Medial temporal lobe lesions reduce visual working memory precision

Yoojeong Choo,[1,†] Sanikaa P. Thakurdesai,[1,†] Asbah Qadri,[1] Oceane E. Fruchet,[2] Samantha N. Jackson,[2] Radhika Chatterjee,[2] Sara K. Inati,[2] Kareem A. Zaghloul[2] and Weizhen Xie[1,2,3]

[†]**These authors contributed equally to this work.**

Abstract

Classic lesion case-control studies suggest minimal involvement of the medial temporal lobe (MTL) in visual working memory (VWM), particularly for simple stimulus features like color or orientation. However, recent intracranial recordings implicate the MTL – especially the hippocampus – in supporting VWM precision by distinguishing similar visual features to reduce representational variability during short retention intervals. Meanwhile, reports that MTL activity scales with VWM set size have raised the possibility that the MTL contributes not only to the quality but also the quantity of retained VWM content – an idea motivated by models positing a unitary memory strength metric to account for behavioral expressions of both VWM quantity and quality.

To clarify the extent to which MTL lesions affect VWM quality, quantity, or both, we examined VWM recall performance in 40 neurological cases with drug-resistant epilepsy before and after their brain surgery for seizure treatment. Of these, 19 had lesions involving the hippocampus, while 21 had either no lesions or lesions outside the hippocampus. Using a controlled VWM task with fixed set size and minimal non-target recall errors, we modeled participants' recall responses to estimate recall variability as an inverse measure of VWM precision and the probability of recall success as the proportion of trials not attributable to failed, uniform recall responses.

We found that lesions affecting the hippocampus in the MTL led to a significant increase in recall variability, indicating reduced VWM precision after surgery. Voxel-based lesion-symptom mapping further revealed a robust association between hippocampal damage and increased recall variability, even after controlling for overall brain lesion volume. In contrast, total lesion volume

– but not hippocampal lesion extent – predicted reduced recall success rate, suggesting that broader lesion burden constrains how much content is retained, resulting in more failed recall responses. An alternative model assuming a unitary memory strength metric captured the overall performance decline with increasing total lesion volume but could not account for the MTL-specific effects.

Together, these findings highlight the MTL's role in preserving the fidelity – rather than the mere presence – of VWM representations. They challenge models that treat VWM quality and quantity as interchangeable consequences of a single underlying memory strength parameter. By identifying distinct neural correlates for each component, our results point to VWM precision as a sensitive behavioral marker – one that may be useful for tracking functional changes in individuals with memory impairment, including those with focal brain lesions.

Author affiliations:

1 Department of Psychology, University of Maryland, College Park, MD 20742, USA

2 Surgical Neurology Branch, NINDS, National Institutes of Health, Bethesda, MD 20892, USA

3 Department of Neurosurgery, University of Maryland, Baltimore, MD 21201, USA

Correspondence to: Weizhen Xie

Department of Psychology, University of Maryland, College Park 2123L Biology-Psychology Building, 4094 Campus Dr., College Park, MD 20742, USA

E-mail: zanexie@ume.edu

Correspondence may also be addressed to: Kareem Zaghloul

Surgical Neurology Branch, NINDS, National Institutes of Health, Bethesda, MD 20892, USA

E-mail: kareem.zaghloul@nih.gov

Running title: MTL and visual working memory

Keywords: visual working memory, quality, precision, medial temporal lobe, hippocampus

Introduction

The ability to distinguish between similar memories – known as pattern separation[1] – is closely tied to the precision or quality of stored memory representations[2,3]. This ability declines markedly with age[4], often manifesting as increased recall variability in memory tasks, regardless of retention interval[5–9]. Such declines in long-term memory (LTM) are typically attributed to compromised medial temporal lobe (MTL) function[4], particularly within the hippocampus[10], where aging may disrupt the sparse activation of granule cells that normally reduce interference among overlapping neocortical inputs[2,11,12]. However, the extent to which the MTL also supports the precision of visual short-term/working memory (VSTM/VWM) has remained a debated question[13–15]. Traditional research has viewed the MTL as specialized for LTM[13,16], whereas VWM is thought to rely on a distributed network of neocortical regions[17], often excluding the MTL. This view is supported by lesion case studies showing that MTL damage typically does not impair overall rates of VWM recall or recognition success[18–21]. Indeed, many prior reports of MTL involvement in VWM have been attributed to LTM contributions during ostensibly VWM tasks[13,21].

