Memory's avalanche: Recent feelings of familiarity and resultant DA nuclei activity enable subsequent memory reactivation

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Abstract

Memory retrieval is notoriously variable. Various neurocognitive states have been theorized to affect retrieval success from moment to moment, but the presence and catalysts of these states in the human brain remain largely understudied. Building on previous work, we studied how recent memory experiences (i.e. novelty vs. familiarity) and their corresponding neural activity prepare the brain to reactivate memories. Our data uncover a pronounced neural bias, whereby regions representing episodic information fail to reactivate memories following recent experiences of novelty. Drawing on computational models, we hypothesized that novelty-evoked activity in cholinergic nuclei underlie this bias. The data revealed an unexpected alternative mediator of memory reactivation in response to recent novelty, namely recent dopaminergic nuclei activity. By identifying dopamine as a potential mediator of retrieval variability, our results challenge existing models and open new avenues for investigating how neuromodulatory states dynamically shape memory accessibility.

Keywords: episodic memory, human, fMRI, retrieval, novelty, familiarity, dopamine, acetylcholine, neuromodulators, reinstatement

Introduction

Making effective decisions hinges on recalling relevant experiences, but memory retrieval is notoriously inconsistent. At times, past events vividly spring to mind with little effort; at other times, we fail to even recall a colleague's name. What drives this frustrating variability? Decades of memory research have highlighted the quality of memory formation as a major determinant (1–5). When a well-learned memory is cued with a congruent reminder, successful retrieval often follows (6, 7). However, even well-formed memories can fail to surface when cued, suggesting that factors beyond initial learning shape variability in moment-to-moment retrieval success (7, 8). Here, we investigate the cognitive and neural mechanisms that contribute to this variability, revealing factors that prepare our brains to recall past experiences.

The idea that retrieval depends on fluctuating preparatory states of mind was first proposed by Endel Tulving in 1983. He theorized that successful episodic retrieval requires proactively recruiting the retrieval mode, a neurocognitive state including the goal to retrieve memories and the orientation of attention towards reactivated information (9). Recent theoretical and empirical work has revived and extended Tulving's ideas, characterizing neural states contributing to retrieval goals and internal attention (10–12). For the retrieval mode to be fruitful, though, the brain must reactivate memories, a process termed ecphory by Tulving (1983), and more recently formalized as pattern completion (13–15). Specifically, the hippocampus can reactivate full memories in response to partial retrieval cues, which in turn reinstates memory components in corresponding neocortical regions (16, 17) that can be observed through analyses of functional magnetic resonance imaging (fMRI) patterns (17–20). While hippocampal pattern completion is conventionally construed as automatic, it might be possible to prime this process as well (12, 21, 22). Hinting at this, Patil and Duncan (2018) behaviourally showed that people were less

accurate at retrieving associations after detecting a novel image than they were after recognizing a familiar but unrelated image.

Here we leverage novelty's impact on memory to explore neural mechanisms underlying retrieval variability. One possible mechanism is that novelty engages neuromodulatory systems that suppress upcoming retrieval. Dopamine (DA), acetylcholine (ACh), and norepinephrine (NE)—each of which is released in response to novelty (23–28)—have lingering effects on attention (29–34), goal maintenance (34–38), and memory (22, 30, 33, 38–41). DA and NE are well-positioned to engage the retrieval mode by enhancing goal maintenance and attention (29, 32–34, 36–38), making them unlikely to underpin novelty's suppression of retrieval. A more plausible candidate is ACh. Cholinergic neurons in the septum (CH1 and CH2) and portions of the diagonal band of Broca (CH3) project to the hippocampus(42), where increased ACh levels are hypothesized to suppress retrieval-based processing (i.e. pattern completion) in favour of encoding-based processing (i.e. pattern separation(22)). This cholinergically mediated hippocampal switch would reduce brain-wide memory reactivation and retrieval success. Thus, comparatively, recent familiarity would beget more fluid pattern completion and memory reactivation than recent novelty, consistent with the behavioral results of Patil and Duncan (2018).

In this study, we used functional magnetic resonance imaging (fMRI) to test this possibility. Specifically, we measured activity across regions known to display memory reactivation along with neuromodulatory nuclei while participants learned and retrieved associations. We predict that, if Patil and Duncan's (2018) findings reflect a novelty-evoked bias away from hippocampal pattern completion, then neural reinstatement of memories will also be lower following novelty compared to familiarity. We also hypothesized that preceding activity in cholinergic nuclei would

mediate recent novelty's effect on reinstatement. This pattern of results would be consistent with the idea that ongoing fluctuations in ACh release could explain retrieval variability. While our results confirmed that neural reinstatement is robustly modulated by recent memory experiences, they also revealed an unexpected set of neuromodulatory mechanisms mediating this effect.

Results

Creating an fMRI paradigm suited to investigate the preparatory states affecting memory reactivation

We designed a memory task to evaluate how novelty, and the neuromodulatory nuclei activity it evokes, influences the upcoming neural reinstatement of memories. As this neuromodulatory influence is expected to last for only a few seconds (43, 44), we carefully designed our experiment to overcome the slow nature of the blood-oxygen-level-dependent (BOLD) signal (45). Specifically, we limited inter-trial-intervals (ITIs) to 1 second to measure these short-lived neuromodulatory biases, and we used representationally distinct stimulus categories to disambiguate signals arising from consecutive trials. In retrieval blocks, trials were presented in a series of pairs, such that participants retrieved different stimulus categories from trial to trial (Fig. 1a). The first trial of each pair was designed to induce novelty/familiarity, in which participants viewed a trial-unique new or previously studied object (*induction trials*). When they recognized an object, they attempted to recall the word associated with it during encoding ("Plain" or "Safe"). The second trial of each pair was designed to assess associative retrieval performance and neural reinstatement following novelty/familiarity, in which participants viewed trial-unique new or previously studied words (*probe trials*). When they recognized a word, they attempted to recall the stimulus category of the image associated with it during encoding ("Face" or "Scene"; see *Methods: Procedure* for full design specifications). For analyses, we categorized induction trials according to participants' subjective memory judgements. If they responded with "new," trials were considered inductions of novelty; if they recognized the objects, regardless of their associative retrieval success, trials were

considered inductions of familiarity (see *Methods: Retrieval Session* for response options). We extended ITIs between trial pairs to 5 seconds to increase the sensitivity of our reinstatement analyses.

First, we assessed how our induction trial manipulation influences memory retrieval in this unique paradigm. After replicating Patil and Duncan (2018), we assessed how this manipulation influenced the neural reinstatement of memories using encoding-retrieval similarity analyses. We then measured how neuromodulatory nuclei responded to novelty on induction trials, before determining if these responses mediated novelty's impact on neural reinstatement.

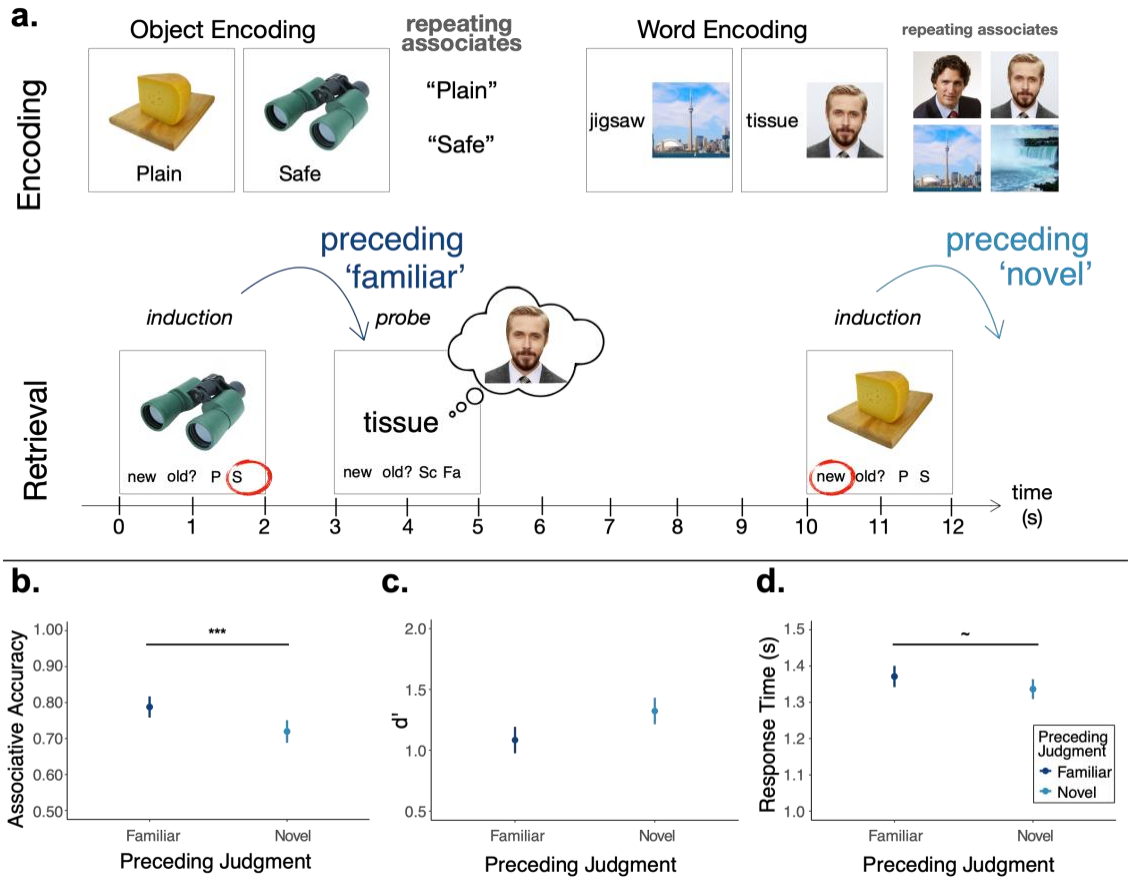

Fig. 1 | Task Design & Behavioral Analyses. **a**, Schematic of encoding & retrieval tasks. During Object Encoding, participants associated trial-unique objects with repeating words. During Word Encoding, participants associated trial-unique words with repeating face and scene

