Title

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

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Abstract

When retrieved, seemingly stable memories can become sensitive to significant events, such as acute stress. The mechanisms underlying these memory dynamics remain poorly understood. Here we show that noradrenergic stimulation after memory retrieval impairs subsequent remembering, depending on hippocampal and cortical signals emerging during retrieval. In a three-day study, we measured brain activity using fMRI during initial encoding, 24h-delayed memory cueing followed by pharmacological elevations of glucocorticoid or noradrenergic activity, and final recall. While post-retrieval glucocorticoids did not affect subsequent memory, the impairing effect of noradrenergic arousal on final recall depended on hippocampal reactivation and category-level reinstatement in ventral temporal cortex during memory cueing. These effects did not require a reactivation of the original memory trace and did not interact with offline reinstatement during rest. Our findings demonstrate that, depending on the retrieval-related 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[1,2]. 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; [3–5]). During the reconsolidation window, memories are assumed to be modifiable[6,7]. 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[8–10]. 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[5,11,12]. 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[13–15]. Given these potential far reaching implications, understanding the mechanisms underlying post-retrieval dynamics of memory is essential.

Stress has a major impact on memory[16–18]. 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 ([19–23], but see[24,25] 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. Recently, we showed a detrimental impact of post-retrieval stress on subsequent memory that was contingent upon reinstatement dynamics in the Hippocampus, VTC and PCC during memory reactivation[26]. While this study provided initial insights into the potential brain mechanisms involved in the effects of post-retrieval stress on subsequent memory, the underlying neuroendocrine mechanisms remained elusive.

It is well known that that stress triggers complex neurotransmitter and hormonal cascades[27]. Among these, noradrenaline and glucocorticoids appear to be of particular relevance for stress-induced changes in memory[16,28,29]. 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 in post-retrieval memory dynamics are unclear. Some studies, using emotional recognition memory or fear conditioning in healthy humans, suggest enhancing effects of post-retrieval glucocorticoids on subsequent memory[30,31]. However, rodent studies on neutral recognition memory[21], fear conditioning[32], as well as evidence from humans on episodic recognition memory[33] report impairing effects of glucocorticoid receptor activation on post-retrieval memory dynamics. For noradrenaline, post-retrieval blockade of noradrenergic activity impairs putative reconsolidation or future memory accessibility in human fear conditioning[34], as well as drug (alcohol) memory[35] and spatial memory in rodents[36]. However, this effect is not consistently observed in human studies on fear conditioning[40], speaking anxiety[37], inhibitory avoidance[39], traumatic mental imagination (PTSD patients)[38], and might depend on the arousal state of the individual[21] or the exact timing of drug administration as

suggested by studies in humans[41] and rodents[42]. Thus, while there is evidence that glucocorticoid and noradrenergic activation after retrieval can affect subsequent memory, the direction of these effects remains elusive. Moreover, 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[43–45]. 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[46]. 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 [47–51]. 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[52,53]. Offline reactivation offers a pivotal window for the consolidation and stabilization of these memory alterations[54–56]. The transition from online to offline reactivation involves complex neural cascades, influencing the persistence and strength of the reactivated memory trace[57]. 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[3,9], only cued items that were reinstated should be susceptible to post-retrieval manipulations. We distinguished between responses with short and long reaction times indicative of high and low confidence responses because previous research showed that reaction times are inversely correlated with hippocampal memory involvement[58–60] and memory strength[61,62], and that high confidence memories associated with short reaction times may be particularly sensitive to stress effects[63]. 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[64,65], such as the ventral temporal cortex (VTC), which represents stimulus categories (scenes, objects) encountered during encoding[66,67], and the posterior cingulate cortex (PCC), which is assumed to represent memory traces formed during retrieval[49,68], we focused our analysis on these key regions. Building on our recent findings in humans[26] as well as current insights from rodents[47], 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.