However, recent human intracranial EEG studies challenge this dichotomy, demonstrating that activity within the MTL's entorhinal-hippocampal circuit can differentiate between similar VWM items maintained over brief intervals (<1 s) and predict immediate recall precision[15]. These effects emerge even under minimal VWM load using simple stimuli prone to interference (e.g., colored squares from a small, repeated set)[15] – conditions typically designed to minimize LTM involvement while promoting active memory maintenance[22,23]. Given that VWM precision is dissociable from the overall rate of recall or recognition success[24–26], it has therefore been hypothesized that the MTL – particularly the hippocampus – supports the quality of VWM representations[3,23,27,28], even if it is not required for maintaining the quantity of retained information in VWM[18].

Despite these recent advances, key questions remain about the MTL's role in VWM[29]. For instance, direct recording from the MTL has demonstrated that increasing VWM load via set

size manipulations often elicits greater hippocampal activation[30–32]. However, given that set size can affect various aspects of VWM representations, this activation could reflect changes in the number of stored items (quantity)[33,34], associations across multiple items/features[35–37], reduced precision (quality)[38,39], or some combination thereof[24–26]. While mixture models are designed to dissociate these components[24,25,37], their respective neural correlates remain difficult to disentangle[15,40,41], especially in lesion control case studies with small sample sizes and heterogeneous task designs[14,15,35]. For example, given the MTL's role in representing associative, complex information[42–46] , increased VWM recall error in MTL damage cases may be attributed to a tendency to report the property of the wrong item stored in memory – namely misbinding[37], rather than simple degradation of memory precision[35]. Adding to this complexity, some theoretical accounts propose that VWM recall is driven by a single, continuous memory strength signal[47], rather than separable components such as quality, quantity, or misbinding[24–26,37]. Whether such a unitary process model can explain the MTL's contribution to VWM remains largely unresolved[3,48]. These uncertainties present a central challenge for the necessity of the MTL – especially the hippocampus – in supporting the quality of VWM representations.

To address these issues, we extend prior work using a VWM continuous recall paradigm in MTL lesion case studies[14,15,35] by examining VWM recall performance on a simple visual feature – namely color – in 40 individuals before and after neurosurgical treatment for epilepsy (**Figure 1A**). We implemented several design improvements to mitigate limitations in earlier studies. First, to reduce confounding effects of individual differences that may complicate lesion case-control comparisons[49], we compared outcomes both within each participant before and after their brain resection surgery and between patients who underwent resection affecting the hippocampus and those with extra-hippocampal or no lesions (see **Figure 1B** for lesion locations). In addition to this mix-effects design, we also conducted voxel-based lesion-symptom mapping[50] across all participants to identify key brain regions whose removal predicted changes in VWM performance. Finally, to isolate the effect of MTL lesions on representational precision rather than VWM quantity or misbinding errors, we used a color recall task with a fixed set size that required participants to report the color of a studied item following a brief delay[24,51] with non-target colors present in the test display (**Figure 1A**). This manipulation reduces the likelihood of misbinding by encouraging participants to report the remembered color instead of mistakenly reporting a non-target color[36,52]. Together, these design choices enabled us to test

whether MTL involvement in VWM is better captured by a mixture versus a unitary process model of VWM representations.

In the mixture model framework[24,25], minimizing misbinding errors under a fixed memory set size allows changes in memory quality to be isolated [37]. If the MTL primarily supports the quality of VWM, then its removal should lead to increased recall variability – that is, reduced VWM precision – without affecting the rate of random, failed recall responses (upper left panel, **Figure 1C**). Conversely, if the hippocampus contributes to VWM quantity, its removal should decrease the overall amount of retained information, resulting in more failed recall responses (lower left panel, **Figure 1C**). Alternatively, a unitary memory strength model[47] may account for lesion-induced changes in VWM recall performance (see **Supplementary Figure S1**), without requiring distinctions between different aspects of VWM representations in driving recall responses[3].