images (see *Methods: Encoding Blocks*). At retrieval, participants were shown the trial-unique half of an encoded pair (object image or non-repeating word) and asked to retrieve its associate. Trials were structured in pairs, with object trials acting as inductions of novelty/familiarity and word trials acting as probes to measure neural reinstatement & associative memory accuracy (see *Methods: Retrieval Session*). **b**, Associative memory accuracy on probe trials as a function of preceding memory experiences. Points represent the estimated marginal means and error bars represent their standard error from a generalized linear mixed effects model (see *Methods: Behavioral data analyses*). **c**, Item-only recognition memory (d') on probe trials as a function preceding memory experiences. Points represent mean d' across participants for trials preceded by familiarity and novelty, respectively. Error bars represent the standard error of the mean, applying the Morey, 2008 correction for within-participant comparisons. **d**, Response time on probe trials as a function of preceding memory experiences. Points represent the estimated marginal means and error bars represent their standard error from a linear mixed effects model (see *Methods: Behavioral data analyses*). ~ indicates $0.10 > p > 0.05$, *** indicates $p < 0.001$.

Experiences of novelty compared to familiarity reduce successive associative memory, but not recognition memory

We first sought to replicate and extend Patil & Duncan's (2018) demonstration that associative memory accuracy was lower following experiences of novelty compared to familiarity. In this experiment, associative memory accuracy was, indeed, significantly lower following experiences of novelty ($b = 0.184$, $SE = 0.0674$, $p < 0.001$, 95% CI = [0.059, 0.310]; Fig. 1b). This effect held when controlling for the associate's stimulus class (i.e. face vs. scene) and the preceding trial's response time (SI Appendix, Table S1). Like Patil & Duncan (2018), we

also found that item-only recognition memory accuracy (i.e., recognition in the absence of associative memory) was not significantly influenced by preceding experiences of novelty ($t(26) = -1.55$, $p = 0.134$, $d = -0.3$, 95% CI = [-0.68, 0.09]; Fig. 1c). Numerically, this recognition accuracy was even higher following novelty. Our novelty manipulation's specific influence on associative memory is consistent with our hypothesis that the hippocampus is biased away from pattern completion following novelty compared to familiarity (21, 47).

However, two trends raise the possibility that another mechanism could also contribute to these sequential memory effects. First, participants were marginally slower to correctly retrieve associations following experiences of familiarity compared to novelty ($b = 0.013$, $SE = 0.015$, $p = 0.063$, 95% CI = [-0.001, 0.026], Fig. 1d). This potential speed-accuracy trade-off suggests that associative accuracy benefits could reflect participants being more willing to engage in effortful processing following familiarity. We further probed this possibility in an exploratory analysis; we asked if the relative benefits of recent familiarity extend beyond retrieval to also foster memory formation. At the end of the experiment, participants completed a short recognition test (see *Methods: Localizer Tasks*), which assessed their memory for 16 words first shown during retrieval blocks. Critically, these novel foils were presented on probe trials following either the induction of novelty or familiarity. Participants were marginally better at recognizing words encoded following experiences of familiarity compared to novelty ($b = 0.223$, $SE = 0.121$, $p = 0.065$, 95% CI = [-0.014, 0.461]; SI Appendix, Table S2). This encoding effect could be explained by participants adopting more effortful processing following familiarity compared to novelty, but it would be hard to explain with a pattern completion bias, as this process is unlikely to facilitate memory formation. We caution over-interpretation of these marginal findings, but the new ideas they raise merit additional testing.

148

149 **Experiences of novelty compared to familiarity reduce neural reinstatement across high-**
150 **level ventral stream regions**

151 To more directly test our hypothesis that hippocampal pattern completion would be
152 reduced following experiences of novelty compared to familiarity, we used encoding-retrieval
153 similarity (ERS(48)) to measure memory reinstatement. While more invasive methods
154 convincingly demonstrate pattern completion in the hippocampus (14), this is inconsistently
155 observed with fMRI (49–52). Fortunately, the cortical reinstatement of memories, which depends
156 on the hippocampus (16, 17), can be robustly measured with fMRI. Accordingly, in addition to
157 the hippocampus, we analyzed probe trial ERS in high-level ventral stream and frontoparietal
158 ROIs that display reliable signatures of memory reinstatement (*a priori:* hippocampus, medial
159 temporal lobe (MTL) cortex, fusiform cortex (fusiform), medial parietal cortex; *post-hoc:* dorsal
160 & lateral prefrontal cortex (d&lPFC), ventromedial prefrontal cortex (vmPFC), and lateral
161 parietal cortex(52–57)), referred to as *reinstatement ROIs* (SI Appendix, Table S3). We
162 calculated ERS in three ways, beginning with the most inclusive definition (*broad ERS*). This
163 calculation captures reinstatement of information about the category of the to-be-retrieved item
164 (Scene or Face, necessary for the judgement) and information about the trial-specific association
165 (e.g. Ryan Gosling + tissue). Broad ERS values above zero suggest that a region reinstated traces
166 present during encoding at retrieval (see Fig. 2a for schematic and *Methods: fMRI data analysis*
167 for calculation specifics).

168 Medial parietal, MTL, and fusiform cortices all demonstrated above-chance levels of
169 broad ERS (MTLcortex: $b = 0.005$, $SE = 0.002$, $p = 0.006$, $CI = [0.002, 0.009]$; fusiform: $b =$
170 0.008, $SE = 0.003$, $p = 0.006$, 95% $CI = [0.002, 0.014]$; mPar: $b = 0.011$, $SE = 0.002$, $p < 0.001$,

95% CI = [0.006, 0.015]). Unsurprisingly, the hippocampus did not show evidence of reinstatement (b < 0.001, SE = 0.003, p = 0.956, 95% CI = [-0.005, 0.005]; Fig. 2c; SI Appendix, Table S4). Importantly, preceding novelty influenced ERS much like it did memory accuracy. ROIs across the ventral processing stream all demonstrated significantly lower levels of broad ERS following experiences of novelty compared to familiarity (Hipp: b = 0.005, SE = 0.002, p = 0.027, 95% CI = [0.001, 0.010]; MTLcortex: b = 0.006, SE = 0.002, p = 0.005, 95% CI = [0.002, 0.010]; fusiform: b = 0.009, SE = 0.003, p = 0.003, 95% CI = [0.003, 0.015]; mPar: b = 0.002, SE = 0.003, p = 0.538, 95% CI = [-0.004, 0.007]; Fig. 2c; SI Appendix, Table S5). The influence of the preceding experience was so pronounced that broad ERS was only observed following familiarity in the MTL and fusiform cortices, not following novelty (MTLcortex following familiar: estimated marginal mean (EMM) = 0.014, p < 0.001; MTL cortex following novel: EMM = 0.002, p = 0.358; fusiform following familiar: EMM = 0.021, p < 0.001; fusiform following novel: EMM = 0.002, p = 0.554; p-values FDR corrected for multiple comparisons; Fig. 2d; SI Appendix, Table S6). These effects all held in control models accounting for response time and accuracy (SI Appendix, Table S5 & S6), suggesting that the reinstatement effects are not secondary to the observed behavioural biases. Analyses of frontoparietal *post-hoc* ROIs demonstrated similar trends to those seen in the medial parietal cortex, with the d&lPFC and lateral parietal cortex demonstrating significant broad ERS insensitive to the preceding trial experience (Fig. 2c & 2d; SI Appendix, Table S4, S7 & S8). Taken together, these results suggest that memory reinstatement is reduced across high-level ventral processing regions following experiences of novelty compared to familiarity, but that reinstatement in frontoparietal regions is insensitive to these preceding experiences.

