not sufficient to influence post-retrieval updating and necessitates concurrent noradrenergic arousal for its memory-modulating effects to fully manifest (Maroun and Akirav 2008; Roozendaal et al. 2006).

There is evidence suggesting that memory updating depends not only on neural processes during retrieval (i.e., online processing) but also on offline neural reinstatement or replay during post-retrieval rest (Schlichting and Preston 2014; Staresina et al. 2013). However, whether offline neural reinstatement after retrieval is involved in post-retrieval changes of subsequent memory remains unclear. Here, we tested for the first time whether post-retrieval manipulations of memory are dependent on neural offline reinstatement after memory cueing. While we generally observed significant offline reactivation events in the post-cueing interval compared to pre-cueing (see Supplement Results), our findings revealed that neither drug significantly affected subsequent memory via interacting with offline reinstatement dynamics. To explain this absence of an effect, it is important to note the differences between the estimated neural online compared to offline parameters. While it might seem that offline reinstatement reflects a mere repetition of the neural signal reactivated during retrieval, these two parameters are not directly comparable.

We investigated offline reactivation in the brain during rest periods before and after a Memory Cueing task by examining neural patterns with RSA. We compared neural activity from the Memory Cueing task with resting-state fMRI scans taken before and after the task, focusing on the hippocampus, VTC, and PCC. To identify reactivation events, we calculated the mean correlation plus 1.5 standard deviations from the pre-cueing phase and applied this threshold to assess pre- and post-cueing correlation matrices. We repeated this process using the post-cueing threshold. Finally, we quantified the number of offline reactivation events by counting the correlations that exceeded these thresholds. The reported offline reinstatement events are hence based on differences in correlations that exceed a threshold, and do not reflect the direct strength of the underlying neural correlate (such as e.g. trial-wise hippocampal activity). Given that the observed impairments in subsequent memory in the YOH group were directly dependent on the trial-specific strength of online neural reactivation (i.e., hippocampal activity and reaction times) one would need to derive a comparable assay from the offline intervals. Finally, on that matter is important to note that the reaction time (confidence) during memory cueing was the most powerful predictor of post-retrieval effects; a predictor that can not be derived from resting state intervals.

In line with central tenets of reconsolidation theory (Lee et al. 2017; Nader and Einarsson 2010; Schwabe et al. 2014) , the disruptive effects of YOH were contingent on memory reactivation. There were no differential effects of noradrenergic activation on cued but incorrectly recalled events relative to uncued events, suggesting that memories, if not correctly recalled, remained resistant to modification. Moreover, the extent of neural reactivation on Day 2 correlated with subsequent memory performance, further underlining the crucial role of neural memory reactivation for post-retrieval modifications of memory. Notably, the triggering of putative reconsolidation is posited to be initiated by prediction errors (PEs; Díaz-Mataix et al. 2013; Fernández, Boccia, and Pedreira 2016; Sevenster, Beckers, and Kindt 2013). In the present study, PEs may have resulted from the incomplete reminder structure during cued recall (Kroes et al. 2014; Sinclair and Barense 2019). That said, our findings are more in line with disruption of the consolidation of retrieval-related memory presentations rather than reconsolidation theory, as we did not observe interactions of any drug with the reinstatement of the original memory trace. Thus, the observed effects of post-retrieval noradrenaline on subsequent remembering were potentially owing to alterations in new memory traces formed during retrieval, as suggested by multiple trace theory (or interference) accounts of post-retrieval changes in memory. This interpretation is speculative and limited by the fact that we also did not observe any drug interactions with pattern reconfigurations across days.

Finally, it is important to note that we administered drugs before memory cueing on Day 2, in order to achieve, in light of the known pharmacodynamics of hydrocortisone and yohimbine (Krenz et al. 2021; Schwabe et al. 2010), effective drug actions shortly after memory reactivation, during the proposed (re)consolidation window. However, as we administered drugs before memory cueing, these could have potentially affected the memory reactivation itself, rather than post-retrieval processes. Our physiological data indicated that the drugs were effective only after the Memory Cueing task. Moreover, groups did not significantly differ in performance or associated neural activity in the Memory Cueing task. These data support the assumption that the drugs did not interfere with memory cueing or reactivation processes, but rather most likely affected post-retrieval (re)consolidation processes.