To adjudicate among these possibilities, we leveraged our larger sample (n = 40) – a 1.5-fold increase over our original study (n = 16)[15] – and conducted both region-of-interest (ROI) based comparisons between lesion groups and voxel-based lesion-symptom mapping across all participants[50]. Both approaches revealed a selective decline in VWM precision following damage to hippocampal tissues within the MTL. In contrast, the rate of recall failures was associated only with total lesion volume, likely reflecting attentional lapses[53] due to broader cortical disruption[54]. Although a unitary memory strength model[47] could account for the overall reduction in task performance[3], it fails to capture any MTL-specific effects. Together, these findings highlight the critical role of the MTL – particularly the hippocampus – in supporting the quality of VWM representations captured by the mixture model[24,25], underscoring the value of lesion-based evidence[49] in delineating distinct neural constraints on VWM.

Materials and methods

Participants

Forty neurological patients (34.73 ± 1.74 years old [mean ± s.e.m.]; 18 female; Wechsler IQ = 89.00 ± 2.17; **Supplemental Table S1)** participated at the NIH Clinical Center (Bethesda, MD, USA). All participants or their legal guardians provided written informed consent. Patients

were recruited during evaluation and treatment for drug-resistant epilepsy requiring brain resection. As part of standard presurgical workup, each underwent neurological and neuropsychological assessments, structural MRI, scalp EEG, and/or intracranial EEG with subdural and/or stereo-EEG electrodes. Of the 40 participants, 10 showed MRI-positive seizures and proceeded directly to resection without intracranial monitoring. The remaining 30 underwent 1-2 weeks of intracranial EEG to localize seizure foci, which were resected during electrode explantation when clinically appropriate. The VWM color recall task was administered 1 to 2 days before either direct resection or electrode implantation surgery (i.e., preOp; pre-operative), and again approximately 3 months later at clinical follow-up (i.e., postOp; post-operative). This study focuses on behavioral data before and after lesion, regardless of whether intracranial EEG data were collected.

The current participants were included as they met all of the following inclusion criteria: (1) normal color vision and normal or corrected-to-normal visual acuity; (2) no history of prior brain resection; (3) available preOp and postOp MRI scans for lesion verification; and (4) completion of the VWM color recall task at both the preOp and postOp testing sessions. Of the 40 included participants, 19 had hippocampal lesions, 17 had extra-hippocampal (e.g., insular, frontal, parietal), and 4 opted for no surgical resection after intracranial EEG recordings. The no-lesion cases were grouped with the extra-hippocampal lesion group due to their shared clinical trajectory and surgical recovery from electrode implantation and explantation. These subgroup sizes, $n = 19$ and 21 respectively for hippocampal and non-hippocampal groups, provide 80% power to detect within-group differences of Cohen's $d = 0.57$ (paired-sample t-test, $\alpha = 0.05$). The full sample provides 80% power to detect a lesion group × testing time interaction effect with Cohen's $f = 0.45$ (partial $\eta^2 = 0.17$) in a repeated-measures ANOVA, or a point-biserial correlation of $r = 0.37$ between lesion type and behavioral change. Our observed effect sizes are on par with the estimates from these a priori power sensitivity analyses. Preliminary findings from a subset of 16 participants have been reported previously[15]. The expanded sample in the current study enables new analyses that were not feasible in the earlier work. Additionally, we re-analyze the updated dataset using a recently proposed alternative modeling approach[47], yielding new insights beyond those available in the prior work.

Behavioral testing

Participants completed two behavioral testing sessions, one before and one after neurosurgical treatment. All stimuli were generated using Psychtoolbox-3 in MATLAB (MathWorks, Natick, MA, USA) and displayed on a 15-inch laptop monitor (60 Hz refresh rate) with a gray background. Participants were seated approximately 57 cm away from the screen. Each session included a perceptual/motor control task followed by a VWM color recall task. Although these tasks shared a common structure, they differed in the cognitive demands. In brief, each trial began with the presentation of three perceptually distinct colored squares (~1.5° × 1.5° of visual angle) displayed for 400 ms at locations randomly selected from six equally spaced placeholders arranged on an invisible circle (with a radius of ~5.5° centered on the screen). Colors were randomly drawn from a continuous circular color space (spanning 180 evenly spaced hues in CIELAB color space: L = 70, a = 20, b = 38), with at least 20° from one another in the color space[24]. After a 1000 ms retention interval with a blank screen, a test display appeared featuring a continuous circular color wheel with all the 180 colors, randomly rotated on each trial to prevent location-based recall (**Figure 1A**).