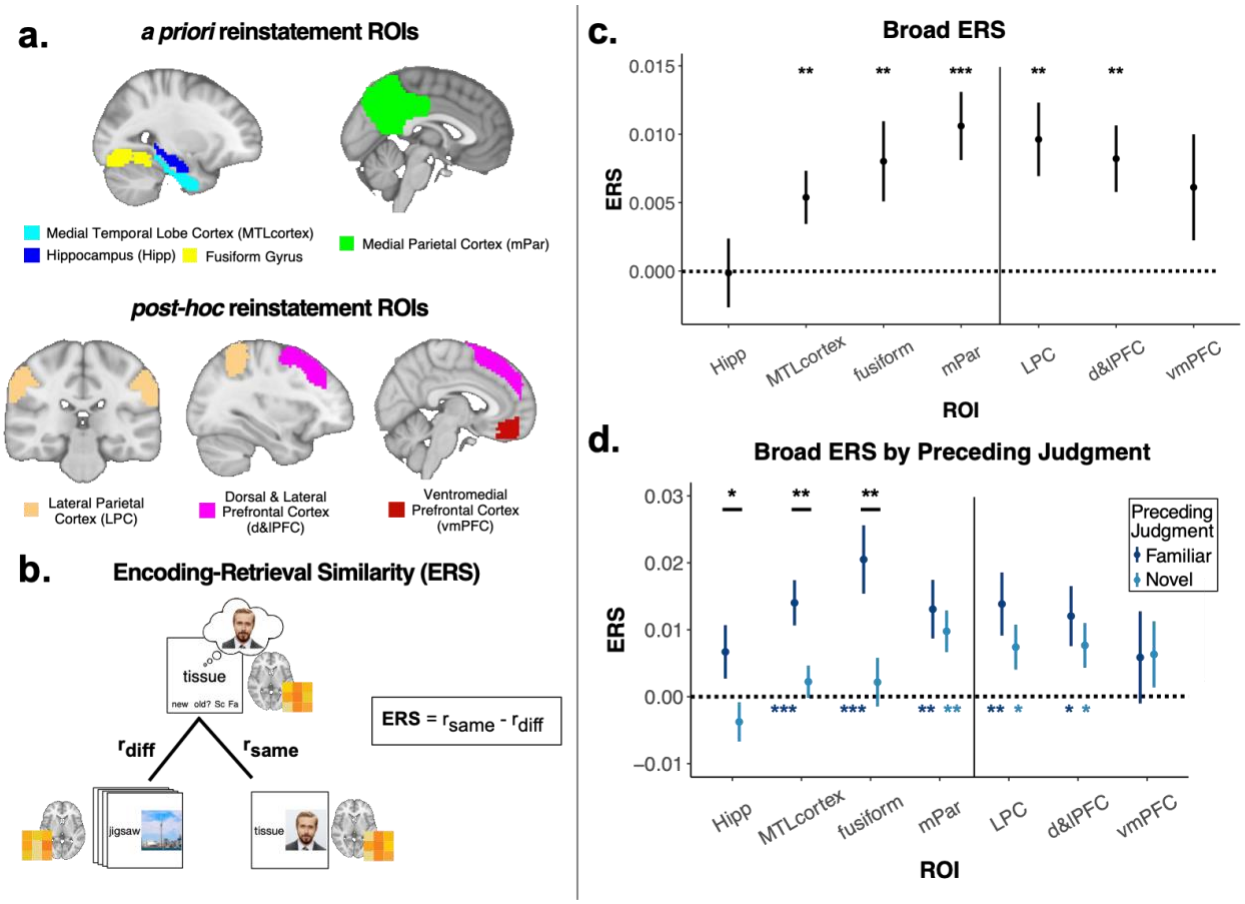

Fig. 2 | Broad ERS. **a**, *A priori* and *post-hoc* reinstatement ROIs selected for ERS analyses. **b**, Schematic of broad ERS calculation. Activity patterns from probe trials were correlated with patterns from corresponding encoding trials (r_{same}). r_{same} was corrected by subtracting retrieval trials' average correlation with encoding trials that included the unprobed image category (r_{diff}; See *Methods: fMRI data analysis*). **c**, Broad ERS on probe trials against chance. Points represent intercepts and error bars represent their standard error from a linear mixed effects model (see *Methods: fMRI data analyses*). **d**, Broad ERS on probe trials as a function of preceding memory experiences. Points represent estimated marginal means and error bars represent their standard error from a linear mixed effects model (see *Methods: fMRI data analyses*). Black stars represent significance of the main effect of preceding memory experiences on broad ERS, while dark and light blue stars represent significance of broad ERS against chance following

familiarity and novelty, respectively. * indicates $p < 0.05$, ** indicates $p < 0.01$, *** indicates $p < 0.001$. Post-hoc ROI p-values are FDR corrected for multiple comparisons.

Category & Trial-Specific Reinstatement

We designed our task to also evaluate whether ROIs reinstate information about the category of the to-be-retrieved image (Scene or Face; *category ERS*) or information about the trial-specific association (e.g. Ryan Gosling with tissue*; trial-specific ERS*). Of note, participants only needed to reinstate categories to accurately perform the retrieval task (judgment of Scene vs. Face). In fact, category ERS was higher for source-correct compared to incorrect trials in both the medial parietal and MTL cortices (MTLcortex: b = 4.715, SE = 2.130, p = 0.027, 95% CI = [0.541, 8.890]; mPar: b = 4.144, SE = 1.758, p = 0.018, 95% CI = [0.698, 7.590]). Among both our *a priori* and *post-hoc* ROIs, only the fusiform cortex significantly reinstated category information, and the medial parietal cortex demonstrated a marginal effect (fusiform: b = 0.002, SE = 0.001, p = 0.035, 95% CI = [0.000, 0.003]; mPar: b = 0.002, SE = 0.001, p = 0.050, 95% CI = [<0.001, 0.004]; Fig. 3c; SI Appendix, Table S9). As faces were one of the two reinstated categories, it is unsurprising that the fusiform cortex demonstrated robust category ERS (58). The fusiform cortex was also sensitive to preceding memory experiences, so much so that it only showed significant category ERS following familiarity (fusiform: b = 0.004, SE = 0.000, $p < 0.001$, 95% CI = [0.002, 0.005]; fusiform following familiar: EMM = 0.007, $p < 0.001$; fusiform following novel: EMM = -0.001, p = 0.437; Fig. 3d see SI Appendix, Table S10 & S11). On the whole, the reinstatement of task-relevant category information was only modestly influenced by preceding memory experiences.

We next used trial-specific ERS to identify regions where reinstatement extends beyond task-relevant category information. Medial parietal and MTL cortices both showed significant trial-specific ERS, while this metric was marginal in fusiform cortex (Hipp: b < 0.001, SE = 0.002, p = 0.984, 95% CI = [-0.005, 0.005]; MTLcortex: b = 0.004, SE = 0.002, p = 0.028, 95% CI = [<0.001, 0.008]; fusiform: b = 0.006, SE = 0.003, p = 0.054, 95% CI = [0.000, 0.012]; mPar: b = 0.008, SE = 0.002, p = 0.002, 95% CI = [0.003, 0.012]; Fig. 3c, SI Appendix, Table S14). Notably, preceding memory experiences influenced trial-specific ERS across all our ventral stream ROIs (Hipp: b = 0.005, SE = 0.002, p = 0.029, 95% CI = [0.001, 0.010]; MTLcortex: b = 0.006, SE = 0.002, p = 0.005, 95% CI = [0.002, 0.010]; fusiform: b = 0.008, SE = 0.003, p = 0.011, 95% CI = [0.002, 0.014]; mPar: b = 0.003, SE = 0.003, p = 0.209, 95% CI = [-0.002, 0.008]; Fig. 3d, SI Appendix, Table S15), with above-chance reinstatement in MTL and fusiform cortices only following familiarity (MTLcortex following familiar: EMM = 0.013, p = 0.001; MTLcortex following novel: EMM = 0.001, p = 0.655; fusiform following familiar: EMM = 0.016, p = 0.004; fusiform following novel: EMM < 0.001, p = 0.910; p-values FDR corrected for multiple comparisons; Fig. 3d; see SI Appendix, Table S15 & S16). As with broad ERS, frontoparietal *post-hoc* ROIs once again displayed a similar pattern to that seen in the medial parietal cortex, with the dorsal & lateral PFC and the lateral parietal cortex both demonstrating above-chance levels of trial-specific ERS insensitive to preceding experiences (Fig. 3d; see SI Appendix, Table S14, S17 & S18). Overall, preceding memory experiences had a more pronounced impact on the reinstatement of trial-specific episodic details as compared to task-relevant category information across high-level dorsal stream regions. The influence also closely tracked that observed in broad, ERS suggesting that reinstatement of trial-specific largely underpinned those effects.

These ERS analyses illuminate how preceding memory experiences prepare the brain to retrieve. We primarily observed modulation of memory reactivation in the ventral stream and not in frontoparietal regions. Additionally, recent memory experiences tended to modulate granular trial-specific reinstatement, rather than more general and task-relevant category reinstatement. These results are consistent with the hypothesis that hippocampal pattern completion may be biased by recent novelty. As the ventral stream ROIs are robustly connected with the hippocampus, their reinstatement patterns may more closely reflect hippocampal pattern completion than frontoparietal regions. Perhaps this is why their trial-specific ERS, similar to the hippocampus, was analogously modulated by the prior memory experience. These results are less consistent with the retrieval mode account. Category information was most task-relevant in this experiment, and if reinstatement was modulated by goal-maintenance, one would anticipate modulation of category rather than trial information. Further, the retrieval mode is thought to be instantiated by frontoparietal networks, which were insensitive to recent memory experiences. While these results provide some support for our hypotheses, what remains unclear is whether this memory reinstalment bias is mediated through basal forebrain responses.

