

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 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 α 2-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.

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.

eLife assessment

This work presents **valuable** findings of a modulatory effect of yohimbine, an alpha2-adrenergic antagonist that raises noradrenaline levels, on the reconsolidation of emotionally neutral word-picture pairs, depending on the hippocampal and cortical reactivation during retrieval. The evidence supporting the conclusion is **incomplete** so far, particularly considering concerns about the median-splitting approach for reaction times and hippocampal activity. The work will be of broad interest to researchers working on memory.

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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 [↗](#); Cocoz, 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, Roulet, 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 α 2-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 P s > .481; see Supplemental Table S1). Moreover, groups did not differ in mood, arousal, or cortisol levels before encoding on Day 1 (all P s > .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 P s > .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.

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,

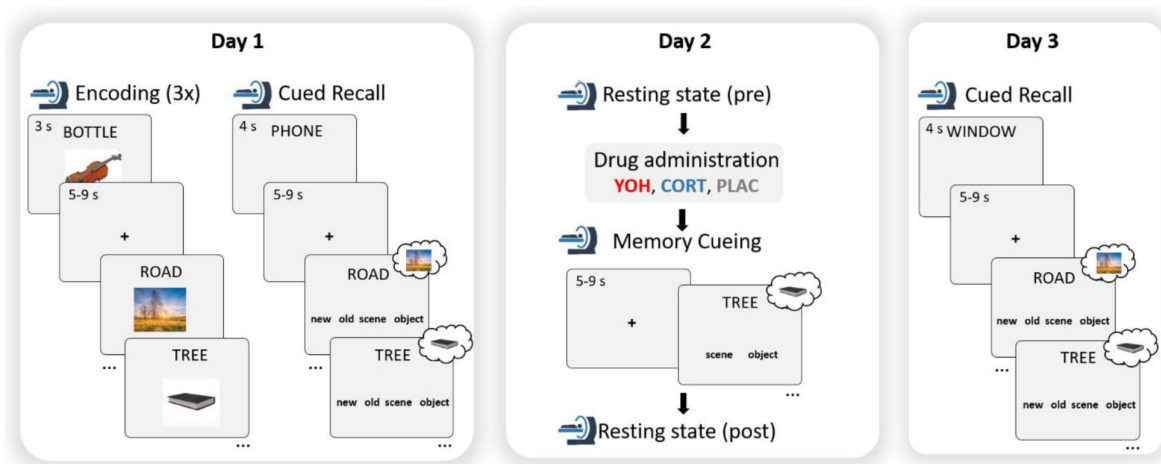


Fig. 1.

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.

autonomic arousal, or salivary cortisol (all P s > .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], $t = 7.93$, $P(\text{FWE}) < .001$; Right: [32, -40, -12], $t = 7.89$, $P(\text{FWE}) < .001$), ventral temporal cortex (VTC; Left: [-30, -40, -12], $t = 7.75$, $P(\text{FWE}) < .001$; Right: [52, -50, -14], $t = 7.26$, $P(\text{FWE}) < .001$), and PCC ([4, -42, 38], $t = 8.10$, $P(\text{FWE}) < .001$), 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* $\times$ *Group* interaction P s > .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: $\beta = -0.51 \pm 0.18$, $t = -2.88$, $P = .018$, $R^2_{\text{conditional}} = 0.08$; Right hippocampus: $\beta = -0.47 \pm 0.18$, $t = -2.60$, $P = .033$, $R^2_{\text{conditional}} = 0.11$; PCC: $\beta = -0.75 \pm 0.20$, $t = -3.67$, $P < .001$, $R^2_{\text{conditional}} = 0.09$), 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 P s > .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 ($M \pm SD$: $90.0\% \pm 0.1\%$); $t(60) = 25.99$, $P < .001$, $d = 3.83$) 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 ($M \pm SD$: $77.9\% \pm 0.9\%$, $t(60) = 29.88$, $P < .001$, $d = 3.80$), 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)