In the perceptual/motor control task, all three original colors re-appeared at their original locations, and one of them was randomly cued with a bold outline. Participants were asked to match this cued color as precisely as possible on the color wheel. Because the target colored square remained visible throughout the test, this condition imposed minimal demands on active VWM maintenance and primarily indexed perceptual and motor components of performance. In contrast, in the VWM task, two of the original three squares were shown at test, while the third location – now empty – was indicated with a bold outline. Participants tried to recall the color that had previously appeared at this cued location and select it from the color wheel – requiring them to retain the study colors over a brief delay. In both tasks, participants used the same motor response method, allowing a direct comparison of memory-based and perceptual-based performance. The presence of the two non-target colors at test also minimized the likelihood of mistakenly reporting a non-target color due to misbinding errors[35,55,56].

To prioritize accuracy over speed, participants were given unlimited time to respond. After each response, the feedback was provided by displaying an arrow indicating the correct color for 1000 ms, followed by a random inter-trial interval of 1000 to 2000 ms. Each session

began with 6 practice trials of the perceptual/motor control task, followed by 1 block of 30 trials. This was then followed by 6 practice trials and 3 to 5 blocks of the VWM task (30 trials per block), yielding between 90 and 150 usable VWM trials per participant. Due to logistical constraints in the clinical setting – such as clinical examinations or MRI scheduling – some behavioral sessions were abbreviated. In such cases, the VWM task was prioritized, and the perceptual/motor control task was omitted when necessary. All included participants completed a sufficient number of VWM trials (approximately 150 trials on average) to support the behavioral modeling described below, ensuring acceptable model recovery or split-half reliability[48,57]. Perceptual/motor control task data were missing for 5 participants (see **Supplemental Table S2** for individual trial counts).

Behavioral Modeling

We analyzed participants' responses in both the perceptual/motor control and VWM tasks separately for each testing session to assess changes in perceptual and memory performance following brain surgery. Typically, participants' recall color ($\hat{\theta}$) in these tasks closely approximated the target color (θ), albeit with some variability (see **Supplementary Figure S1**). In the VWM condition, recall errors often exhibited a long tail in addition to a central bell-shaped distribution, suggesting a mixture of successful recalls and random guess responses distributed uniformly across the feature space[24–26], especially when misbinding errors are minimized[37]. To quantify this mixture, we modeled participants' response errors using a model that decomposes the distribution into two components[24]: a von Mises distribution (ϕ) centered on the target, capturing noisy but successful recall, and a uniform distribution reflecting failed recall:

$$P(\theta) = Pm \times \phi_{SD}\left(\hat{\theta} - \theta\right) + (1 - Pm) \times \frac{1}{2\pi} \qquad (1)$$

, where *Pm* denotes the probability of successful recall, ϕ_{SD} is the von Mises distribution with standard deviation *SD*, and $\hat{\theta}$ and θ are the reported and target colors, respectively. When fitting this model to the perceptual/motor control task data as a sanity check, participants' *Pm* values were high (preOp vs. postOp: 0.95 ± 0.02 vs. 0.98 ± 0.01), suggesting that performance variability in this condition is primarily driven by response noise attributable to perceptual and motor processes.

For the VWM data, we also fitted an alternative model that does not assume failed recall responses to capture the evaluated tail in recall error distribution, namely the target confusability competition (TCC) model[3,47]. In its original form, the TCC models uses the signal detection rule to transform the signal function into a response distribution without assuming failed recall responses or misbinding errors (see **Supplementary Figure S1**). In each trial, the target color (θ) with the most robust memory-match signal (m_θ) is chosen as the response color. Every color in the feature space generates a memory-match signal modeled as a sample from a Gaussian distribution, $m_\theta \sim N(d_\theta, 1)$. The mean of the memory-match signal for each color, d_θ, is determined by its psychophysical similarity to the target color, based on a measured similarity function $f(\theta)$, such that $d_\theta = d' f(\theta)$, plus additional motor noise. Here, d' is the only free parameter, assuming uncorrelated perceptual noise across nearby feature values. For $f(\theta)$, we used a smooth, empirically derived similarity function from prior research to capture relative color similarities[3,47].