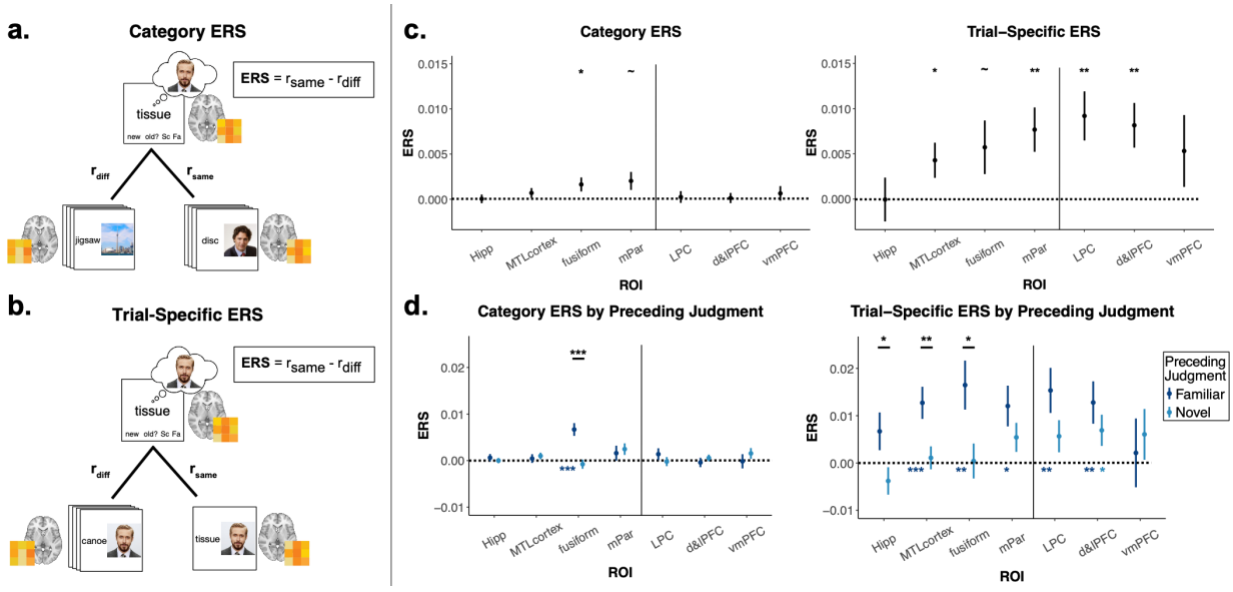

Fig. 3 | Category and Trial-Specific ERS. **a**, Schematic of Category ERS calculation. Activity patterns from probe trials were correlated with encoding trials that included the unprobed associate from the same image category (r_{same}). r_{same} was corrected by subtracting retrieval trials' average correlation with encoding trials that included the unprobed image category (r_{diff}; See *Methods: fMRI data analysis*). **b**, Schematic of Trial-Specific ERS calculation. Activity patterns from probe trials were correlated with patterns from corresponding encoding trials (r_{same}). r_{same} was corrected by subtracting retrieval trials' average correlation with all other encoding that included the same associate (r_{diff}; See *Methods: fMRI data analysis*). **c**, Category and Trial-Specific ERS on probe trials against chance. Points represent intercepts and error bars represent their standard error from a linear mixed effects model (see *Methods: fMRI data analyses*). **d**, Category and Trial-Specific ERS on probe trials as a function of preceding memory experiences. Points represent estimated marginal means and error bars represent their standard error from a linear mixed effects model (see *Methods: fMRI data analyses*). Black stars represent significance of the main effect of preceding memory experiences on broad ERS, while dark and light blue stars represent significance of broad ERS against chance following familiarity and novelty, respectively. ~ indicates $0.10 > p > 0.05$, * indicates $p < 0.05$, ** indicates $p < 0.01$, *** indicates $p < 0.001$. Post-hoc ROI p-values are FDR corrected for multiple comparisons.

Neuromodulatory regions signal familiarity, rather than novelty, that indirectly & directly predicts subsequent neural reinstatement of memories across the brain

We next turned to the neural mechanisms that incite these reinstatement and retrieval biases by analyzing the preceding induction trials. Based on computational models (22, 59), we hypothesized that novelty would evoke stronger basal forebrain activity than familiarity,

resulting in reduced reinstatement on successive probe trials. However, to remain open to other mechanisms, we selected four nuclei that contain dense concentrations of neurons that project neuromodulators throughout the brain (dopaminergic neurons in SN/VTA, noradrenergic neurons in LC, and cholinergic neurons in hippocampally projecting CH123 and neocortically projecting CH4(42, 60–62)). As induction trials consisted of object stimuli, we also analyzed activity in the anterior hippocampus and perirhinal cortex, regions associated with contextual and object novelty signalling (63, 64).

We predicted that each of these ROIs (*induction ROIs*) would respond more when detecting novelty compared to familiarity. This, however, was far from the case. Counter to our hypothesis, CH123 was insensitive to the manipulation (CH123: b = -0.008, SE = 0.020, p = 0.698, 95% CI = [-0.047, 0.031]). The anterior hippocampus displayed the expected novelty preference (b = -0.085, SE = 0.024, p = 0.001, 95% CI = [-0.132, -0.038]), though it was most active during the implicit baseline. This resulted in negative beta estimates, which are common when passive fixation separates memory trials (65). The perirhinal cortex and LC were insensitive to the manipulation (PRC: b = 0.028, SE = 0.022, p = 0.214, 95% CI = [-0.015, 0.071]; LC: b = 0.008, SE = 0.021, p = 0.711, 95% CI = [-0.033, 0.048]). Most surprisingly, the opposite was seen in SN/VTA and the CH4, which responded more when identifying familiarity compared to novelty (SN/VTA: b = 0.086, SE = 0.023, p = 0.001, 95% CI = [0.043, 0.130]; CH4: b = 0.043, SE = 0.020, p = 0.040, 95% CI = [0.004, 0.083]; Fig 4b; SI Appendix, Table S19).

While unexpected from a novelty signalling perspective, a related literature might explain the observed SN/VTA and CH4 familiarity preferences. SN/VTA and CH4 responses have respectively been linked to motivational salience (66, 67) and shifting attentional focus towards motivationally-relevant information (68–70). This begs the question; what goal orientation do

312 participants adopt during retrieval tasks? It has been argued that people see identifying "old"
313 trials as their goal and are less focused on correctly rejecting "new" trials (71, 72) in recognition
314 tasks. Notably, in these tasks, SN/VTA and the highly interconnected striatum preferentially
315 respond to the most motivationally salient trials, regardless of novelty (73, 74). In addition to
316 being the implicit targets in our task, old trials also required more effort than new trials because
317 participants were tasked with recalling associates. Accordingly, elevated SN/VTA and CH4
318 responses to familiarity compared to novelty could reflect participants' feeling of goal attainment
319 and attentional recruitment for effortful memory search. Regardless of the cause, these nuclei's
320 preferential responses to familiar trials position them to mediate the impact of recent familiarity
321 on successive memory reinstatement.

322 To identify potential mediators, we focus on ROIs sensitive to the induction trial
323 manipulation: CH4, anterior hippocampus, and SN/VTA. We asked whether any of these regions
324 predicted subsequent ERS in the ventral stream ROIs that were biased by preceding familiarity.
325 Here, we focus on trial-specific ERS, which appeared to underpin broad ERS effects. We
326 replicate these analyses with broad ERS in the supplement (see SI Appendix, Table S20 & S21).
327 CH4 responses on induction trials did not predict successive ERS, but responses in the two other
328 ROIs did. MTL cortex ERS tended to be weaker following induction trials with high anterior
329 hippocampus activity ($b = -0.004$, $SE = 0.002$, $p < 0.05$, 95% CI [-0.008, 0.000]) and stronger
330 following induction trials with high SN/VTA activity ($b = 0.006$, $SE = 0.002$, $p = 0.001$, 95% CI
331 = [0.002, 0.010]). Moreover, SN/VTA univariate activity was also marginally predictive of trial-
332 specific ERS in the hippocampus ($b = 0.005$, $SE = 0.002$, $p = 0.058$, 95% CI = [<0.001, 0.009];
333 SI Appendix, Table S20). We also explored reinstatement ROIs that did not demonstrate a
334 preceding familiarity bias, and found that SN/VTA activity predicted trial-specific ERS in the

d&lPFC (b = 0.007, SE = 0.002, p = 0.023, 95% CI = [0.002, 0.012]; SI Appendix, Table S21). These results reveal that the SN/VTA may play an important role in preparing ventral and frontoparietal regions to reactivate the details of individual experiences.