Previous research demonstrated that acute stress after retrieval, during the proposed reconsolidation window, can impair subsequent memory (Dongaonkar et al. 2013; Hupbach and Dorskind 2014; Larrosa et al. 2017; Maroun and Akirav 2008; Schwabe and Wolf 2010). Here, we show that post-retrieval increases of noradrenergic arousal, but not of cortisol, reduce subsequent remembering. Critically, the observed memory impairment depended on the strength of online neural reinstatement occurring during retrieval, but not offline reinstatement after retrieval, especially in the hippocampus and neocortical representation areas. Our findings provide novel insights into the mechanisms involved in post-retrieval dynamics of memory in general and in those involved in the impact of stress mediators after retrieval in particular. Beyond their theoretical relevance, these findings may have relevant implications for attempts to employ post-retrieval manipulations to modify unwanted memories in anxiety disorders or PTSD (Parsons and Ressler 2013; Wessa and Flor 2007). Specifically, the present findings suggest that such interventions may be particularly promising if combined with cognitive or brain stimulation techniques ensuring a sufficient memory reactivation.

Materials and Methods

This study was preregistered before the start of data collection at the *German Clinical Trials Register* (DRKS; https://drks.de/search/en/trial/DRKS00029365).

Participants

Sixty-eight healthy, right-handed adults (28 women, 40 men) without a life-time history of any neurological or psychiatric disease were recruited for this experiment. Further exclusion criteria comprised smoking, drug abuse, prescribed medication use, pregnancy or lactation, a history of kidney- or liver-related diseases, body-mass index below 19 or above 26 kg/m², diagnosed cardiovascular problems as well as any contraindications for MRI measurements. Women were excluded if they used hormonal contraceptives and were not tested during their menses as these factors may interact with the pharmacological intervention. Participants were instructed to refrain from caffeinated beverages, exercise, and eating or drinking (with the exception of water) for 2 hours prior to the experiment. Seven participants were excluded from analyses due to acute claustrophobia (n = 1) or technical failure (n = 3), no Day 3 memory performance (n =1), or because they did not return on Day 2 or 3 (n = 2), thus leaving a final sample of n = 61 participants (25 women, 36 men, age = 19-34 years, mean = 25 years, SD = 4 years). We employed a fully crossed, PLAC-controlled, double-blind, between-subjects design in which participants were randomly assigned to one of three groups: PLAC, YOH, or CORT. All participants provided written informed consent before the start of the experiment and received a monetary compensation for their participation. An a priori power calculation with G*Power (Faul et al. 2007) indicated that a sample size of N = 66 is required to detect a medium-sized *Group* × *Reactivation* interaction effect with a power of .95. The study was approved by the ethics committee of the Medical Chamber of Hamburg (PV5960). Groups did not differ significantly from each other with respect to depressive mood, chronic stress, state or trait anxiety (see Supplemental Results S1 and Supplemental Table S6).

Experimental Procedure

The study took place on three consecutive days, with all tasks conducted in the MRI scanner during morning hours (8:30 am - 12:30 pm) to control for the diurnal rhythm of cortisol. On each day we obtained measures of blood pressure, heartrate, salivary cortisol and mood to control for potential baseline differences between groups as well as to assess the effective pharmacological manipulation on Day 2.

Experimental Day 1: associative encoding task

Participants underwent a brief (~5 min) training session before the encoding task to familiarize themselves with the procedure. This training replicated the 3-day paradigm structure, involving an encoding session and a cued recall test with word-picture associations that were not part of the actual experiment. In the actual encoding task, participants were instructed to memorize 164 unique word-picture pairs presented in three runs. Each pair appeared three times (once in each run), including German nouns (see Supplemental Methods S1) and

pictures of coloured scenes (Xiao et al. 2010) or objects (Brodeur, Guérard, and Bouras 2014). During each trial, a word and picture were presented for 3 s (words on top of the screen, pictures in the centre), and participants rated their fit on a 4-point Likert scale using an MRI-compatible button box. A black fixation cross appeared between trials for 5-9 s (jitter: 0 – 4 s, mean-jitter: 2 s). Each run took about 25 min, with a 2-minute break after each run, resulting in a duration of about 90 min for the three runs. Importantly, out of the 164 word-picture pairs presented during encoding, 20 pairs were designated as catch trials for the subsequent cued recall tasks (see Supplemental Methods S2). As such, all memory analyses were based on 144 of the encoded word-picture pairs.