Here, we show that pharmacological elevations of noradrenergic but not glucocorticoid activity after retrieval impair subsequent remembering. These memory impairments were specific to items that were cued and correctly recalled behaviourally and associated with strong hippocampal and cortical neural reactivation before the action of yohimbine; that is, the mere cueing and behavioural expression of memories was not sufficient to render memories sensitive to modification. As such, our neural data revealed that the disruptive effects of yohimbine on subsequent memory was contingent on the strength of hippocampal reactivation and category-level pattern reinstatement in the VTC during memory retrieval. Critically, the impact of noradrenaline specifically depended on the preceding online reactivation specifically, as the level of offline reactivation prior to drug activation did not impact subsequent memory.

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). To test for potential group differences in reaction times for correctly remembered associations on Day 1, we fit a linear model including the factors *Group* and *Cueing*. Critically, we did not observe a significant *Group* x *Cueing* interaction, suggesting no RT difference between groups for later cued and not cued items ($F(2,58) = 1.41$, $P = .258$, $\eta^2 = 0.01$; 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.

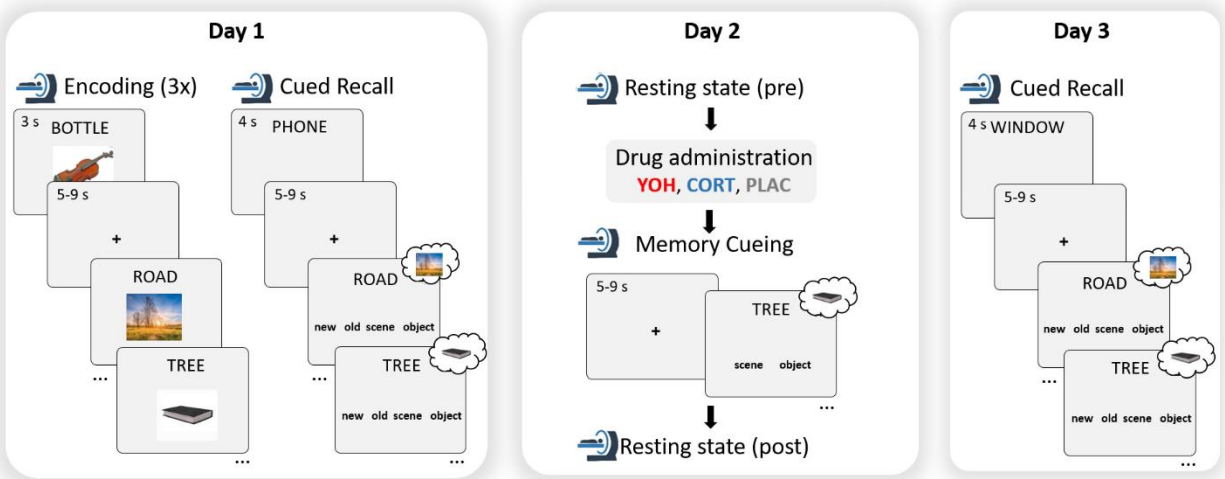

Fig. 1. Experimental task. The impact of post-retrieval yohimbine and hydrocortisone on subsequent memory was tested in a 3-day paradigm, recording fMRI data on all days. On Day 1, participants encoded word-picture pairs across three runs and then underwent an immediate cued recall test. On Day 2, 24 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 ($F(2,58) = 1.53$, $P = .224$, $\eta^2 = 0.05$; see Supplemental Table 1). To test for potential group differences in reaction times for correctly remembered associations on Day 2, we fit a linear model including the factors *Group* and *Reaction time (slow/fast)* following the subject specific median split. The model did not reveal any main effect or interaction including the factor *Group* (all Ps > .535; Supplemental Table S1), indicating that there was no RT difference between groups, nor between low and high RT trials in the groups.