We next asked whether anterior hippocampus and SN/VTA univariate activity also mediated the effect of preceding familiarity on memory reinstatement. Here, we again focus on trial-specific ERS (SI Appendix, Table S22 for broad ERS mediation findings). The mediation analyses did not yield significant findings for two of the three pairs: anterior hippocampus activity did not significantly mediate preceding familiarity's effect on MTL cortex ERS (indirect effect (ab) b = 0.003, p = 0.354, 95% CI = [-0.002, 0.010]; total effect (c) b = 0.066, p = 0.020, 95% CI = [0.009, 0.120]; direct effect (c') b = 0.063 p = 0.026, 95% CI = [0.008, 0.110]), nor did SN/VTA activity significantly mediate preceding familiarity's effect on hippocampal ERS (indirect effect (ab) b = 0.004, p = 0.154, 95% CI = [-0.001, 0.010]; total effect (c) b = 0.051, p = 0.078, 95% CI = [-0.007, 0.011]; direct effect (c') b = 0.047, p = 0.100, 95% CI = [-0.010, 0.110]). However, SN/VTA univariate activity partially mediated preceding familiarity's effect on MTL cortex ERS (indirect effect (ab) b = 0.004, p = 0.038, 95% CI = [0.000, 0.010]; total effect (c) b = 0.067, p = 0.020, 95% CI = [0.013, 0.120]; direct effect (c') b = 0.063, p = 0.034, 95% CI = [0.009, 0.120]; Fig 4c; SI Appendix, Table S23). This finding suggests that preceding SN/VTA activity not only predicts upcoming memory reinstatement, it also partially accounts for the power that recent familiarity exerts over memory reactivation.

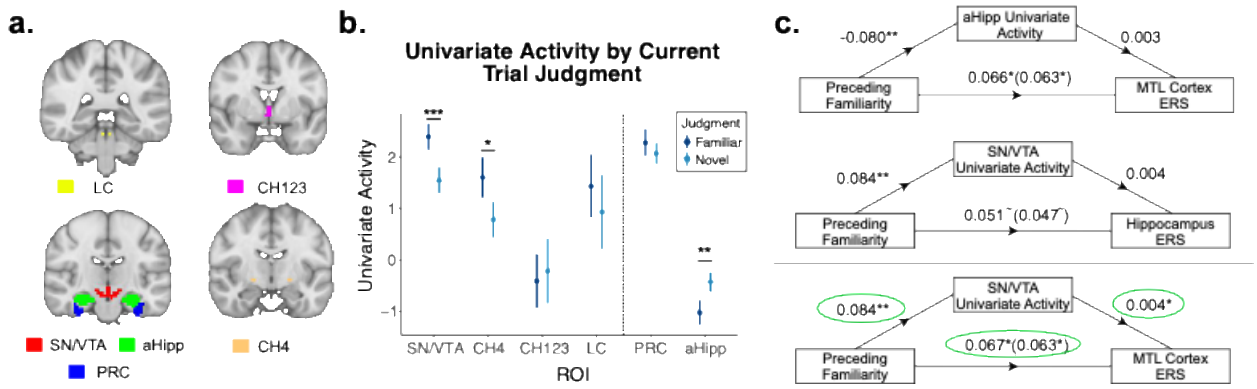

Fig. 4 | Induction ROI Univariate Activity & ERS Relationships. a, Induction ROIs. **b**, Univariate activity on induction trials separated by memory judgments. Points represent mean beta estimates across participants for trials given familiar and novel judgements. Error bars represent the standard error of the mean, applying the Morey (2008) correction for within-participant comparisons. **c**, Analyses testing whether univariate activity in induction trial ROIs mediate the impact of recent memory experiences on reinstatement ROI ERS. Models with circled beta values indicate significant mediation (See *Methods: fMRI data analyses*). ~ indicates $0.10 > p > 0.05$, * indicates $p < 0.05$, ** indicates $p < 0.01$, *** indicates $p < 0.001$.

One lingering question is whether the SN/VTA is particularly involved in preparing ventral and frontoparietal regions to reinstate memories, or whether concurrent interactions may also be at play. Accordingly, we conducted a final set of exploratory analyses investigating whether univariate activity during probe trials related to simultaneous reinstatement. None of our induction ROIs demonstrated significant preferences for experiences of novelty or familiarity (SI Appendix, Table S24), perhaps because of design differences between induction and probe trials (see Discussion). Critically, activity in induction ROIs did not significantly relate to concurrent broad or trial-specific ERS after correcting for multiple comparisons (see SI Appendix, Table S25 & S26). Of note, however, the negative relation between SN/VTA responses and

simultaneous hippocampal trial-specific ERS was significant before this correction (SI Appendix, Table S26), in stark contrast to the positive predictive relationship reported above. On the whole, the null concurrent relations provide important context, highlighting how SN/VTA specifically prepares the brain for memory reactivation, rather than facilitating it in the moment.

Discussion

Here, we explored the cognitive and neural mechanisms that contribute to the variability of memory retrieval. First, we replicated prior reports that recent experiences of novelty compared to familiarity reduce people's upcoming ability to recall associations(47). Then, we asked how novelty influenced the fidelity of upcoming memory reinstatement in the brain. When associative memory was tested following novelty compared to familiarity, patterns of activity in high-level ventral stream regions less closely resembled patterns evoked during corresponding encoding trials. In fact, these regions did not display evidence of memory reinstatement following novelty. Notably, recent novelty tended to modulate granular trial-specific reinstatement, rather than more general and task-relevant category reinstatement. Lastly, we explored whether neuromodulatory nuclei activity on the preceding trial set the stage for upcoming memory reinstatement. Counter to our predictions, no neuromodulatory nuclei of interest signaled novelty. Rather, the SN/VTA and CH4 both preferentially responded to familiar trials. Moreover, SN/VTA responses significantly predicted upcoming reinstatement across frontal and ventral stream ROIs. Most notably, SN/VTA activity partially mediated the effect of recent memory experiences on MTL cortex reinstatement, uncovering a mechanism through which dopamine may prepare the brain to remember.

Our findings revealed how preceding memory experiences powerfully modulate neural memory reinstatement. We used ERS analyses to characterize reinstatement in regions previously shown to reinstate category and/or trial-specific information during retrieval (52–57). Reinstatement in all high-level ventral stream ROIs was biased by preceding memory experiences. The MTL and fusiform cortices both reliably reinstated memories only following familiarity, and while hippocampal reinstatement was stronger following familiarity compared to

400 novelty, it did not reliably exceed chance levels. FMRI signatures of hippocampal reinstatement
401 are inconsistently observed (49–52), despite this region being the source of associative retrieval
402 (75). Some studies suggest that this inconsistency is rooted in the hippocampus only reinstating
403 trial-specific details (50, 52, 76, 77), leaving designs targeting the reinstatement of
404 decontextualized content insensitive to the episodic representations contained in the
405 hippocampus. Our findings somewhat align with this proposal, in that only trial-specific
406 hippocampal ERS was influenced by our novelty manipulation. Our findings also provide new
407 insights into the inconsistency of hippocampal reinstatement. Two of the first studies to find
408 reliable hippocampal reinstatement (78, 79) both only included previously studied items in their
409 retrieval tests. Our findings suggest that omitting novel foils may have amplified hippocampal
410 reinstatement, as each trial in these experiments was experienced following a series of familiar
411 stimuli. More broadly, our findings highlight how neural reinstatement of memories can be
412 surprisingly state dependent, with important implications for the interpretation of previous data,
413 the design of future experimental paradigms, and the understanding of preparatory memory
414 states.

415 Motivated by computational models (44, 80, 81), we hypothesized that preceding
416 novelty-evoked cholinergic nuclei activity would mediate novelty's impact on memory
417 reinstatement. Anchored in rodent physiology, the models propose that increases in cholinergic
418 innervation of the hippocampus following novelty induce a lingering bias away from pattern
419 completion and towards pattern separation (30, 44, 80–82). These predictions have been
420 indirectly supported by prior behavioural research: people are better at forming memories (83)
421 and making fine-grained memory discriminations (84) in the seconds following novelty,
422 consistent with a pattern separation bias. Conversely, people are better at retrieving (47) and

using (83) associative memories in the seconds following familiarity, consistent with a pattern completion bias. Our initial results more directly support prediction: pattern completion-dependent signatures of memory reinstatement were reduced following novelty compared to familiarity in the hippocampus and interconnected ventral stream regions.

However, we failed to observe comprehensive evidence for this mechanism, as cholinergic nuclei did not mediate reinstatement biases. The hippocampally projecting CH123 ROI did not preferentially respond to novel induction trials, and its activity did not predict hippocampal ERS on the following trial ($b = -0.002$, $SE = 0.002$, $p = 0.380$, 95% CI = [-0.006, 0.002]). Several methodological limitations, though, caution against an overinterpretation of these null effects. First, CH3—a region that does not strongly project to the hippocampus—was combined with hippocampally projecting CH1 and CH2 regions in the available probabilistic ROI (62). Second, the compositions of these nuclei are heterogeneous, with cholinergic neurons outnumbered by functionally distinct GABA-ergic and glutaminergic neurons (85). Accordingly, while BOLD responses in CH123 should correlate with hippocampal cholinergic innervation, the relationship is not direct and will not be very strong. By contrast, CH4—the largest basal forebrain nucleus—is composed of approximately 90% cholinergic neurons (86). BOLD activity in this region was sensitive to our task manipulations, showing similar preferences to the SN/VTA, adding to a growing literature that CH4 can be a fruitful target for MRI imaging (87–89). Taken together, while our imaging results did not support the hypothesis that dips in basal forebrain activity prepare the hippocampus to retrieve memories, they also do not undermine decades of relevant research using invasive methods in animals (90–94).