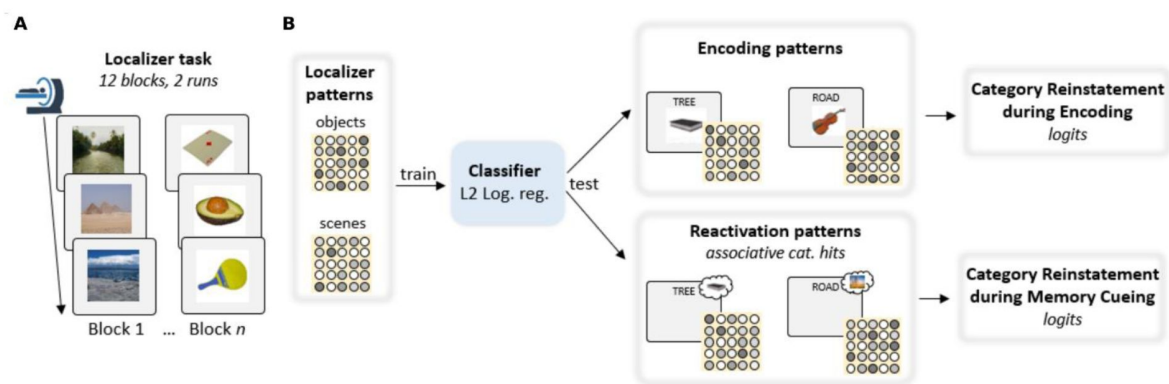


Fig. 2.

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).

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, $P_s > .504$). 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* $\times$ *Retrieval success* interaction (both $P_s = 1$), 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%; $M \pm SE = 54.4\% \pm 1.0\%$; $t(60) = 4.44$, $P < .001$, $d = 1.14$), 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 ($M \pm SE = 50.1\% \pm 1.7\%$; $P = 1$). 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: $M \pm SD: 53.3\% \pm 1.8\%$, $t(60) = 1.72$, $P = .501$, $d = 0.22$; Right: $M \pm SD: 52.9\% \pm 1.5\%$, $t(60) = 1.50$, $P = .520$, $d = 0.18$), 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: $M \pm SD: 53.8\% \pm 0.9\%$, $t(60) = 3.29$, $P = .006$, $d = 0.42$; Right: $M \pm SD: 53.4\% \pm 0.9\%$, $t(60) = 3.71$, $P < .001$, $d = 0.93$) 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: $M \pm SE = 50.71\% \pm 1.0\%$; $t(60) = 0.69$, $P = 1$, $d = 0.09$; Right: $M \pm SE = 51.82\% \pm 0.9\%$; $t(60) = 2.10$, $P = .156$, $d = 0.23$), nor forgotten scenes and forgotten objects (Left: $M \pm SE = 47.95\% \pm 1.6\%$; $t(60) = -1.31$, $P = 1$, $d = 0.17$; Right: $M \pm SE = 49.61\% \pm 1.3\%$; $t(60) = -0.27$, $P = 1$, $d = 0.09$) 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%; $M \pm SD: 62.4\% \pm 2.24\%$, $t(60) = 5.39$, $P < .001$, $d = 0.69$), 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%; $M \pm SD: 54.6\% \pm 1.0\%$, $t(60) = 4.43$, $P < .001$, $d = 0.57$), 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 ($M \pm SE = 52.3\% \pm 0.98\%$; $P = .092$), nor forgotten scenes and forgotten objects ($M \pm SE = 49.5\% \pm 1.70\%$; $t(60) = -0.27$, $P = 1$, $d = 0.03$).

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 ($t(60) = -2.61$, $P = .034$, $d = 0.34$).

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 s $> .296$). 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 [\[4\]](#); Krenz et al. 2021 [\[5\]](#)), 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* $\times$ *Group* interaction in systolic blood pressure ($F(8.71, 256.99) = 5.87$, $P < .001$, $\eta^2 = .03$; **Fig. 3A** [\[6\]](#)), but not in diastolic blood pressure or heart rate (both P s $> .120$; 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 P s $> .229$). 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 P s $> .485$).