Neural Reactivation in Hippocampus and Cortical Areas during Memory Cueing

Drawing upon recent discoveries in rodent studies[46], 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: $\beta = -0.51 \pm 0.18$, $t = -2.88$, $P_{Corr} = .018$, $R^2_{conditional} = 0.08$; Right hippocampus: $\beta = -0.47 \pm 0.18$, $t = -2.60$, $P_{Corr} = .033$, $R^2_{conditional} = 0.11$; PCC: $\beta = -0.75 \pm 0.20$, $t = -3.67$, $P_{Corr} < .001$, $R^2_{conditional} = 0.09$), while no such relation was observed in the VTC ($P_{Corr} = .282$). 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 [69]).

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. Classifier accuracy is derived from the sum of correct predictions the trained classifier made in the test-set, relative to the total amount of predictions. For the VTC, the average classifier accuracy was high (M±SD: 90.0% ± 0.1%); $t(60) = 25.99$, $P_{Corr} < .001$, $d = 3.83$) indicative of reliable category-level processing in the VTC. Importantly, there were no significant group differences in classification accuracy ($F(1,59) = 2.56$, $P_{Corr} = .115$, $\eta^2 = 0.04$). 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%, $t(60) = 29.88$, $P_{Corr} < .001$, $d = 3.80$), further supporting category-level processing in the VTC, again without significant group differences in classification accuracy ($F(2,58) = 0.44$, $P_{Corr} = .643$, $\eta^2 = 0.01$).

Next, we quantified the reinstatement of visual category-level representations during successful memory cueing on Day 2 in the VTC. Neural reinstatement reflects the extent to which a neural activity pattern (i.e., for objects) that was present during encoding is reactivated during retrieval (e.g., memory cueing). 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*: $F(1,58) = 12.45$, $P_{Corr} < .001$, $\eta^2 = 0.13$). 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. The logits here reflect the log-transformed trial-wise probability of a pattern either representing a scene or an object. A generalized linear mixed model revealed a main effect of *Retrieval success* ($F(1,58) = 12.61$, $P_{Corr} = .003$, $\eta^2 = 0.13$), 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%; $t(60) = 4.44$, $P_{Corr} < .001$, $d = 1.14$), 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%; $P_{Corr} = 1$). Again, classifier accuracy on remembered trials in VTC did not differ between groups ($F(2,58) = 0.86$, $P_{Corr} = 1$, $\eta^2 = 0.03$).

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_{Corr} = .501, d = 0.22; Right: M±SD: 52.9% ± 1.5%, t(60) = 1.50, P_{Corr} = .520, d = 0.18), indicating poor category-coding in the hippocampus[70]. 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_{Corr} = .006, d = 0.42; Right: M±SD: 53.4% ± 0.9%, t(60) = 3.71, P_{Corr} <. 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, η^2 < .01; Right: F(1,59) = 0.03, P_{Corr} = .784, η^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_{Corr} = 1, d = 0.09; Right: M±SE = 51.82% ± 0.9%; t(60) = 2.10, P_{Corr} = .156, d = 0.23), nor forgotten scenes and forgotten objects (Left: M±SE = 47.95% ± 1.6%; t(60) = -1.31, P_{Corr} = 1, d = 0.17; Right: M±SE = 49.61% ± 1.3%; t(60) = -0.27, P_{Corr} = 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_{Corr} < .001, d = 0.69), indicating category-coding in PCC, without group differences (F(1,59) = 0.81, P_{Corr} = .370, η^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_{Corr} < .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_{Corr} = 1, η^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_{Corr} = .092), nor forgotten scenes and forgotten objects (M±SE = 49.5% ± 1.70%; t(60) = -0.27, P_{Corr} = 1, d = 0.03).