Our imaging results did, however, uncover that DA may play a role in preparing the brain to retrieve. Animal research has convincingly demonstrated that DA is critical for the formation

446 of memories in the hippocampus; pharmacological and optogenetic activation of hippocampal
447 dopamine receptors around the time of memory formation enhances later expression of these
448 memories (95–99). By contrast, similar manipulations applied around the time of retrieval do not
449 influence memory performance (98), leading to the general consensus that DA is important for
450 the formation, but not retrieval of hippocampal memories (100). However, studies that measure
451 or manipulate DA more systemically—rather than targeting the hippocampus—have yielded
452 mixed results. In both humans and animals, retrieval performance has been positively linked to
453 pharmacological manipulations and SN/VTA activity in some studies (39, 101–105), while others
454 found no relation (95, 100, 106–109). These findings suggest that DA may facilitate retrieval
455 under some circumstances via extra-hippocampal targets. Our results further inform this mixed
456 literature. We observed that SN/VTA responses positively predict memory reinstatement on
457 successive, but not concurrent, trials. While pharmacological manipulations can more directly
458 assess DA, they lack the temporal specificity to delineate these complex relations across time. By
459 providing temporally precise evidence linking SN/VTA activity to retrieval dynamics, our results
460 refine existing models of DA's role in memory and suggest future avenues for investigation using
461 invasive and non-invasive techniques.

462 Elements of how the SN/VTA prepares the brain to remember may align with retrieval
463 mode mechanisms. Firstly, this region was more responsive on trials that strongly recruit the
464 retrieval mode, preferentially responding to familiar induction trials. These trials likely elicited
465 strong retrieval goal-maintenance, as participants commonly see detecting familiarity as their
466 primary job in recognition tasks (71, 72). Further, familiar trials also required strong attentional
467 and control orientations toward retrieved content, as participants needed to recall associations.
468 This preferential responsivity, however, was not seen on probe trials. Multiple experimental

design factors might explain why probe trials were less sensitive than induction trials, including stimulus class differences, shorter anticipatory delays blunting DA neuron ramping (110, 111), and the predominance of old trials. The latter point could have both reduced statistical power and made the rare new trials more salient. Secondly, unlike the novelty/familiarity manipulation, SN/VTA activity predicted upcoming reinstatement in both high-level ventral and frontal regions. In particular, SN/VTA activity predicted reinstatement in the dorsal and lateral portions of the PFC. These regions are heavily involved in executive functioning, particularly attending to goal-relevant information and shifting between internally and externally oriented attention (112, 113), and have been implicated in the retrieval mode (114). SN/VTA's preferential signaling to motivationally relevant familiar experiences, as well as its relationship with upcoming reinstatement in both ventral and frontal regions, suggest that it may play a role as a catalyst of the retrieval mode.

Pulling these potential mechanisms together, our results raise the possibility that variability in memory retrieval may be best understood by considering interactions between pattern completion and retrieval mode biases. At any given moment, ongoing hippocampal states may make it easier or harder for the region to reinstate specific episodic memory traces. For example, the details of specific memories were more fluently reactivated across connected ventral stream regions when in a state triggered by recent familiar trials. But reinstatement also depends on recent SN/VTA engagement. These dopaminergic nuclei may directly facilitate hippocampal pattern completion, though there is little physiological evidence for this mechanism (100). Alternatively, or additionally, SN/VTA engagement could support goal maintenance and appropriate attentional orientations. In this way, SN/VTA activity, and the retrieval mode it potentially fosters, could boost retrieval-relevant input to the hippocampus as well as its pattern

completed output. Future research designed to measure the retrieval mode could explore this possibility in more detail.

In sum, our findings reveal that the fidelity of memory reinstatement is dynamically shaped by recent experiences and neuromodulatory states, providing new insights into the long standing puzzle why our memory retrieval abilities are so variable across time. We show that preceding familiarity, compared to novelty, enhances neural reinstatement across high-level ventral stream regions. While we found limited evidence for cholinergic modulation of reinstatement, our results highlight a potential role for dopamine in fostering a retrieval mode that facilitates memory reactivation. These findings advance our understanding of the state-dependent nature of memory retrieval and point to an emerging framework in which hippocampal pattern completion and retrieval goal maintenance are jointly modulated by recent experience and neuromodulatory tone. We hope that our work will inspire new research into this dynamic account of episodic memory retrieval, probing how this foundational ability is deeply shaped by ongoing mental and neural states.

Resource Availability

All post-processed data and code used to run analyses can be found at https://doi.org/10.17605/OSF.IO/UY9ZV.

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Author Contributions

MD led formal analysis, visualization, data curation, writing- draft. and writing- review & editing. AP led investigation, methodology, and project administration. AP & MD contributed equally to software. KDD led supervision, funding acquisition, and resources. AP & KDD led conceptualization. MD, AP, and KDD contributed equally to validation.

Declaration of Interests

The authors declare no competing interests.

Materials & Methods

Participants

Forty-four adults were recruited via convenience sampling from the University of Toronto community through online advertisements and flyers. Two participants withdrew from the study before completing all experiment tasks. Data from 13 participants were excluded from analyses due to previously participating in the study (n = 1), showing signs of drowsiness (n = 3), failing to follow instructions to stay still inside the scanner (n = 1), moving excessively during the study (framewise displacement > 0.3 mm for more than 10% of the volumes on the retrieval and word encoding tasks and 20% of the volumes on the localizer task; n = 1), vision issues (n = 1), or lower than chance performance on the associative memory task (n = 6). Participants were categorized as having lower than chance performance if a binomial test demonstrated that significantly over half of associative judgments were source errors. The final analyses included 29 participants (21 self-identified females, 7 self-identified males, 1 declined to answer, mean age = 22.9 years [19, 30], mean years of education = 16.43 [13, 22]). Participants identified their race and ethnicity as follows: Japanese/Korean/Chinese (10), Indian/Pakistani/Sri Lankan (8), White (5), Bangladeshi (1), Vietnamese (1), Mixed (Black & White 1, White & Chinese 1), Euroasian (1), and Declined to Answer (1). Participants were right-handed, fluent in English, had normal or corrected-to-normal vision, and had no history of psychiatric, neurological, or learning disorders. Demographic information regarding gender, socioeconomic status, and ancestry were not collected. Convenience sampling resulted in uneven groupings of participants by race/ethnicity and self-identified sex, and as such, we were not sufficiently statistically powered to analyze whether these variables influenced our study's main results. The racial and ethnic

heterogeneity of the University of Toronto community resulted in a diverse sample, increasing generalizability across race and ethnicity. However, the skew of self-identified sex towards female may limit sex-based generalizability. Participants gave written informed consent and were compensated $20-25 CAD/hour for their participation. All experimental procedures were approved by the University of Toronto Research Ethics Board (REB).

Stimuli

Stimuli consisted of colored images of 144 common objects (115), two faces of famous individuals (Justin Trudeau, Ryan Gosling, derived from Google Search), two famous Canadian landmarks (CN Tower, Niagara Falls, derived from Google Search), 192 object nouns, and two adjectives ("Plain" and "Safe"). The set of object nouns were selected to not overlap with the images of common objects. For example, if an image of a violin was a part of the 144 object images, the word "violin" was not included in the set of 192 object nouns. Stimuli were presented using PsychoPy (116) on an MR-compatible BOLDscreen monitor (32", 1920 x 1080) placed behind the scanner. Participants viewed the stimuli through a system of mirrors installed on the head coil. Another image set of objects, faces, places, and scrambled objects were presented in a functional localizer with Matlab & PsychToolbox, but this data is not reported here (see Localizer Tasks).

Procedure

Patil & Duncan (2018) demonstrated that the effect of recent novelty on associative memory declines over seconds. Studying this effect necessitates the use of short intertrial intervals (ITIs) during retrieval. However, consistently short ITIs pose challenges for statistically

disambiguating responses to consecutive trials due to the slow BOLD response (117). To resolve this issue, we (a) arranged trials into pairs of novelty/familiarity induction trials and successive probe trials, on which we measured neural reinstatement, (b) fixed the ITIs within trial pairs to 1 second, and (c) orthogonalized content across these two kinds of trials. Specifically, we used images of objects to induce novelty/familiarity. During probe trials, we tested how well participants retrieved a face or a scene when probed with a previously associated word. This alternating pattern, where each pair of trials consisted of independent content, allowed us to estimate how preceding memory experiences influence successive neural reinstatement (see Fig. 1a). To increase the sensitivity of our reinstatement analyses, we included 5 second fixation periods between retrieval pairs.

The experiment consisted of multiple blocks of encoding, retrieval, and localizer tasks. All tasks were completed inside the MRI scanner. Participants were given instructions and practiced all tasks outside of the scanner until they were comfortable with each task. Participants were aware that their memory for stimuli would be tested before they started the experiment.

Encoding Blocks

Participants completed two encoding tasks, corresponding to the induction and probe retrieval trials: object encoding and word encoding, respectively. Their order was counterbalanced across participants.

Object Encoding

Participants were shown a series of object images (72 randomly selected from a pool of 144) paired with one of two repeating words, “Plain” or “Safe,” and asked to imagine a scenario

in which the word could describe the image. This task was chosen to encourage deep encoding of the object-word pairs. The presentation order of objects was intermixed such that the repeating word associate would not repeat across more than three consecutive trials, and the pairing of each object image with "Plain" or "Safe" was randomized for each participant. Each pair was shown for 2.5 seconds. Participants were then given 1.5 seconds to rate the vividness of the association on a 4-point scale of "very vivid" to "not vivid at all," followed by a 1-second fixation cross. Participants completed one 6.2-minute block of the object encoding task. The memories formed during object encoding were always used to induce novelty/familiarity during retrieval. fMRI data from the object encoding blocks were not analyzed.