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-

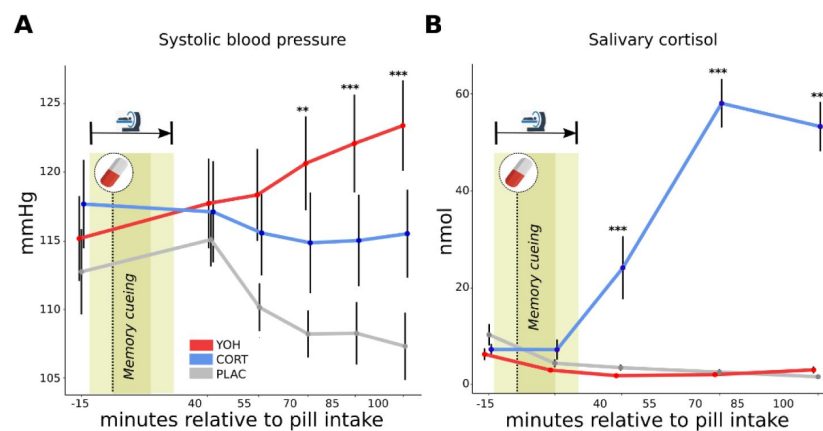


Fig. 3.

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 ($\pm$ SE). *** $P < .001$, ** $P < .01$.

and post-reactivation resting-state scans showed no *Time* $\times$ *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* $\times$ *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 P s $> .350$). 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 s $> .162$). Finally, subjective mood analyses across Day 2 revealed no significant *Time* $\times$ *Group* interaction on any scale (all interaction P s $> .460$; Supplemental Table S5).

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 P s $> .158$, 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 ($M \pm SE = 1.14 \pm 0.15$; $F(1,58) = 143.51$, $P < .001$, $\eta^2 = 0.29$; **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* $\times$ *Group* interaction nor a main effect of *Group* (all F s < 2.08 , all P s $> .134$), 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* $\times$ *Group* interactions in whole-brain or ROI activity.

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

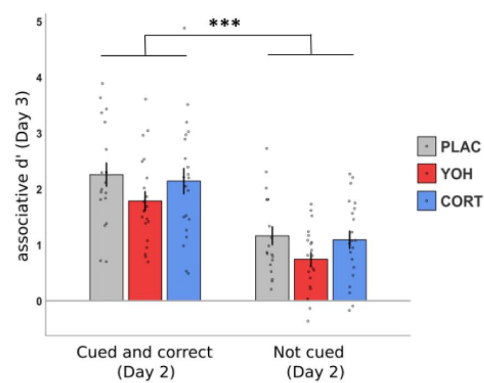


Fig. 4.

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 $\pm$ SE. *** $P < .001$.

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 s > .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* $\times$ *Reaction time (Day 2)* interaction: $\beta = 0.79 \pm 0.30$, $z = 2.61$, $P = .008$, $R^2_{\text{conditional}} = 0.27$; **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 ($\beta = 2.55 \pm 0.94$, $z\text{-ratio} = 2.55$, $P = .031$) and YOH vs. PLAC ($\beta = 0.34 \pm 0.14$, $z\text{-ratio} = -2.55$, $P = .032$). By contrast, comparing CORT vs. PLAC revealed no such difference ($\beta = 0.88 \pm 0.37$, $z\text{-ratio} = -0.29$, $P = 1$), 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* $\times$ *Hippocampal activity (Day 2)* $\times$ *Reaction time (Day 2)* interaction: $\beta = 0.90 \pm 0.36$, $z = 2.45$, $P = .038$, $R^2_{\text{conditional}} = 0.27$) but not in the CORT group ($\beta = 0.89 \pm 0.39$, $z = 2.28$, $P = .068$). Post-hoc comparisons confirmed significant differences in strongly reinstated trials between YOH and PLAC groups ($\beta = -1.12 \pm 0.35$, $z\text{-ratio} = -3.13$, $P = .005$) and between YOH and CORT groups ($\beta = 0.88 \pm 0.34$, $z\text{-ratio} = 2.58$, $P = .029$), but not between PLAC and CORT groups ($\beta = -0.23 \pm 0.36$, $z\text{-ratio} = -0.63$, $P = 1$; **Fig. 5A**). Parallel models with univariate PCC and right hippocampal activity did not yield a significant interaction with *Group* (all P s > .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 s > .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 ($\beta =$