Both the mixture model and the TCC model provided good fits to participants' recall performance (e.g., overall $R^2 > 98\%$ for the aggregated data across participants)[3,47]. However, the models make fundamentally different assumptions about the role of failed recall in VWM. Notably, the TCC model summarizes recall performance using a single compound parameter, d', reflecting overall memory strength. As shown previously[3] and replicated in our sample, d' correlates strongly with the probability of recall success (Pm) relative to recall variability (SD) from the mixture model (see **Supplementary Figure S2A**). This suggests that d' may primarily reflect the overall memory likelihood more so than the fidelity of recalled content[3]. This pattern highlights the potential utility of d' as a general index of VWM performance, though it may not disentangle distinct internal memory representations and processes[3].

Lesion masking based on structural MRIs

Two high-resolution T1-weighted anatomical magnetization-prepared rapid gradient echo (MP-RAGE) images were obtained for each participant: one prior to surgical resection and another 1-3 months post-resection (239 sagittal slices, 0.8 mm slice thickness, field of view = 24 cm). These images were processed through the following steps to generate subject-specific and normalized lesion masks for subsequent analyses[58] (see **Supplementary Figure S3**).

First, each participant's skull-stripped postOp image was aligned to their respective preOp image using AFNI tools (*3dSkullStrip*, *texttt3dAllineate*)[59]. Next, the aligned postOp image was used for user-guided lesion segmentation in ITK-SNAP[60]. Briefly, lesions were initialized using spherical bubbles and segmented via Active Contour evolution (region competition force = 0.8; smoothing curvature force = 0.8), followed by manual refinement with the Paintbrush tool. Once the initial lesion mask was created by a trained rater, it was reviewed by a second rater, and any discrepancies were discussed and resolved collaboratively. This process helped avoid mislabeling of sulcal gaps or other anatomical features as lesions. When disagreement persisted, a third rater or a member of the clinical research team was consulted. The final lesion mask retained only regions agreed upon by at least two raters. Third, each finalized lesion mask and the aligned postOp MRI were co-registered and normalized to MNI space using SPM12 (Wellcome Trust Centre for Neuroimaging, London, UK). Forward deformation fields were applied to the lesion masks and resampled to 2 mm isotropic voxels. A group-level lesion overlap map was then generated by averaging voxel-wise lesion presence across participants (**Figure 1B**).

Based on the normalized lesion masks, hippocampal involvement was quantified using the Automated Anatomical Labeling (AAL) atlas[50]. These normalized binary lesion masks were also used to compute lesion overlap volumes across participants, as well as hippocampal lesion volume and total lesion volume in each individual.

Voxel-based lesion-symptom mapping

We performed voxel-based lesion-symptom mapping using data from all 40 participants to identify voxels where lesions were most associated with behavioral changes across preOp and postOp tests, following the steps outlined below. First, we defined the overall lesion area as voxels where more than 5 participants had overlapping lesions, to exclude less informative voxels from the analysis[50]. Second, for each voxel, we coded whether it was lesioned (1) or not (0) for each participant, and then computed the point-biserial correlation between this binarized lesion status and behavioral change scores (postOp - preOp). To account for the potential confounding effect of overall lesion volume on behavioral outcomes, we computed partial correlations, controlling for each participant's lesion volume. The resulting partial correlation

coefficients (r) were then converted to equivalent t-values based on the degrees of freedom for partial correlation ($df = n - 3$):

$$t = r\sqrt{\frac{df}{1-r^2}} \qquad (2)$$

This yielded a t-map representing the strength of association between lesion status at each voxel and behavioral change in the VWM task. To correct for multiple comparisons, we employed a cluster-level permutation test (1000 permutations; cluster-level $\alpha = 0.05$; voxel-level $\alpha = 0.05$; two-tailed). Briefly, for each permutation, we randomly flipped preOp and postOp behavioral scores within participants to generate a null distribution of lesion-behavior associations[62]. We then recomputed voxel-wise partial point-biserial correlations as described above and obtained a corresponding t-map. This permuted t-map was thresholded at the voxel level ($\alpha = 0.05$), and clusters were identified using MATLAB's *bwconncomp* function. For each permutation, we recorded the maximum t-value within each cluster. Significant clusters in the original, unshuffled data were identified by comparing their cluster sizes against the empirical null distribution, applying the cluster-level α threshold.