Word Encoding

Participants were shown a series of words (96 object-nouns randomly selected from a pool of 192) paired with one of four repeating images of famous landmarks (CN Tower, Niagara Falls) or celebrities (Ryan Gosling, Justin Trudeau). Each image was presented twenty-four times across the two encoding blocks, and the presentation order of images was intermixed such that the image category would not repeat across more than three consecutive trials. The pairing of each word with the repeating images was randomized for each participant. The word was presented on the left side of the screen for 1.5 seconds, followed by one of the four repeating images on the right. The pair together was shown for 2.5 seconds, resulting in 4 second trials. For words paired with a scene, participants were asked to imagine themselves in that scene using that object from a first-person perspective. For words paired with a face, participants were asked to imagine the celebrity using that object against a white background. Participants were then given 1.5 seconds to provide their vividness rating, followed by a 4.5 second fixation cross.

Participants completed two 8.2-minute blocks of the word encoding task. Encoding trials in each block were evenly split between scenes and faces. The memories formed during word encoding were used to measure reinstatement during retrieval, and as such, we used a longer ITI than in the object encoding task to facilitate estimates of single-trial fMRI responses.

Retrieval Session

Participants completed an associative retrieval session with alternating induction (72 old and 72 new objects) and probe (48 old face-associated, 48 old scene-associated, and 48 new words) trials. Note that we include twice as many old probe trials compared to new because reinstatement can only be measured on old trials. New stimuli were also randomly selected from the same stimulus pools for each participant, excluding the encoded, old stimuli. Trial order was pseudorandomized such that an equal number of “old” and “new” induction trials preceded “old” probe trials, with no more than three consecutive “old” or “new” trials. During each retrieval trial, an object or word was shown on the screen for 2 seconds. Participants were asked to indicate if the object/word was new (by pressing the thumb key) or old, in which case, they were asked to recall the paired associate. For the object trials, the associate responses were Plain (middle finger key) or Safe (ring finger key). For the word trials, the associate responses were Scene (middle finger key) or Face (ring finger key). Participants were asked to press the index finger key if they recognized the object/word but were unable to recall its associate (labelled “old?”). Response options were presented at the bottom of the screen in an intuitive order to help participants remember the mappings. A 1-second and 5-second fixation cross followed each induction and probe trial, respectively. Participants completed four 6.2-minute retrieval blocks.

Localizer tasks

After the retrieval blocks, participants completed two functional localizer tasks. Both are beyond the scope of the current project, but we analyzed behavioural data from one condition of the second localizer. In this retrieval mode localizer, participants made one of three judgments in response to a presented word: whether the real-world cost of the object was expensive or cheap (semantic), whether the object word was previously shown in the preceding retrieval session or novel (recognition), and whether the font color changed or remained the same (sensory). Across tasks, half of the words were old (i.e., first seen as novel foils during retrieval probe trials) and half were new (i.e., the remaining 48 words from the pool of 192). Words were presented for a maximum of 2 seconds. At the end of the 2 seconds, participants saw a fixation cross for 3 seconds before beginning the next trial. We analyzed the 32 recognition judgments (16 old and 16 new words) made across two blocks.

Behavioural data analysis

All analyses were conducted in R (version 4.0.2). Linear mixed effects models were used to reflect the hierarchical nature of our data in which multiple trials are clustered within participants. These models were run with unstructured covariance matrices (lmer function in *lme4* package, version 1.1-23(118) with uncorrelated random intercepts and slopes for each within-participant fixed effect varying across participants. We estimated the marginal means of predictors to evaluate their simple effects (*emmeans* package, version 1.11.0(119)).

We categorized induction trials according to participants' subjective memory judgements. If they responded with "new," trials were considered inductions of novelty; if they recognized the objects, regardless of their associative retrieval success, trials were considered inductions of

familiarity. We also divided probe trials to focus on our pattern completion hypothesis. Specifically, we obtained independent measures of associative memory (pattern completion dependent) and item-only recognition memory (comparatively pattern completion independent). To do this, we calculated associative accuracy only on probe trials where participants correctly recognized words as "old," and item-only recognition memory on trials where participants failed to recall the correct association.

We ran a binomial linear mixed effect model to examine the influence of preceding experiences (novelty vs. familiarity on induction trials) on successive probe trial associative memory accuracy. Associative accuracy was dummy coded in these models, where correct associative judgments were coded as 1 and incorrect associative and "old?" judgments were coded as 0. For these and all following models, we effect coded the preceding judgment predictor (*preceding judgement*: novelty as -1; familiarity as 1). We added a covariate to correct for potential response priming, indicating whether the correct associative response on the probe trial was the same as the participants' response on the preceding trial (*response bias*: dummy coded, unaffected probe trials as 0; affected probe trials as 1). In addition, we ran a separate model to control for the effects of current trial stimulus class ("Scene" or "Face", *stimulus class*) and the preceding trial response time (*preceding response time*). Stimulus class was effect coded ("Scene" as -1; "Face" as 1). Preceding response time was z-scored across all induction trials within each participant. We used a paired sample t-test to assess the impact of preceding judgement on item-only recognition accuracy. We calculated d' (z(hit rate) – z(false alarm rate)) for each participant separately for probe trials preceded by novelty and familiarity.

We ran a linear mixed effect model to examine the influence of preceding judgment on accurate probe trial response time. We used an inverse gaussian log linking function to account

for the shape of the response time distribution. In addition to preceding judgement, we included four covariates: Response bias, stimulus class, retrieval block number (*centered block number*) and trial number (*scaled trial number;* z-scored within block*)*. The latter two were included to control for task fatigue/learning.

As previously stated, recognition for a subset of probe trial novel foils was tested in a retrieval mode localizer. We ran a binomial linear mixed effect model to determine if judgments made on preceding induction trials affected participants' learning of these words. "Old" trial recognition accuracy during the retrieval mode localizer was dummy coded (misses as 0; hits as 1). Preceding judgment and response bias were included as predictors.

fMRI data acquisition

Whole-brain imaging data were acquired on a Siemens Prisma 3T MRI scanner at the Toronto Neuroimaging Facility (ToNI) of the University of Toronto using a 32-channel head coil. Functional images were collected using a T2*-weighted multi-band accelerated EPI sequence (TR = 1.5 s, TE = 26 ms, flip angle = 70º, GRAPA parallel imaging factor = 2, multiband acceleration factor = 2, distance factor = 20%, field of view = 220 mm, matrix size = 88 x 88, 54 slices oriented parallel to the anterior commissure-posterior commissure line, voxel size = 2.5 x 2.5 x 2.5 mm). One field map was collected (TR = 888 ms, TE 1 = 4.92 ms, TE 2 = 7.38 ms, flip angle = 60º, voxel size = 2.5 x 2.5 x 2.5 mm) to correct EPI images for susceptibility-induced distortions. In addition, one anatomical T1-weighted 3D magnetization-prepared rapid gradient echo (MPRAGE) image (TR = 2 s, TE = 2.67 ms, flip angle = 9º, field of view = 256 mm, matrix = 256 x 256, voxel size = 1 x 1 x 1 mm) was also collected.

714 ***Neuroimaging data processing***

715 Preprocessing was performed using fMRIPrep 1.2.5 (120, 121), which is based
716 on Nipype 1.1.6 (122, 123).

717

718 *Anatomical data preprocessing*

719 The T1-weighted (T1w) image was corrected for intensity non-uniformity (INU)
720 using N4BiasFieldCorrection (ANTs 2.2.0(124)) and used as T1w-reference throughout the
721 workflow. The T1w-reference was then skull-stripped using antsBrainExtraction.sh (ANTs
722 2.2.0), using OASIS as the target template. Spatial normalization to the ICBM 152 Nonlinear
723 Asymmetrical template version 2009c (125, 126) was performed through nonlinear registration
724 with antsRegistration (ANTs 2.2.0(127)), using brain-extracted versions of both T1w volume and
725 template. Brain tissue segmentation of cerebrospinal fluid (CSF), white-matter (WM) and gray-
726 matter (GM) was performed on the brain-extracted T1w using FAST (FSL 5.0.9(128, 129)).

727

728 *Functional data preprocessing*

729 The first 4 volumes (6 s) of each of the task BOLD scans were removed to allow for
730 scanner magnet stabilization. For each of the BOLD runs per participant (across all tasks), the
731 following preprocessing was performed. First, a reference volume and its skull-stripped version
732 were generated using a custom methodology of fMRIPrep. A deformation field to correct for
733 susceptibility distortions was estimated based on a field map that was co-registered to the BOLD
734 reference, using a custom workflow of fMRIPrep derived from D.
735 Greve's epidewarp.fsl script (https://www.nmr.mgh.harvard.edu/~greve/fbirn/b0/epidewarp.fsl)
736 and further improvements of HCP Pipelines (130). Based on the estimated susceptibility-induced

distortion, an unwarped BOLD reference was calculated for a more accurate co-registration with the anatomical reference. The BOLD reference was then co-registered to the T1w reference using FLIRT (FSL 5.0.9(131)) with the boundary-based registration (132) cost-function. Co-registration was configured with nine degrees of freedom to account for distortions remaining in the BOLD reference. Head-motion parameters with respect to the BOLD reference (transformation matrices, and six corresponding rotation and translation parameters) were estimated before any spatial transformations using MCFLIRT (FSL 5.0.9(133)). The BOLD time-series were resampled onto their original, native space by applying a single, composite transform to correct for head-motion and susceptibility distortions.