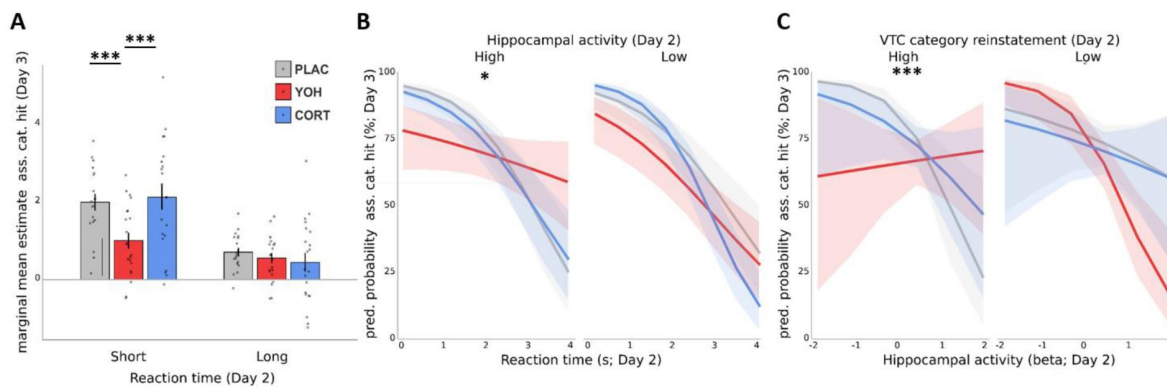


Fig. 5.

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. * $P < .05$, ** $P < .001$.

-0.21 ± 0.07 , $z = -3.08$, $P = .002$, $R^2_{\text{conditional}} = 0.18$; **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: $\beta = 0.14 \pm 0.05$, $z\text{-ratio} = 2.57$, $P = .030$; YOH vs. CORT: $\beta = 0.13 \pm 0.05$, $z\text{-ratio} = 1.31$, $P = .708$; **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 P s $> .210$). 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: $\beta = 0.12 \pm 0.05$, $z\text{-ratio} = 2.72$, $P = .018$; CORT: $\beta = -0.02 \pm 0.05$, $z\text{-ratio} = -0.42$, $P = 1$; PLAC: $\beta = -0.09 \pm 0.05$, $z\text{-ratio} = -1.68$, $P = .274$).

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 $\times$ 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](#) [↗](#); [Przybylski 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](#) [↗](#); [Else 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 ([Debiec 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 cannot 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 [↗](#); Hubbach 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) with no history of neurological or psychiatric diseases were recruited for this experiment. Additional exclusion criteria included 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 not tested during their menses and excluded if they used hormonal contraceptives due to potential interactions with the pharmacological intervention. Participants were instructed to abstain from caffeinated beverages, exercise, and eating or drinking (except water) for 2 hours before the experiment (Heinbockel, Wagner, and Schwabe 2024). 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). The study employed a fully crossed, placebo-controlled, double-blind, between-subjects design, with participants randomly assigned to one of three groups: placebo (PLAC), Yohimbine (YOH), or Cortisol (CORT). All participants provided written informed consent and received monetary compensation. 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* $\times$ *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, and 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. The used three-day memory task including the training session was identical to the paradigm applied in Heinbockel, Wagner, and Schwabe 2024.