Statistical Analyses

We used both parametric and non-parametric procedures to estimate effect sizes and assess statistical significance at the participant level. To compare VWM task performance between preOp and postOp sessions, we conducted within-group paired-sample t-tests and mixed-effects repeated-measures ANOVAs (lesion group: hippocampal vs. non-hippocampal; testing time: preOp vs. postOp) on individual best-fit model parameters derived from maximum likelihood estimation. Complementing this approach, we also performed hierarchical Bayesian model fitting and inference on the mixture model parameters[15,56,63]. Both approaches yielded highly consistent results (see **Supplemental Table S3** for hierarchical Bayesian model fitting details and outcomes). To examine individual differences in lesion volume and behavioral change, we computed Spearman rank-order correlations, which reduce assumptions about data distribution inherent in parametric tests. To identify voxels where lesion status was most strongly associated with behavioral change across sessions, we performed voxel-wise point-biserial correlations, controlling for total lesion volume. Multiple comparisons were corrected using a cluster-wise correction procedure to mitigate Type I error inflation as detailed above. p-values

are reported as two-tailed unless otherwise specified. Effect sizes are reported as $r_{equivalent}$, calculated as follows:

$$r_{equivalent} = \sqrt{\frac{t^2}{t^2 + df}} \qquad (3)$$

Results

Of the 40 participants participated in the study (**Figure 1A**), 36 eventually underwent resection affecting a distributed set of brain regions (**Figure 1B**); the remaining 4 did not proceed with surgery due to bilateral seizure onset or other clinical considerations. Based on co-registration of preOp and postOp T1-weighted MRI scans and manual lesion tracing[58] (**Supplementary Figure S3**), we identified 19 participants with resections involving the hippocampus, and 21 with either extra-hippocampal lesions or no resection-related lesions. This anatomically heterogeneous sample enabled direct comparisons of changes in VWM performance between individuals with hippocampal versus non-hippocampal lesions.

Lesions affecting the hippocampus impair VWM precision

We first examined changes in VWM performance across preOp and postOp sessions, stratifying participants based on whether their resections involved the hippocampus. The hippocampal group (n = 19, **Figure 2A**) included individuals with unilateral lesions affecting either the left or right hippocampus. The non-hippocampal group (n = 21; **Figure 2B**) included participants with extra-hippocampal lesions (n = 17) or no lesions (n = 4). The no-lesion cases were included in the non-hippocampal group because they underwent similar clinical procedures (e.g., electrode implantation and explantation surgeries for intracranial EEG monitoring) with intact bilateral hippocampi.

We found that participants with hippocampal lesions exhibited a selective increase in VWM recall variability, with no evident change in the rate of uniform (i.e., random) recall responses (**Figure 2C**). Confirming this observation, mixture model fits revealed a significant increase in *SD* after surgery (preOp vs. postOp: 26.54 ± 1.48 vs. 33.14 ± 2.25; $t(18) = -3.74$, $p = 0.0015$, $r_{equivalent} = 0.66$), indicating reduced memory precision. In contrast, the probability of recall success (*Pm,* calculated as one minus the probability of failed recall responses) showed no

significant change (preOp vs. postOp: 0.69 ± 0.03 vs. 0.70 ± 0.03; $t(18) = -0.27$, $p = 0.79$, $r_{equivalent} = 0.06$; **Figure 2E**). In the non-hippocampal group, no significant changes were observed in either *SD* (preOp vs. postOp: 28.30 ± 1.86 vs. 27.99 ± 1.54; $t(20) = 0.19$, $p = 0.85$, $r_{equivalent} = 0.04$) or *Pm* (preOp vs. postOp: 0.74 ± 0.04 vs. 0.73 ± 0.03; $t(20) = 0.18$, $p = 0.86$, $r_{equivalent} = 0.04$; **Figures 2D** & **2F**). A mixed-effect repeated-measures ANOVA revealed a significant interaction between lesion group (hippocampal vs. non-hippocampal) and testing session (preOp vs. postOp) on *SD* ($F(1, 38) = 8.441$, $p = 0.006$, partial $\eta^2 = 0.182$), suggesting the selective impact of hippocampal lesions on VWM precision. These results were corroborated by Bayesian hierarchical modeling across the entire dataset, which did not rely on subject-level parameter fits (**Supplementary Table S3**).