Contrasting within-localizer classifier accuracies revealed a main-effect of *Region* (F(2,174) = 101.74, P_{Corr} < .001, η^2 = .054). Post-hoc tests revealed significantly higher accuracy for the VTC compared to PCC (t(60) = -12.00, P_{Corr} < .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_{Corr} < .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, η^2 = 0.69) revealed significantly higher accuracy for the VTC compared to PCC (t(60) = -16.90, P_{Corr} < .001, d = 2.18) and hippocampus (t(60) = -19.01, P_{Corr} < .001, d = 2.45). Classifier accuracy of PCC and hippocampus did not differ during the Encoding task (t(60) = 0.94, P_{Corr} = 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, η^2 = 0.04). Post-hoc tests showed no difference between VTC and PCC (t(60) = -1.69, P_{Corr} = .283, d = 0.22) nor PCC and hippocampus (t(60) = 1.24, P_{Corr} = .660, d

= 0.16), whereas VTC accuracy was significantly higher than hippocampal accuracy (t(60) = -2.61, P_{Corr} = .034, d = 0.34).

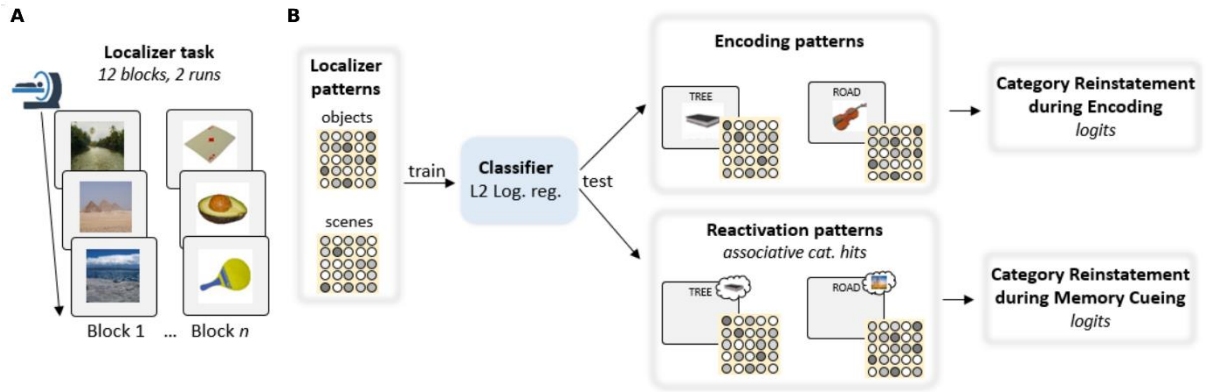

Fig. 2. Trial-wise pattern reinstatement during Encoding and the Day 2 Memory Cueing task. A To derive an index of visual category reinstatement in the VTC, an independent localizer task was conducted at the end of Day 3. During this task, pictures of scenes and objects were presented block-wise to participants. **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). Assocaitive cat. hits = associative category hits.

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 P_{Corr} > .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_{Corr} < .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_{Corr} < .001, d= 0.71; VTC: t(60) = -11.83, P_{Corr} < .001, d= 1.51; PCC: t(60) = 8.25, P_{Corr} < .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[71,72], 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 S6). Post-hoc t-tests showed significantly higher systolic blood pressure in the YOH group compared to the PLAC group 70 minutes ($t(29.77) = -3.31$, $P_{Corr} = .014$, $d = 1.02$), 85 minutes ($t(34.15) = -3.33$, $P_{Corr} = .012$, $d = 1.03$), and 100 minutes after pill intake ($t(36.94) = -3.98$, $P_{Corr} < .001$, $d = 1.23$). 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 ($t(27.91) = 2.30$, $P_{Corr} = .020$, $d = 0.99$), 70 minutes ($t(20.64) = -11.23$, $P_{Corr} < .001$, $d = 3.42$), 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 $P_{Corr} > .350$). 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 $P_{Corr} > .162$).Finally, subjective mood analyses across Day 2 revealed no significant *Time* × *Group* interaction on any scale (all interaction Ps > .460; Supplemental Table S7). Our data demonstrate that, despite the distinct pharmacodynamics of CORT and YOH, both substances are active within the time window that is critical for potential reconsolidation effects[3,4,43].