Experimental Day 1: associative encoding task Participants engaged in a brief (~5 min) training session before the encoding task to become familiar with the procedure. This training replicated the 3-day paradigm structure, which included an encoding session and a cued recall test using word-picture associations that were not part of the main experiment. For the actual encoding task, participants were required to memorize 164 unique word-picture pairs across three runs. Each pair was presented three times (once per run), consisting of German nouns (see Supplemental Methods S1) paired with images of colored scenes (Xiao et al. 2010) or objects (Brodeur, Guérard, and Bouras 2014). During each trial, a word and picture appeared for 3 s (words on top of the screen, pictures in the centre), and participants rated the fit of each pair on a 4-point Likert scale using an MRI-compatible button box. A black fixation cross was displayed between trials for 5–9 s (jitter: 0–4 s, mean-jitter: 2 s). Each run lasted about 25 min, with a 2-minute break between runs, making the total duration for the three runs approximately 90 minutes. 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 took a 15 min break before receiving instructions for the immediate cued recall task. Returning to the MRI scanner, they were presented with 152 words from the prior encoding phase ('old') and 152 new words, including eight catch trials. 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 if participants recognized the word as old and to indicate the category of the associated image. Responses were made using an MRI-compatible button box, with the positions of 'old/scene' and 'old/object' randomized (50%) between the ring and little fingers for each trial. A black fixation cross appeared between trials for 5-9 seconds (jitter: 0-4 seconds, mean jitter: 2 seconds).

Experimental Day 2: drug administration and memory cueing

Participants returned to the MRI scanner on Day 2, and initially underwent 10 minutes of eyes-open resting state scanning. Next, participants orally received one of the pharmacological agents (YOH, CORT) or a PLAC, depending on the experimental group. YOH is a α 2-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 involved a two-alternative forced choice (2AFC) for categories, hits and misses could indicate not only correct or incorrect retrieval of the associated category, but also correct or incorrect guesses about the associated category. Hits could result from recognizing the word as old and accurately guessing the category, while misses could result from failing to recognize the word but correctly or incorrectly guessing the category. This complexity underscores the importance of neural measures of memory reactivation, which can differentiate between associative hits based on strong, moderate, or minimal memory reactivation. Examining the gradient between stronger and weaker reactivation is crucial for understanding the effects of post-retrieval interventions on memory processes. Strong reactivation during Day 2 may render the memory more susceptible to the effects of pharmacological agents. The task aimed to reactivate half of the word-picture pairs, allowing for the examination of 'testing effects' and potentially opening a reconsolidation window. The remaining pairs were not reactivated and served as baseline/control memories. After the Memory Cueing task, participants underwent a 10-minute, eyes-open resting state scan. Following this, they were taken out of the scanner and led to a separate room where they spent an hour completing mood questionnaires and having physiological measurements (e.g., blood pressure) taken to validate the action of the drugs, all while being provided with magazines to read. 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. In line with previous studies, 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; see [Heinbockel, Wagner, and Schwabe 2024](#); [Meier and Schwabe, 2024](#)). 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, identical to the recall task on Day 1. Participants were presented with 152 of the encoded words and 152 new words in random order. For each word, they had to indicate it was ‘new’, ‘old’, ‘old’ and associated with a scene (‘old/scene’), or ‘old’ and associated 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 ([Gagnon et al., 2018](#); [Heinbockel, Wagner, and Schwabe 2024](#)). This task aimed to identify subject-specific patterns of category-level visual representations, particularly in the VTC. During this task, participants made judgments about images from three different 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 investigation of word-picture associative memory during the cued recall tasks on Day 1 and Day 3 (using a 4AFC paradigm), we recorded associative category hits when participants correctly matched old word cues with the corresponding picture category (e.g., responding ‘old/scene’ for a scene associate). This indicated the 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 termed all old trials that did not result in associative category hits as ‘associative misses’, encompassing instances where 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 (from the 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. 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 play a critical role 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