The BOLD time-series were resampled to MNI152NLin2009cAsym standard space, generating a preprocessed BOLD run in MNI152NLin2009cAsym space. All resamplings were performed with a single interpolation step by composing all the pertinent transformations (i.e. head-motion transform matrices, susceptibility distortion correction, and co-registrations to anatomical and template spaces). Gridded (volumetric) resamplings were performed using *antsApplyTransforms* (ANTs (134)), configured with Lanczos interpolation to minimize the smoothing effects of other kernels (135). Lastly, functional images were further spatially smoothed using a Gaussian kernel of 2mm full-width at half-maximum in FSL.

Several confounding time-series were calculated based on the preprocessed BOLD. Framewise displacement (FD) and DVARS were calculated for each functional run, both using their implementations in Nipype(136). Additionally, a set of physiological regressors were extracted to allow for component-based noise correction (CompCor(137)). Principal components were estimated after high-pass filtering the preprocessed BOLD time-series (using a discrete cosine filter with 128s cut-off) for anatomical CompCor (aCompCor). Firstly, a subcortical mask

was obtained by heavily eroding the brain mask, which ensured it did not include cortical grey matter (GM) regions. Six aCompCor components were then calculated within the intersection of the aforementioned mask and the union of cerebrospinal fluid (CSF) and white matter (WM) masks calculated in T1w space, after their projection to the native space of each functional run (using the inverse BOLD-to-T1w transformation). The head-motion estimates calculated in the correction step were also placed within the corresponding confounds file.

Many internal operations of fMRIPrep use Nilearn 0.5.0 (138), mostly within the functional processing workflow. For more details of the pipeline, see the section corresponding to workflows in fMRIPrep's documentation (https://fmriprep.org/en/1.2.5/workflows.html).

ROI selection

To measure reinstatement, we defined four *a priori* ROIs (Fig. 2a) that have previously been shown to reinstate trial-specific and category information (52, 53, 55, 56): whole hippocampus, medial temporal lobe cortex (MTLcortex), fusiform cortex (fusiform), and medial parietal cortex (mPar). After conversations with colleagues, we added three additional frontoparietal *post-hoc* ROIs (Fig. 2a) that have previously been shown to reinstate trial-specific or category information (54, 55, 57): lateral parietal cortex (LPC), dorsal & lateral prefrontal cortex (d&lPFC), and ventromedial prefrontal cortex (vmPFC). We refer to all seven of these regions as *reinstatement ROIs*. To measure novelty/familiarity responses during the induction trials, we evaluated six *a priori induction ROIs* (Fig. 4a): basal forebrain medial septum and the diagonal band of Broca (CH123), basal forebrain nucleus basalis (CH4), substantia nigra and ventral tegmental area (SN/VTA), locus coeruleus (LC), anterior hippocampus (aHipp), and perirhinal cortex (PRC). The probabilistic atlases and thresholds used for each brain region are

783 listed in SI Appendix, Table S3. All masks were defined in T1 MNI space and resampled to the
784 functional MNI space.
785
786 ***Generating Single Trial Estimates***
787 GLMs were constructed for each of the 96 word encoding and 288 retrieval trials to
788 estimate single-trial beta values. This was done using the LS-S method (139) implemented in
789 *FSL* with *Nipype* (version 1.8.5) and in custom Python (version 2.7) scripts in which separate
790 GLMs were conducted for each trial. These GLMs included a regressor for the trial of interest,
791 and responses to all other trials were modelled together with a second regressor. Each trial was
792 modelled at stimulus onset (for word encoding, the time when the word and the image were first
793 displayed together) using a 2.0-second (retrieval task) or a 2.5-second (word encoding task)
794 boxcar function convolved with a double-gamma hemodynamic response function. In addition to
795 these primary regressors of interest, each GLM also included the following nuisance regressors:
796 the temporal derivatives of six motion estimates and six aCompCor motion components.
797 Volumes for which the framewise displacement was greater than 0.3 mm were added as spike
798 regressors in the GLMs.
799
800 ***fMRI data analysis***
801 We obtained three estimates of neural reinstatement that differed in their levels of
802 specificity. The first (broad ERS) estimated both category information of the trial (required to
803 make a retrieval judgment; “Scene” vs. “Face”), as well as specific information about the trial
804 itself (the specific scene/face and its association with the probed word). The second (category
805 ERS) estimated only the reinstatement of the trial category, while the third (trial-specific ERS)

806 estimated only the reinstatement of each trial's specific association. For each ERS measure, we
807 calculated two Pearson correlations and operationally defined ERS as the difference between
808 them ($r_{same} - r_{diff}$). For broad ERS, activity patterns from probe trials were correlated with
809 patterns from corresponding encoding trials (r_{same}) and corrected by subtracting retrieval trials'
810 average correlation with encoding trials that included the unprobed image category (e.g., scenes
811 if the retrieval trial probed a face; r_{diff}; Fig. 2b). For category ERS, activity patterns from probe
812 trials were correlated with encoding trials that included the unprobed associate from the same
813 image category (e.g. if the retrieval probe was studied with Ryan Gosling, all Justin Trudeau
814 encoding trials; r_{same}) and corrected by subtracting retrieval trials' average correlation with
815 encoding trials that included the unprobed image category (e.g., scenes if the retrieval trial
816 probed a face; r_{diff}; Fig. 3a). For trial-specific ERS, activity patterns from probe trials were
817 correlated with patterns from corresponding encoding trials (r_{same}) and corrected by subtracting
818 retrieval trials' average correlation with all other encoding that included the same associate (e.g.,
819 if tissue were the probe, all Ryan Gosling encoding trials except for Ryan Gosling + tissue; r_{diff};
820 Fig. 3b). For all ERS analyses, we Fisher z-transformed correlation coefficients and only
821 included probe trials on which participants correctly recognized words as "old."

822 We ran a linear mixed effect model for each ERS measure to examine whether regions
823 significantly reinstated learned information. We included response bias as a covariate in all ERS
824 analyses, as it significantly related to ERS in several reinstatement ROIs (SI Appendix, Table
825 S5).

826 We tested whether preceding memory experiences (novelty vs. familiarity) influenced
827 ERS on probe trials in each of the reinstatement ROIs using linear mixed effects models.
828 Preceding judgment and response bias were included as covariates. We ran an additional model

for each ROI to control for the effects of each trial's *accuracy* and *response time*. Accuracy was effect coded (accurate trials as 1; inaccurate trials as -1), while response time was z-scored across all probe trials for each participant.

We were interested in whether category ERS significantly related to participants' associative accuracy, as category information was needed for correct judgments ("Scene" vs. "Face"). We ran a generalized linear mixed effects model for each of our *a priori* reinstatement ROIs predicting whether associative accuracy significantly related to category ERS. Each model included Fisher z transformed category ERS, response bias, and preceding judgment as covariates.

To evaluate whether induction ROIs preferentially responded to experiences of familiarity or novelty, we ran linear mixed effects models predicting average univariate signal, z-scored within participant. Each model included the current trial judgment (*judgment*) as a predictor, effect coded with novelty as -1 and familiarity as 1. We ran additional follow up analyses exploring this on probe trials using models with identical structure.

To determine whether induction trial univariate signal in our induction ROIs predicted successive reinstatement, we ran linear mixed effect models predicting trial-by-trial ERS estimates in each of our reinstatement ROIs. Each model included univariate signal on the preceding induction trial in each of the induction ROIs, z-scored within participant, and response bias as predictors. We ran additional follow up analyses using models with identical structure evaluating the relationship between concurrent probe trial univariate activity in induction ROIs and ERS, rather than successive relationships.

We then performed multilevel mediation analyses using *lme4* (version 1.1-23) and *mediation* (version 4.5.0) packages in R (version 4.0.2) to assess if univariate signal in induction

ROIs (mediator) mediated the effects of preceding judgments (independent variable; IV) on successive ERS (outcome). To establish mediation, there must be evidence for all pair-wise relations. Only three pairs of ROIs met this criteria: SN/VTA induction trial activity as a mediator for preceding judgement on hippocampal and MTL cortex ERS, as well as anterior hippocampus induction trial activity as a mediator for preceding judgement on MTL cortex ERS (ultimately, these models were run for both broad and trial-specific ERS estimates). The following multilevel models were run as part of the mediation:

Model (1): Influence of preceding judgment on univariate activity in induction ROI (mediator ~ IV)

Model (2): Influence of preceding judgment and univariate activity in all of the induction ROIs on successive ERS (outcome ~ IV + mediator).

These models were run on data that included correctly recognized probe trials only. Response bias was included as a covariate in Model (2). Both univariate activity and ERS estimates were z-scored within participant for these models.

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