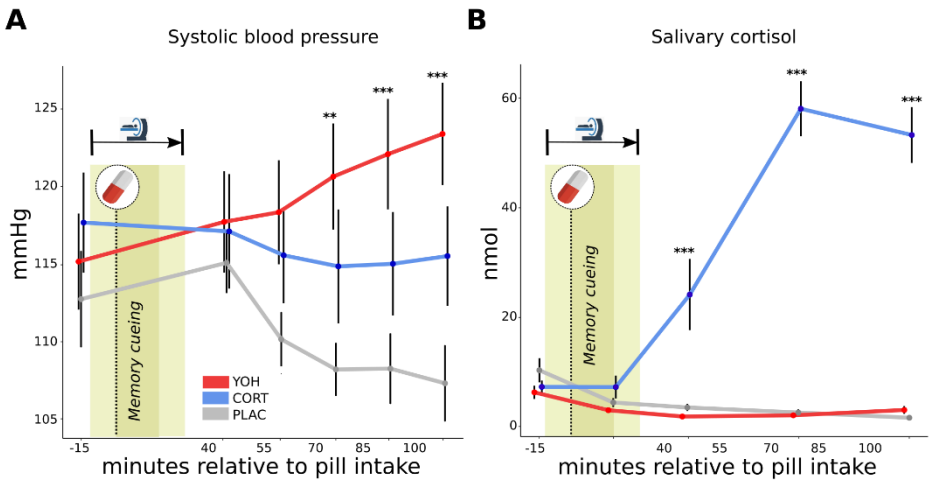

Fig. 3. Effective noradrenergic and glucocorticoid action after Day 2 memory cueing. Systolic blood pressure **(A)** and salivary cortisol **(B)** did not differ between groups before or immediately after the Memory Cueing task. However, 70 minutes after pill intake, systolic blood pressure was significantly 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; see Supplemental Table S1), in line with the established testing effect[73,74], 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. To test for potential group differences in reaction times for correctly remembered associations on Day 3 we fit a linear model including the factors *Group* and *Cueing*. This model did not reveal any main effect or interaction including the factor *Group* (all Ps > .267), indicating that there was no average RT difference between groups. As expected we observed a main effect of the factor *Cueing*, indicating a significant difference of reaction times across groups between trials that were successfully cued and those not cued on Day 2 ($F(2,58) = 153.07$, $P < .001$, $\eta^2 = 0.22$; Supplemental Table S1). Furthermore, univariate analyses showed no *Cued* × *Group* interactions in whole-brain or ROI activity.

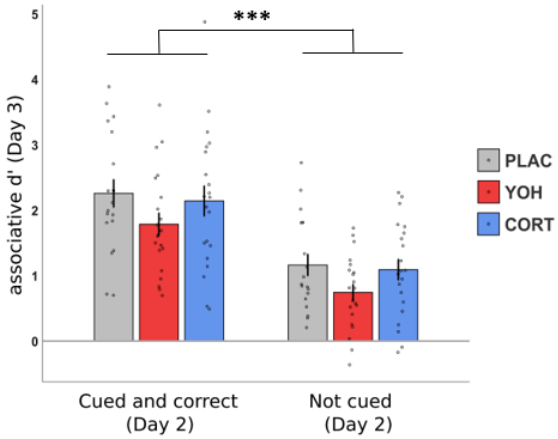

Fig. 4. Subsequent memory performance on Day 3, split for cued and correct (Day 2) and uncued trials. Average memory performance (associative d') was significantly increased for cued and correct (Day 2) trials compared to uncued trials. This effect was, however, unaffected by the pharmacological manipulation. 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 reactivation 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 $P_{Corr} > .711$).