A 3 T Magnetom Prisma MRI scanner (Siemens, Germany), equipped with a 64-channel head coil, was used to collect functional and structural imaging data. Gradient-echo T2*-weighted echoplanar images (EPis) were obtained for the functional volumes, with a slice thickness of 2 mm and an isotropic voxel size of 2 mm². A descending interleaved multiband method aligned sixty-two slices to the anterior commissure–posterior commissure line. The imaging parameters included a repetition time (TR) of 2000 ms, an echo time (TE) of 30 ms, a flip angle of 60%, and a field of view of 224 x 224 mm. Before the Day 2 Memory Cueing task, we acquired high-resolution T1-weighted structural images for each participant using a magnetization-prepared rapid acquisition gradient echo (MPRAGE) sequence. These structural images had a voxel size of 0.8 x 0.8 x 0.9 mm and comprised 256 slices. The imaging parameters for the MPRAGE sequence included a TR of 2.5 s and a TE of 2.12 ms. Both the structural and functional images underwent preprocessing using SPM12 (<http://www.fil.ion.ucl.ac.uk/spm/>) implemented in MATLAB. To mitigate T1 saturation effects, we discarded the first three functional images of each run. Preprocessing steps involved 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 hitCued and correct, associative misscued and correct, associative category hitUncued, and associative missUncued. 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.

Region of interest analyses

We investigated task-evoked activation in the hippocampus and VTC, given their crucial role in episodic memory retrieval (Kim 2010; Ranganath et al. 2004). Region of interest (ROI) masks were taken from the Harvard-Oxford cortical and subcortical atlas with a 50% probability threshold. The VTC mask consisted of relevant regions from the Harvard-Oxford Atlas, excluding the hippocampus. In the overall GLMs, the same regressors were employed, but voxels were masked by specific ROIs, and ROI-specific effects were small-volume corrected.

The inverse deformation field, derived from segmentation, was used to back-transform ROIs into subject-specific native space. In all ROI analyses on voxel-wise modeled data, single-trial beta estimates were computed for all days and tasks to provide a detailed characterization of memory-related neural responses. A high-pass filter with a cut-off of 128 s was applied to remove low-frequency drifts. The models, following the ‘Least-squares all’ approach, were conducted on realigned, slice-time corrected, native space images for subsequent multivariate pattern analyses (MVPA, RSA).

Multivariate pattern classification

Multivariate/voxel pattern analyses (MVPA) were conducted utilizing The Decoding Toolbox (Hebart et al. 2015 [\[1\]](#)) in order to gauge trial-wise cortical reinstatement strength. Three L2-penalized logistic regression models ($C = 0.1$) were utilized for this purpose. The first model was employed to evaluate the classification performance within the localizer task, using leave-one-run-out cross-validation (scenes vs. objects) to validate the overall task quality and data integrity. In the subsequent model, we developed a “category” detection framework trained on neural patterns extracted from both sessions of the visual localizer task. We tested its performance on the day 2 Memory cueing task data to estimate category-level reinstatement (scenes vs. objects). This way we could examine the single-trial reinstatement evidence of memory responses and subsequently ascertain whether reinstatement evidence tended to be higher for cued and correct responses (i.e., associative hits) in comparison to cued but incorrect trials (i.e., associative misses). The evidence of category resurgence on a trial-wise basis was evaluated using classification accuracy and logits. The third model was specifically trained on neural patterns derived from the visual localizer task. Its objective was to differentiate remembered scenes from remembered objects, thus serving as the category pattern reinstatement index for subsequent analyses. Evidence of trial-wise category pattern reinstatement was evaluated utilizing logits and balanced classification accuracy, a metric designed to address potential imbalances in the number of samples during testing (Chen et al. 2021 [\[2\]](#)).

Tracking online reactivation

To comprehensively evaluate trial-wise reactivation on Day 2, we integrated reaction times, trial-wise univariate beta activity in the hippocampus, PCC and VTC, category pattern reinstatement indexed via MVPA in the VTC, and Hippocampal pattern reactivation from encoding to reactivation (Encoding-Reactivation-Similarity via RSA) in LMMs. These models were utilized to forecast single-trial beta activity of the hippocampus, PCC and VTC, along with category pattern reinstatement, incorporating trial-specific Day 2 reaction times. Additionally, a LMM was fitted to univariate hippocampal activity, predicted by category pattern reinstatement, aligning with previous findings that showed a positive correlation between hippocampal activity and VTC pattern reinstatement (Gagnon et al. 2019 [\[3\]](#)). The category pattern reinstatement index and hippocampal pattern reactivation were employed to classify trials as ‘high’ or ‘low’ online reactivation. These classifications were used to predict Day 3 performance in GLMMs, integrating data 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 (Hebart et al. 2015 [\[1\]](#)). 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