Experimental Day 1: immediate cued recall

After the encoding task, participants were provided a 15 min break before receiving instructions for the immediate cued recall task. Back in the MRI scanner, 152 words (including eight catch trials) from the prior study phase ('old') and 152 new words were presented. Each test word appeared for 4 s, prompting participants to make one of four memory decisions: 'new,' 'old,' 'old/scene,' or 'old/object.' The latter two responses were used upon recognizing the word as old and indicating the associated images category. Responses were made using an MRI-compatible button box. The positions of 'old/scene' and 'old/object' were randomized (50%) between the ring and little fingers on each trial. Between trials, there was an ITI of 5 to 9 s (jitter: 0 – 4 s, mean jitter: 2 s), during which a black fixation cross was presented. The task lasted 60 min in total, divided into two 30-min sessions with a 2-min break in between.

Experimental Day 2: drug administration and memory cueing

On Day 2, participants returned to the MRI scanner and initially underwent 10 minutes of eyes-open resting state scanning. Next, participants received orally one of the pharmacological agents (YOH, CORT) or a PLAC, depending on the experimental group. YOH is a α2-adrenoceptor antagonist that leads to increased adrenergic stimulation, while CORT is the synthetic variant of the stress hormone cortisol. The timing and dosage of the drugs were chosen in accordance with previous studies (Kausche et al. 2021; Zerbes, Kausche, and Schwabe 2022). They were taken orally under supervision of the experimenter immediately before the Memory Cueing task, in order to ensure the action of the drug shortly after the reactivation, i.e. during the reconsolidation window. The pills were indistinguishable, and the experimenter remained unaware of participants' group assignments, ensuring double-blind testing. Following pill intake, participants completed a Memory Cueing task, which lasted about 20 minutes. The task included half of the previously studied old words (72 trials, 36 word-scene associations and 36 word-object associations) and four catch-trials. The words from Day 1 were re-presented for 4 s, with an ITI of 5 to 9 s (jitter: 0 – 4 s, mean-jitter: 2 s). On each trial, participants were asked to remember the specific picture that had been associated with this word (i.e., the retrieval cue) during the Day 1 encoding session. Participants were requested to indicate the category of the picture belonging to the presented word. The position of the response options (objects vs. scene; category level 2AFC) were randomly switched between the ring and little fingers on each trial. 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. Examining the gradient between stronger and weaker reactivation is also pivotal for understanding the impact of post-retrieval interventions on memory processes, as a strong reactivation during Day 2 may make the memory more susceptible to the effects of pharmacological agents. This task aimed to reactivate half of the word-picture pairs, allowing examination of 'testing effects' and potentially opening a reconsolidation window. The remaining half of the pairs were not reactivated and served as baseline/control memories. After the Memory Cueing task, another 10 minute, eyes-open resting state scan was performed. Participants were then taken out of the scanner and led into a separate room were they were seated for 1 hour (provided with magazines to read) while they completed mood questionnaires and we took physiological measurements (e.g. blood pressure) to validate the action of the drugs.

To assess the efficacy of the pharmacological manipulation and the temporal dynamics of the drug action, we measured systolic and diastolic blood pressure, heart rate, salivary cortisol (Sarstedt, Germany) and subjective mood before drug administration (baseline), after the post-reactivation resting state scan (40 min) and then in four further intervals of 15 minutes (55, 70, 85, 100 min after drug intake). In order to verify that neither agent would take effect during the critical Memory Cueing task, we additionally obtained a saliva sample directly after the Memory Cueing task (25 min) and recorded the heartrate as well as skin conductance rate continuously throughout the three MRI sessions. Saliva samples were stored at −20 °C until the end of the study. From saliva we analysed the free fraction of cortisol by means of an luminescence assay (IBL, Germany). Inter- and intra-assay coefficients of variance were below 10%.

Experimental Day 3: cued recall and functional localizer

Twenty-four hours after the reactivation 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. Again, participants were presented 152 of the encoded words and 152 new words in random order and were asked to indicate for each word, whether it was 'new", 'old", 'old" and presented with a scene ('old/scene") or 'old" and presented with an object ('old/object"). 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 (Ma, Correll, and Wittenbrink 2015), objects (BOSS database (Brodeur et al. 2014), and scenes (SUN database (Xiao et al. 2010). Ten pictures of each category were presented in twelve blocks (4 blocks per picture category) and repeated in two runs. Categories were randomly switched between blocks. During each block a picture was presented for 0.5 s, with an ITI of 1. During the image presentation, participants had to judge whether in case of scenes it was 'indoor' or 'outdoor', in case of objects it was 'artificial' or 'living', and in case of faces whether it was 'female' or 'male'. Upon completion of the first run, a one-minute break was provided. The second run included the exact same blocks as the first, block-categories were however randomly mixed again.