Reaction times in the Day 2 Memory cueing task revealed a trial-specific gradient in reactivation strength. Thus, we turned to single-trial analyses, differentiating Day 3 trials by short and long reaction times during memory cueing on Day 2 (median split), indicative of high vs. low memory confidence[58–60] and hippocampal reactivation[26,63]. 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: $\beta = 0.79 \pm 0.30$, $z = 2.61$, 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_{Corr} = .031) and YOH vs. PLAC (β = 0.34 ± 0.14, z-ratio = -2.55, P_{Corr} = .032). By contrast, comparing CORT vs. PLAC revealed no such difference (β = 0.88 ± 0.37, z-ratio = -0.29, P_{Corr} = 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_{Corr} = .038, $R^2_{conditional}$ = 0.27) but not in the CORT group (β = 0.89 ± 0.39, z = 2.28, P_{Corr} = .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_{Corr} = .005) and between YOH and CORT groups (β = 0.88 ± 0.34, z-ratio = 2.58, P_{Corr} = .029), but not between PLAC and CORT groups (β = -0.23 ± 0.36, z-ratio = -0.63, P_{Corr} = 1; Fig. 5B). 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 P_{Corr} > .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: $\beta = 0.14 \pm 0.05$, z-ratio = 2.57, $P_{Corr} = .030$; YOH vs. CORT: $\beta = 0.13 \pm 0.05$, z-ratio = 1.31, $P_{Corr} = .708$; 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: $\beta = 0.12 \pm 0.05$, z-ratio = 2.72, $P_{Corr} = .018$; CORT: $\beta = -0.02 \pm 0.05$, z-ratio = -0.42, $P_{Corr} = 1$; PLAC: $\beta = -0.09 \pm 0.05$, z-ratio = -1.68 , $P_{Corr} = .274$). As individual factors, such as metabolism or body weight, can influence the drug's action, we ran an additional analysis in which we included individual (baseline-to-peak) differences in salivary cortisol and (systolic) blood pressure, respectively. This analysis did not show any group by baseline-to-peak difference interaction suggesting that the observed memory effects were mainly driven by the pharmacological intervention group per se and less by individual variation in responses to the drug (see Supplemental Results).

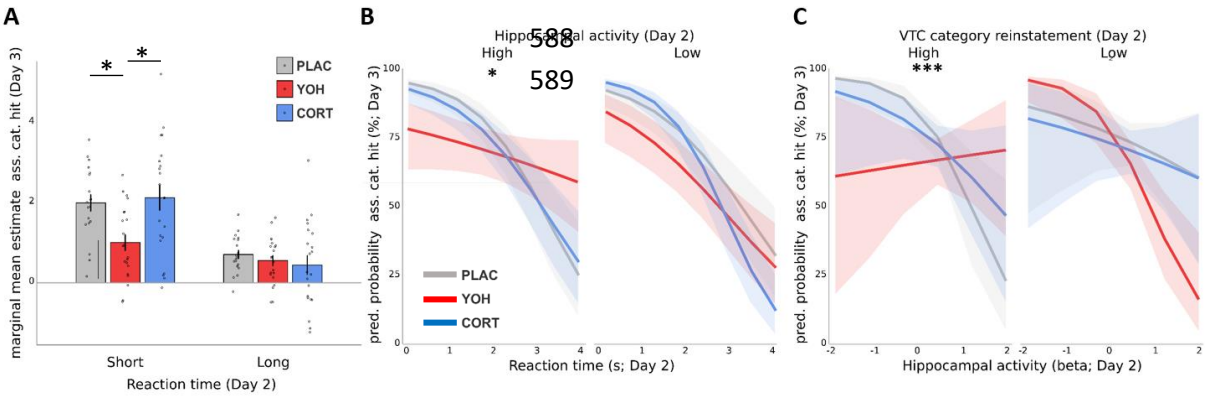

Fig. 5. Subsequent memory impairment by noradrenergic activation depends on hippocampal and VTC online reactivation. A Reactivation strength was initially indexed using trial-wise reaction times (memory confidence) during the Day 2 Memory Cueing task. In all three groups, the probability of a later associative 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. Ass. cat. hit = associative category hit. Coloured shades represent .95 confidence intervals.