fMRI data underwent univariate statistical analyses within the SPM12 environment (<http://www.fil.ion.ucl.ac.uk/spm/>), while all other statistical procedures were executed in R (version 3.3.4). ANOVA-derived p-values were adjusted using Greenhouse-Geisser correction when needed, and voxel-cluster results from univariate fMRI analyses were corrected for family-wise error (FWE). Baseline and control variables from Days 1 and 3, such as blood pressure, were assessed via one-way ANOVAs. Day 2 parameters assessing the effectiveness of the pharmacological manipulation (e.g., blood pressure, heart rate, mood, cortisol, SCR) were tested with repeated-measures ANOVAs with Time as the within-subject factor and Group as the between-subject factor, followed by post-hoc t-tests, which were Bonferroni corrected. Performance metrics (hits, false alarms, d') examining the pharmacological influence on memory for reactivated trials were analyzed through repeated-measures ANOVAs, with Reactivated as the within-subject factor and Group as the between-subject factor, followed by post-hoc t-tests. Associative d' calculations substituted zero values with 0.5/denominator and ones with 1–0.5/denominator (Macmillan and Kaplan 1985).

Single-trial analyses utilized (Generalized) Linear Mixed Models to predict associative category hits/misses on Day 3, incorporating various predictor variables (such as Reactivation, Group). These models, implemented with the lme4 package (Bates et al. 2014), employed a restricted maximum likelihood (REML) approach. Resultant p-values were Bonferroni corrected for the number of regions of interest (ROIs). Post-hoc slope tests were conducted using the emtrends function (Searle, Speed, and Milliken 1980) with Tukey correction. Data visualization was performed using the ggplot2 (Wickham 2011) package and 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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Reviewer #1 (Public review):

Summary:

How reconsolidation works - particularly in humans - remains largely unknown. With an elegant, 3-day design, combining fMRI and psychopharmacology, the authors provide evidence for a certain role for noradrenaline in the reconsolidation of memory for neutral stimuli. All memory tasks were performed in the context of fMRI scanning, with additional resting-state acquisitions performed before and after recall testing on Day 2. On Day 1, 3 groups of healthy participants encoded word-picture associates (with pictures being either scenes or objects) and then performed an immediate cued recall task to presentation of the word (answering is the word old or new, and whether it was paired with a scene or an object). On Day 2, the cued recall task was repeated using half of the stimulus set words encoded on Day 1 (only old words were presented, with subjects required to indicate prior scene vs object pairing). This test was immediately preceded by the oral administration of

placebo, cortisol, or yohimbine (to raise noradrenaline levels) depending on group assignment. On Day 3, all words presented on Day 1 were presented. As expected, on Day 3, memory was significantly enhanced for associations that were cued and successfully retrieved on Day 2 compared to uncued associations. However, for associative d' , there was no Cued $\times$ Group interaction nor a main effect of Group, i.e., on the standard measure of memory performance, post-retrieval drug presence on Day 2 did not affect memory reconsolidation. As further evidence for a null result, fMRI univariate analyses showed no Cued $\times$ Group interactions in whole-brain or ROI activity.

Strengths:

There are some aspects of this study that I find impressive. The study is well-designed and the fMRI analysis methodology is innovative and sound. The authors have made meticulous and thorough physiological measurements, and assays of mood, throughout the experiment. By doing so, they have overcome, to a considerable extent, the difficulties inherent in the timing of human oral drug delivery in reconsolidation tasks, where it is difficult to have the drug present in the immediate recall period without affecting recall itself. This is beautifully shown in Figure 3. I also think that having some neurobiological assay of memory reactivation when studying reconsolidation in humans is critical, and the authors provide this. While multi-voxel patterns of hemodynamic responses are, in my view, very difficult to equate with an "engram", these patterns do have something to do with memory.