Behavioural memory data analysis

In our examination of word-picture associative memory during the cued recall tasks on Day 1 and Day 3 (4AFC), associative category hits were recorded when participants correctly matched old word cues with the corresponding picture category (e.g., responding 'old/scene' for a scene associate), indicating recognition of the presented word as old and retrieval of the associated picture category at the category level. Associative category errors occurred when an old word was recognized, but the wrong category was chosen (e.g., responding 'old/object' for a scene associate). We use the term 'associative misses' to encompass all old trials that did not result in associative category hits (i.e., an old word was presented and the participant responded 'new', 'old', or 'old' with the wrong category). The average rates of associative category hits, misses, and errors were calculated based on correct/incorrect responses relative to the total number of cued and correct (Day 2 Memory Cueing task) and non-cued trials.

During the 2AFC Memory Cueing task on Day 2, participants could only select 'scene' or 'object' as responses. Therefore, associative hits were recorded when participants correctly identified the picture category (e.g., selecting 'object' for an object associate), while associative misses occurred when participants selected the incorrect category. Hits and misses in this task could indicate either correct/incorrect retrieval of the associated category or recognition of the word as old along with a correct/incorrect category guess. Neural measures of memory reactivation are crucial in distinguishing between 2AFC associative hits based on strong, moderate, or minimal reactivation. Average rates of associative hits and misses were calculated based on correct/incorrect responses relative to the total number of trials during the Day 2 Memory Cueing task.

Imaging Methods

fMRI acquisition and preprocessing

Functional imaging data were acquired using a 3 T Magnetom Prisma MRI scanner (Siemens, Germany), 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 x 224 mm. 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 x 0.8 x 0.9 mm 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. The structural and functional images underwent preprocessing using SPM12 (http://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, coregistration 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 (FWHM) Gaussian kernel.

fMRI wholebrain GLM analysis of cued recall on Days 1, 2 and 3

For each participant, a general linear model (GLM) was estimated using smoothed and normalized functional images for all tasks, applying a high-pass cut-off filter at 128 s to eliminate low-frequency drifts. T-statistic maps from GLM analyses represented contrasts of interest. Cluster correction via Gaussian random fields (GRF) theory corrected for multiple comparisons with a significance threshold of $p < .05$. The GLM included regressors for cued recalls on Days 1 and 3: associative category $hit_{Cued\ and\ correct}$, associative $miss_{cued\ and\ correct}$, associative category hit_{Uncued}, and associative $miss_{Uncued}$. Trials that were 'Uncued' on Day 2 were considered not reactivated, 'Cued and correct' trials on Day 2 were considered reactivated, and trials that were cued on Day 2 but not remembered were removed from the analysis. Additionally, six regressors addressed movement realignment parameters (two run-specific and one session-specific regressor for each day). For the Memory Cueing task, regressors covered associative category hits, associative misses, six movement realignment parameters, and one for the session, resulting in 35 regressors in total. Before the group analyses of the cued recall data, we subtracted estimates of associative missed trials from associative category hit trials in first-level estimations. Group-level analyses used a two-factorial model (Group: YOH vs. CORT vs. PLAC; Cued: correct vs. incorrect on Day 2) to examine a *Group* × *Reactivation* interaction. Day 2 group-level analyses employed two-sample unpaired t-tests for participant-level contrasts. The Memory Cueing task on Day 2 preceded the pharmacological manipulation, identifying Regions of Interest (ROIs) more active during associative category hits compared to associative miss during reactivation, independent of Group. A flexible factorial model based on three factors (Group, Reactivation, Day) explored group-level changes in neural activity from Day 1 to Day 3.

ROI analyses

We examined task-evoked activation in the hippocampus and VTC, based on their central role in the domain of episodic memory retrieval (Kim 2010; Ranganath et al. 2004), utilizing ROI-masks derived from the Harvard-Oxford cortical and subcortical atlas with a 50% probability threshold. The VTC mask combined relevant regions from the Harvard-Oxford Atlas, excluding the hippocampus. In overall GLMs, the same regressors were used, but voxels were masked by a given ROI, and ROI-specific effects were small-volume corrected.

For native-space single-trial analyses, ROI-masks were back-transformed using the inverse deformation field from segmentation during preprocessing. In all ROI analyses on voxel-wise modelled data, single-trial beta estimates were calculated for all days and tasks to provide a detailed characterization of memory-related neural responses. A 128 s high-pass cut-off filter removed low-frequency drifts. The models, following the 'Least-squares all' approach, were performed on realigned, slice-time corrected, native space images for subsequent multivariate pattern analyses (MVPA, RSA).