615 **Explorative analyses**

616 Beyond hippocampal and VTC activity during memory cueing (Day 2), we exploratively
617 reanalysed the GLMMs predicting Day 3 memory performance including the PCC, which was
618 relevant during memory cueing in the current study and in our previous work[26]. Predicting
619 Day 3 memory performance by the factors *Group* and *Single trial beta activity* during memory
620 cueing in the PCC did not reveal a significant interaction (P_{Corr} = 1); adding the factor *Reaction*
621 *time* to the model also did not result in a significant interaction (P_{Corr} = 1). We also included
622 the Medial Prefrontal Cortex (MPFC) to predict Day 3 memory performance, as the MPFC has
623 been shown to be sensitive to noradrenergic modulation in previous work[75]. Predicting Day 3
624 memory performance by the factors *Group* and *Single trial beta activity* during memory cueing
625 in the MPFC did not reveal a significant interaction (P_{Corr} = 1); adding the factor *Reaction time*
626 to the model also did not result in a significant interaction (P_{Corr} = 1), which indicates that the
627 MPFC was not modulated by either pharmacological intervention. Finally, we investigated
628 memory cueing from all remaining ROIs that were significantly activated during the Day 2
629 memory cueing task (Day 2 whole-brain analysis; correct-incorrect; Supplemental Table S3).
630 We again fit GLMMs predicting Day 3 memory performance by the factors *Group* and *Single*
631 *trial beta activity* during memory cueing. Again, we did not observe any significant interaction
632 effect any of the ROIs (all interaction P_{Corr} > .060) and these results did not change when
633 adding the factor *Reaction time* to the respective models (all P_{Corr} > .075).

634 **Connectivity Analyses**

635 We conducted general psycho-physiological interaction analysis (gPPI) analyses on the Day 2
636 memory cueing task (remembered – forgotten), which revealed that successful cueing was
637 accompanied by significant functional connectivity between the left hippocampus, VTC, PCC
638 and MPFC (see Supplemental Table S4). However, using these connectivity estimates to predict
639 Day 3 subsequent memory performance (dprime) via regression did not reveal any significant
640 *Group* × *Connectivity* interactions, indicating that the pharmacological manipulation (i.e.
641 noradrenergic stimulation) did not modulate subsequent memory based on functional
642 connectivity during memory cueing (all P_{Corr} > .228). The same pattern of results was observed
643 when including single trial beta estimates from multiple ROIs during memory cueing to predict
644 Day 3 memory (all interaction effects P_{Corr} > .288).

645 **Offline Reinstatement Analyses**

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

655

Discussion

Upon their retrieval, memories can become sensitive to modification[1,2]. Such post-retrieval changes in memory may be fundamental for adaptation to volatile environments and have critical implications for eyewitness testimony, clinical or educational contexts[5,11–15,] 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[34–36,76]. While this impairing influence has not been consistently replicated[24,37–39], 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[77–79], assuming that post-retrieval propranolol may weaken reconsolidation by attenuating the emotional salience of memories, making them more comparable to neutral ones[45]. 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[80–83]. 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[84,85]. Excessive noradrenergic activity in the hippocampus may further have disrupted neurotransmission[86,87]. 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[66,67].

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[21,32,33,88]. 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[18,28,89]. 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[21,90].