Weaknesses:

I have major issues regarding the behavioral results and the framing of the manuscript.

(1) To arrive at group differences in memory performance, the authors performed median splitting of Day 3 trials by short and long reaction times during memory cueing on Day 2, as they took this as a putative measure of high/low levels of memory reactivation. Associative category hits on Day 3 showed a Group by Day 2 Reaction time (short, long) interaction, with post-hocs showing (according to the text) worse memory for short Day 2 RTs in the Yohimbine group. These post-hocs should be corrected for multiple comparisons, as the result is not what would be predicted (see point 2). My primary issue here is that we are not given RT data for each group, nor is the median splitting procedure described in the methods. Was this across all groups, or within groups? Are short RTs in the yohimbine group any different from short RTs in the other two groups? Unfortunately, we are not given Day 2 picture category memory levels or reaction times for each group. This is relevant because (as given in Supplemental Table S1) memory performance (d') for the Yohimbine group on Day 1 immediate testing is (roughly speaking) 20% lower than the other 2 groups (independently of whether the pairs will be presented again the following day). I appreciate that this is not significant in a group $\times$ performance ANOVA but how does this relate to later memory performance? What were the group-specific RTs on Day 1? So, before the reader goes into the fMRI results, there are questions regarding the supposed drug-induced changes in behavior. Indeed, in the discussion, there is repeated mention of subsequent memory impairment produced by yohimbine but the nature of the impairment is not clear.

(2) The authors should be clearer as to what their original hypotheses were, and why they did the experiment. Despite being a complex literature, I would have thought the hypotheses would be reconsolidation impairment by cortisol and enhancement by yohimbine. Here it is relevant to point out that - only when the reader gets to the Methods section - there is mention of a paper published by this group in 2024. In this publication, the authors used the same study design but administered a stress manipulation after Day 2 cued recall, instead of a pharmacological one. They did not find a difference in associative hit rate between stress and control groups, but - similar to the current manuscript - reported that post-retrieval stress disrupts subsequent remembering (Day 3 performance) depending on neural memory

reinstatement during reactivation (specifically driven by the hippocampus and its correlation with neocortical areas).

Instead of using these results, and other human studies, to motivate the current work, reference is made to a recent animal study: Line 169 "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". It is difficult to follow that a rodent study using contextual fear conditioning and examining single neuron activity to remote fear recall and extinction would be relevant enough to motivate a hypothesis for a human psychopharmacological study on emotionally neutral paired associates.

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Reviewer #2 (Public review):

Summary:

The authors aimed to investigate how noradrenergic and glucocorticoid activity after retrieval influence subsequent memory recall with a 24-hour interval, by using a controlled three-day fMRI study involving pharmacological manipulation. They found that noradrenergic activity after retrieval selectively impairs subsequent memory recall, depending on hippocampal and cortical reactivation during retrieval.

Overall, there are several significant strengths of this well-written manuscript.

Strengths:

- (1) The study is methodologically rigorous, employing a well-structured three-day experimental design that includes fMRI imaging, pharmacological interventions, and controlled memory tests.
- (2) The use of pharmacological agents (i.e., hydrocortisone and yohimbine) to manipulate glucocorticoid and noradrenergic activity is a significant strength.
- (3) The clear distinction between online and offline neural reactivation using MVPA and RSA approaches provides valuable insights into how memory dynamics are influenced by noradrenergic and glucocorticoid activity distinctly.

Weaknesses:

- (1) One potential limitation is the reliance on distinct pharmacodynamics of hydrocortisone and yohimbine, which may complicate the interpretation of the results.
- (2) Another point related above, individual differences in pharmacological responses, physiological and cortisol measures may contribute to memory recall on Day 3.
- (3) Median-splitting approach for reaction times and hippocampal activity should better be justified.

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