Multivariate pattern classification

Multivariate/voxel pattern analyses (MVPA) using The Decoding Toolbox (Hebart, GÃ¶rgen, and Haynes 2015) functions assessed trial-wise cortical reinstatement strength. In total, three

L2-penalized logistic regression models (C = 0.1) were employed. The first model served to evaluate the classification performance within the localizer task by utilizing leave one-run-out cross-validation (scenes vs. objects) to validate the overall quality of the task and associated data. The second model evaluated the classification performance within the localizer task by utilizing leave one-run-out cross-validation (scenes vs. objects) to validate the overall quality of the task and associated data. Model performance was assessed using classification accuracy. The third model was trained on neural patterns from the visual localizer task and served to classify remembered scenes from remembered objects, serving as the category pattern reinstatement index in further analyses. Trial-wise category pattern reinstatement evidence was assessed using logits and balanced classification accuracy, which accounts for a potentially unequal number of samples during testing.

Tracking online reactivation

To comprehensively assess trial-wise reactivation on Day 2, we utilized reaction times, trial-wise univariate beta activity in the hippocampus and VTC, category pattern reinstatement indexed via MVPA in the VTC, and Hippocampal pattern reactivation from encoding to reactivation (Encoding-Reactivation-Similarity via RSA). Linear mixed models were employed to predict single-trial beta activity of the hippocampus and VTC, as well as category pattern reinstatement, using trial-specific Day 2 reaction times. A linear mixed model was also fit to univariate hippocampal activity predicted by category pattern reinstatement, aligning with previous findings that showed a positive association between hippocampal activity and VTC pattern reinstatement(Gagnon et al. 2019). The category pattern reinstatement index and hippocampal pattern reactivation were used to classify trials as 'high' or 'low' online reactivation, predicting Day 3 performance in GLMMs with information from all available trials.

Representational similarity analyses

To assess drug- and reactivation-related changes in Day 3 neural patterns between cued and correct and uncued trials, we conducted a Representational Similarity Analysis (RSA), focusing on the hippocampus using customized scripts from The Decoding Toolbox[10]. Beta vectors from single-trial GLMs were extracted, and RSA was conducted in the native space using participant-specific hippocampal masks. The representational similarity (Fisher z-transformed) from Day 1 encoding (average across three encoding runs) to Day 2 reactivation ('Day 1-Day 2 encoding-reactivation similarity (ERS) analysis") captured trial-specific pattern changes, which were assumed to provide a measure of neural memory reactivation and were used to predict Day 3 memory performance in GLMMs on a trial-by-trial basis.

Statistical analyses

Univariate fMRI statistical tests were conducted in the SPM12 environment (http://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 FWE corrected. Baseline and control variables on Days 1 and 3 (e.g., blood pressure) were tested

with one-way ANOVAs. Day 2 parameters validating the effective pharmacological manipulation (i.e., blood pressure, heart rate, mood, cortisol, SCR) were tested with repeated-measures ANOVAs (within-subject factor Time, between-subject factor Group) and subsequent post-hoc t-tests. Post-hoc t-test of ANOVAs were Bonferroni corrected for the points of measurement. Measures of task performance, including hits, false alarms, and d', that investigated the pharmacological effect on later memory for reactivated trials were subjected to repeated-measures ANOVAs (within-subject factor Reactivated, 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 1–0.5/denominator (Macmillan and Kaplan 1985).

Single-trial analyses were modelled using (Generalized) Linear Mixed Models predicting associative category hits/misses on Day 3, based upon several different predictor variables (i.e., Reactivation, Group). Models were fitted with the lme4(Bates et al. 2014) statistical package. Models were estimated using a restricted maximum likelihood (REML) approach. Resulting p-values were Bonferroni corrected for the number of ROIs. Post-hoc slope comparisons of GLMMs were conducted using the *emtrends* (Searle, Speed, and Milliken 1980) function including Tukey correction. Visualization and analysis utilized the R package ggplot2 (Wickham 2011) as well as Inkscape (https://inkscape.org).

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Author contributions

H.H. performed data acquisition and formal analysis. A.D.W. contributed to the conceptualization of the study. L.S. acquired funding, conceptualized, and supervised the project. G.L. provided the pharmacological agents and medical supervision during data collection. H.H. and L.S. wrote the original draft. H.H., A.D.W., G.L. and L.S. reviewed and edited the paper and approved the final manuscript.

Competing interests

Authors declare that they have no competing interests.