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[56,91]. 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[3–5] , 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; [92–94]). In the present study, PEs may have resulted from the incomplete reminder structure during cued recall[7,95]. 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[71,96], 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[19–23]. 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[97,98]. 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,

788 diagnosed cardiovascular problems as well as any contraindications for MRI measurements.
789 Women were excluded if they used hormonal contraceptives and were not tested during their
790 menses as these factors may interact with the pharmacological intervention. Participants were
791 instructed to refrain from caffeinated beverages, exercise, and eating or drinking (with the
792 exception of water) for 2 hours prior to the experiment. Seven participants were excluded from
793 analyses due to acute claustrophobia (n = 1) or technical failure (n = 3), no Day 3 memory
794 performance (n =1), or because they did not return on Day 2 or 3 (n = 2), thus leaving a final
795 sample of n = 61 participants (25 women, 36 men, age = 19-34 years, mean = 25 years, SD = 4
796 years). We employed a PLAC-controlled, double-blind, between-subjects design in which
797 participants were randomly assigned to one of three groups: PLAC, YOH, or CORT. All
798 participants provided written informed consent before the start of the experiment and
799 received a monetary compensation for their participation. An a priori power calculation with
800 G*Power[99] indicated that a sample size of N = 66 is required to detect a medium-sized *Group*
801 × *Reactivation* interaction effect with a power of .95. The study was approved by the ethics
802 committee of the Medical Chamber of Hamburg (PV5960). Groups did not differ significantly
803 from each other with respect to depressive mood, chronic stress, state or trait anxiety (see
804 Supplemental Results and Supplemental Table S7).

805

806 **Experimental Procedure**

807

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

813 *Experimental Day 1: associative encoding task*

814 Participants underwent a brief (~5 min) training session before the encoding task to familiarize
815 themselves with the procedure. This training replicated the 3-day paradigm structure,
816 involving an encoding session and a cued recall test with word-picture associations that were
817 not part of the actual experiment. In the actual encoding task, participants were instructed to
818 memorize 164 unique word-picture pairs presented in three runs. Each pair appeared three
819 times (once in each run), including German nouns (see Supplemental Methods S1) and
820 pictures of coloured scenes[100] or objects[101]. During each trial, a word and picture were
821 presented for 3 s (words on top of the screen, pictures in the centre), and participants rated
822 their fit on a 4-point Likert scale using an MRI-compatible button box. A black fixation cross
823 appeared between trials for 5-9 s (jitter: 0 – 4 s, mean-jitter: 2 s). Each run took about 25 min,
824 with a 2-minute break after each run, resulting in a duration of about 90 min for the three
825 runs. Importantly, out of the 164 word-picture pairs presented during encoding, 20 pairs were
826 designated as catch trials for the subsequent cued recall tasks (see Supplemental Methods S2).
827 As such, all memory analyses were based on 144 of the encoded word-picture pairs.

828 *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[102,103]. We note that yohimbine and hydrocortisone follow distinct pharmacodynamics[104,105], yet selected the administration timing to ensure that both substances are active within the relevant post-retrieval time window. 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 a 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[106]), objects (BOSS database[101]), and scenes (SUN database[100]). 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 $p > 0.05$. 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[64,65], 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[107] 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[63]. 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. All reported p-values from statistical models and post-hoc tests reported throughout the manuscript were corrected for multiple comparison with bonferroni correction (for number of ROIs and tests respectively). 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[108].

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, Reaction times). Reaction times serve as a proxy for memory confidence and memory strength, with faster responses reflecting higher confidence/strength and slower responses suggesting greater uncertainty/weaker memory. The association between reaction times and memory confidence has been established by previous research[58–60], suggesting that the distinction between high from low confidence responses differentiates vividly recalled associations from decisions based on weaker memory evidence. Reaction times are further linked to hippocampal activity during recall tasks[26,53], and stress effects on memory are particularly pronounced for high-confidence memories[53]. We conducted a median-split within each participant to categorize trials as slow vs. fast reaction time trials during Day 2 memory cueing. We chose to conduct this split on the participant- and not group-level because there is substantial inter-individual variability in overall reaction times and to retain an equal number of trials in the low and high confidence conditions. Models were fitted with the lme4[109] 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*[110] function including Tukey correction. Visualization and analysis utilized the R package ggplot2[111] 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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