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Data and code availability

All behavioural and (anonymized) functional MRI data as well as analysis scripts have been deposited and are publicly available as of the date of publication (https://www.fdr.uni-hamburg.de/deposit/14137). Any additional information required to re-analyse the data

reported in this paper as well as raw and native space (not de-faced) MRI images are available from the lead contact upon request.

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Supplementary Material

Title

Post-retrieval noradrenergic activation impairs subsequent memory depending on cortico-hippocampal reactivation

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Supplemental Results

S1: Control variables

We controlled for potential group differences in depressive mood, chronic stress as well as state and trait anxiety. Importantly, the three groups did not differ in any of these variables (depressive mood: $F(1,60) = 0.67$, $P = .406$, $\eta^2 = 0.01$, state anxiety: $F(1,60) = 0.31$, $P = .581$, $\eta^2 < 0.01$; trait anxiety: $F(1,60) = 1.07$, $P = .305$, $\eta^2 = 0.02$, chronic stress: $F(1,60) = 0.35$, $P = .557$, $\eta^2 < 0.01$). See Supplemental Table S6.

S2: Category-Level Pattern Reinstatement Accuracy comparisons

Contrasting within-localizer classifier accuracies revealed a significant main-effect of *Region* ($F(2,174) = 101.74$, $P < .001$, $\eta^2 = .54$). Post-hoc tests revealed a significantly higher accuracy for the VTC compared to PCC ($t(60) = -12.00$, $P < .001$, $d = 1.54$), and hippocampus ($t(60) = -17.40$, $P < .001$, $d = 2.24$). Classifier accuracy of the PCC was significantly higher than hippocampal accuracy ($t(60) = -3,.90$, $P < .001$, $d = 0.50$).

While we found evidence for category-level reinstatement during Day 1 Encoding in the VTC, PCC and hippocampus, a significant main-effect of *Region* was detected ($F(2,174) = 192.32$, $P < .001$, $\eta^2 = .69$). Post-hoc tests revealed a significantly higher accuracy for the VTC compared to PCC ($t(60) = -16.90$, $P < .001$, $d = 2.18$), and hippocampus ($t(60) = -19.01$, $P < .001$, $d = 2.45$). Classifier accuracy of PCC and hippocampus did not differ during the Encoding task ($t(60) = 0.94$, $P = 1$, $d = 0.12$).

Category-level reinstatement during the Day 2 Memory Cueing task relied specifically on cortical areas (VTC, PCC), while there was no such relation observed for the hippocampus. Comparing corresponding accuracy estimates revealed a significant main-effect of the factor *Region* ($F(2,174) = 3.45$, $P = .034$, $\eta^2 = .04$). Post-hoc tests showed no difference between VTC and PCC ($t(60) = -1.69$, $P = .283$, $d = 0.22$) as well as PCC and hippocampus ($t(60) = 1.24$, $P = .660$, $d = 0.16$). VTC accuracy was however significantly higher than hippocampal accuracy during memory cueing ($t(60) = -2.61$, $P = .034$, $d = 0.34$).

Supplemental Methods

S1: Stimulus Material

The words of each associative word-picture pair had 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[84]. Since there was no significant influence of word valence at the behavioural and neural levels, which may be due to the fact that the arousal evoked by emotional words is typically significantly lower than for pictures or movies, we did not include the factor valence in the analyses reported here.

S2: Catch trials

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 category (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 reactivate 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 > .603). All catch trials were subsequently excluded from the analyses to prevent potential biases in memory effects due to the re-presentation of correct or semantically similar picture probes together with old words.

Supplemental Table S1. Memory performance expressed as associative d' during Day 1 cued recall

	PLAC	YOH	CORT
Cued and correct (Day 2)	1.18 (0.12)	0.99 (0.13)	1.24 (0.19)
Not cued (Day 2)	1.15 (0.16)	0.94 (0.12)	1.16 (0.18)

Groups did not differ in associative d' values during the immediate cued recall task at Day 1, suggesting a comparable acquisition of word-picture pairs. Data represent means (±SE).

Supplemental Table S2. Physiological parameters and mood at baseline across Day 1 and Day 3.

		PLAC	YOH	CORT
Day 1	Heart rate (bpm)	78.85 (2.67)	75.97 (2.77)	76.35 (2.52)
	Systolic blood pressure (mmHg)	107.80 (2.80)	116.47 (2.63)	114.66 (3.66)
	Diastolic blood pressure (mmHg)	68.32 (1.87)	71.78 (2.18)	71.00 (2.29)
	cortisol (nmol)	9.49 (2.02)	7.16 (1.16)	10.76 (1.56)
	Mood (good/bad)	34.80 (0.90)	33.47 (0.98)	33.70 (0.87)
	Tiredness (energized/tired)	31.05 (1.06)	30.76 (1.14)	32.30 (1.01)
	Calmity (calm/restless)	30.50 (1.15)	30.95 (1.47)	28.90 (1.07)
Day 3	Heart rate (bpm)	78.65 (2.46)	78.28 (2.31)	78.26 (2.38)
	Systolic blood pressure (mmHg)	112.22 (2.14)	112.42 (3.26)	114.04 (3.86)
	Diastolic blood pressure (mmHg)	72.15 (1.48)	72.66 (1.54)	68.83 (1.95)
	cortisol (nmol)	8.41 (1.59)	5.88 (1.12)	7.32 (1.01)
	Mood (good/bad)	34.30 (1.05)	34.71 (0.81)	34.10 (0.91)
	Tiredness (energized/tired)	33.40 (1.05)	34.09 (0.98)	32.80 (0.85)
	Calmity (calm/restless)	30.50 (1.15)	31.00 (1.20)	30.90 (1.00)

Subjective and physiological parameters of participants taken at the beginning of Day 1 and Day 2. There were no significant difference in either subjective or physiological stress parameters between groups. Data represent means (±SE).

Supplemental Table S3. Significant clusters in the whole-brain analyses of Day 2 memory cueing (correct – incorrect).

Region	**Central coordinates (x,y,z; MNI)**	**Cluster-P(FWE 0.05)**
Frontal Medial, ACC	-4, 50 , -8	< .001
Lateral Occipital L, AG L	-48, -66, 30	< .001
Amygdala L, Striatum L	-14, 4, -16	< .001
Posterior Cingulate Cortex	4, -41, 38	< .001
Supramarginal Gyrus R	62, -44, 20	< .001
hippocampus L	-26, -32, -10	< .001
hippocampus R	32, -40, -12	< .001
Striatum R	8, 12, -8	< .001
Frontal Pole	-22, 38, 42	< .001
Temporooccipital Cortex R	52, -50, -14	< .001
Superior Parietal R	30, -46, 62	< .001
Temporooccipital Cortex L	-52, -62, -2	< .001
Postcentral Gyrus	50, -22, 50	< .001
Superior Frontal Gyrus	-20, 2, 56	< .001
Putamen L	-26, -8, 8	< .001
Mid temporal gyrus L	-62, -16, -8	< .001

Supplemental Table S4. Physiological parameters across Day 2.

		PLAC	YOH	CORT
Heart rate (bpm)	Base	80.42 (2.41)	75.02 (2.10)	77.52 (1.97)
	Task	87.40 (2.29)	81.61 (2.06)	82.76 (1.86)
	Resting state post	80.15 (2.28)	74.42 (2.21)	75.28 (2.18)
	+40	70.35 (2.58)	64.92 (2.06)	67.04 (2.10)
	+55	70.65 (2.28)	65.59 (1.97)	67.52 (2.33)
	+70	69.12 (2.18)	67.45 (2.37)	65.61 (2.03)
	+85	68.90 (2.40)	67.47 (1.97)	65.73 (2.12)
	+100	70.25 (2.78)	69.45 (2.60)	67.85 (2.16)
Systolic BP (mmHg)	Base	113.00 (3.11)	115.42 (3.11)	117.95 (3.23)
	+40	115.35 (1.95)	118.00 (3.27)	117.38 (3.70)
	+55	110.40 (1.75)	118.61 (3.36)	115.83 (3.11)
	+70	108.45 (1.71)	120.92 (3.43)	115.11 (3.68)
	+85	108.50 (2.27)	122.38 (3.57)	115.28 (3.34)
	+100	107.55 (2.46)	123.69 (3.29)	115.78 (3.21)
Diastolic BP (mmHg)	Base	72.53 (1.99)	71.86 (2.61)	74.57 (2.14)
	+40	73.22 (2.26)	74.14 (1.96)	73.76 (2.08)
	+55	72.33 (1.45)	71.02 (2.10)	72.67 (2.05)
	+70	71.28 (1.64)	73.31 (2.36)	72.98 (2.18)
	+85	72.85 (1.67)	75.79 (2.12)	73.31 (2.30)
	+100	71.55 (1.71)	77.29 (2.30)	73.98 (1.81)
cortisol (nmol)	Base	11.14 (2.14)	7.22 (1.17)	8.18 (1.13)
	+20	5.40 (0.78)	4.04 (0.39)	8.15 (2.03)
	+40	4.53 (0.62)	2.92 (0.31)	24.59 (6.32)
	+70	3.63 (0.60)	3.14 (0.41)	57.60 (4.88)
	100	2.70 (0.34)	4.05 (0.69)	52.93 (4.95)
Skin conductance	Resting state pre	5.82 (1.35)	3.32 (0.55)	5.97 (0.86)
	Task	5.88 (1.47)	3.07 (0.75)	6.71 (1.31)
	Resting state post	9.28 (1.63)	6.53 (0.96)	10.02 (1.25)

Physiological parameters of participants across Day 2 relative to drug administration. Systolic blood pressure significantly increased over time in the YOH group, compared to the CORT and PLAC group. Salivary cortisol increased in the CORT group but not in the YOH or PLAC group. Data represent means (±SE).

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Supplemental Table S5. Subjective mood scores across Day 2.

		PLAC	YOH	CORT
MDBF *Base*	Mood (good/bad)	34.85 (1.11)	34.38 (0.78)	34.90 (0.72)
	Tiredness (energized/tired)	33.85 (1.10)	33.33 (1.04)	33.70 (1.03)
	Calmness (calm/restless)	34.85 (1.11)	34.38 (0.78)	34.90 (0.72)
MDBF *+40*	Mood (good/bad)	35.05 (1.08)	34.81 (0.81)	33.70 (0.81)
	Tiredness (energized/tired)	33.70 (0.94)	33.53 (1.06)	32.95 (1.01)
	Calmness (calm/restless)	30.55 (0.87)	28.90 (1.47)	30.04 (0.91)
MDBF *+55*	Mood (good/bad)	34.70 (0.86)	35.14 (0.80)	33.20 (1.09)
	Tiredness (energized/tired)	34.10 (0.98)	33.80 (0.92)	32.90 (1.10)
	Calmness (calm/restless)	30.00 (0.97)	30.47 (1.30)	28.45 (1.75)
MDBF *+70*	Mood (good/bad)	34.55 (1.11)	34.81 (0.86)	32.75 (1.07)
	Tiredness (energized/tired)	33.65 (1.08)	34.28 (1.08)	32.75 (1.16)
	Calmness (calm/restless)	29.55 (1.43)	30.81 (1.34)	29.60 (1.38)
MDBF *+85*	Mood (good/bad)	34.20 (1.14)	34.09 (0.93)	32.30 (1.20)
	Tiredness (energized/tired)	33.20 (1.18)	33.47 (1.23)	31.60 (1.14)
	Calmness (calm/restless)	28.80 (1.73)	30.71 (1.56)	28.55 (1.58)
MDBF *+100*	Mood (good/bad)	33.30 (1.39)	33.19 (1.16)	32.55 (1.02)
	Tiredness (energized/tired)	32.70 (1.34)	32.61 (1.38)	32.50 (1.26)
	Calmness (calm/restless)	30.20 (1.36)	29.19 (1.56)	29.40 (1.48)

Subjective mood ratings according to the *Mehrdimensionale Befindlichkeitsfragebogen* (MDBF[85]) across day 2. Scores did not reveal a significant difference in either scale between groups. Data represent means (±SE).

Supplemental Table S6. Participants' state, trait anxiety, chronic stress and depression scores.

	PLAC	YOH	CORT
Depression score	6.20 (0.89)	9.04 (1.20)	7.47 (1.00)
State anxiety	43.20 (1.02)	42.09 (0.94)	42.38 (1.16)
Trait anxiety	43.05 (1.41)	46.95 (1.79)	45.19 (0.93)
Chronic stress	70.95 (6.86)	90.61 (8.42)	77.14 (5.37)

State and Trait anxiety scores were measured with the State-Trait Anxiety Inventory. Depression Scores were determined utilizing the Beck Depression Inventory. Chronic stress was measured with the Trier Inventory of Chronic Stress. Participants conducted the three questionnaires at home before the actual experiment started. Data represent means (±SE).

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Institut für Psychologie

Erklärung gemäß *(bitte Zutreffendes ankreuzen)*

☐ **§ 4 (1c) der Promotionsordnung des Instituts für Bewegungswissenschaft der Universität Hamburg vom 18.08.2010**

☒ **§ 5 (4d) der Promotionsordnung des Instituts für Psychologie der Universität Hamburg vom 20.08.2003**

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Eidesstattliche Erklärung nach *(bitte Zutreffendes ankreuzen)*

☐ **§ 7 (4) der Promotionsordnung des Instituts für Bewegungswissenschaft der Universität Hamburg vom 18.08.2010**

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