Could the observed effects be attributed to changes in perceptual or motor abilities[64] that indirectly influenced VWM recall performance or other response-level factors (e.g., categorical decision biases[63])? We find these explanations unlikely. First, when fitting participants' performance on the perceptual/motor control task using the same mixture model, we found that performance was primarily driven by response variability, which remained stable across preOp and postOp sessions and did not vary systematically with lesion type (**Supplementary Figure S4**). Second, after directly accounting for individual- and session-specific differences in perceptual/motor response noise (i.e., VWM *minus* perceptual/motor), the average absolute error reflected performance differences between preOp and postOp tests in the hippocampal lesion group (**Supplementary Table S4**), although these results should be interpreted with caution[65,66] (see **Supplementary Discussion**). Third, when fitting a unitary process model designed to capture changes in memory strength as a function of perceptual similarity of the testing colors in the VWM condition[3,47], we found little evidence that this model could account for the observed decline in VWM precision in the hippocampal group (**Supplementary Figure S5A-D**). Fourth, we further ruled out the possibility that declines in VWM precision were due to increased reliance on categorical responses[63,67], as participants' responses based on prototypal colors previously tested in the chosen color space[24,67] remained minimal across testing sessions (**Supplementary Figure S6**). Finally, participants' response times also did not systematically vary across testing sessions and lesion groups (**Supplementary Table S5**). Together, these results suggests that the decline in VWM precision following hippocampal resection reflects a

contribution of the hippocampal circuitry in the MTL, rather than being driven by deficits in perceptual discrimination, global memory strength, or response strategies.

Overall lesion size primarily affects VWM recall probability

One alternative interpretation is that the reduced precision observed in the hippocampal lesion group may reflect overall lesion size, as MTL resections often extend into nearby cortices. Could the decline in VWM precision simply result from larger total lesion volume, rather than a hippocampus-related effect?

To test this, we examined whether the association between hippocampal lesion size and reduced VWM precision would persist after controlling for total lesion volume[68]. We found that hippocampal lesion size remained significantly correlated with increased recall variability during the postOp test (*SD* effect: postOp vs. preOp), even after accounting for total lesion volume – both within the hippocampal lesion group (partial $\rho = 0.50$, $p = 0.036$, $n = 19$) and across all participants (partial $\rho = 0.44$, $p = 0.0052$, $n = 40$; **Figure 3A**). In contrast, hippocampal lesion size was not significantly associated with changes in recall probability (*Pm* effect: postOp vs. preOp) when controlling for total lesion volume neither within the hippocampal lesion group (partial $\rho = -0.35$, $p = 0.16$, $n = 19$) nor across all participants (partial $\rho = 0.13$, $p = 0.42$, $n = 40$; **Figure 3B**). These findings support a dose-dependent relationship between hippocampal damage and VWM imprecision, and argue against total lesion volume as a confounding factor.

However, across all 40 participants, total lesion volume did predict overall task performance. Specifically, reductions in probability of recall success (*Pm*) after surgery were more strongly associated with total lesion volume ($\rho = -0.33$, $p = 0.040$, $n = 40$) than with hippocampal lesion size ($\rho = 0.13$), based on a directional test of correlated correlations[69] ($Z = -2.99$, $p = 0.0014$, one-tailed; **Figure 3B**). In contrast, VWM recall variability (*SD*) showed only a weak, non-significant association with total lesion volume ($\rho = 0.20$, $p = 0.21$, $n = 40$), which was significantly weaker than the corresponding association with hippocampal lesion size ($\rho = 0.44$) based on the same test[69] ($Z = 1.67$, $p = 0.047$, one-tailed; **Figure 3A**). These patterns suggest that while widespread cortical damage may reduce the likelihood of successful recall –

possibly due to increased attentional lapses[54] –, it does not substantially impair the fidelity of retained VWM content.

These findings raise the possibility that a unitary performance metric may more effectively capture global impact of lesion extent on VWM recall performance. Specifically, changes in the overall memory strength parameter (*d′*), derived from a signal detection theory based unitary process model[47] (**Supplementary Figure S1B**), were strongly correlated with changes in overall recall probability (*Pm*: $\rho = 0.82$, $p < 0.0001$, $n = 40$), but only weakly with changes in recall variability (*SD*: $\rho = -0.27$, $p = 0.093$, $n = 40$; **Supplementary Figure S2A**). This pattern aligns with recent findings in healthy young adults[3], suggesting that the *d′* may index global changes in accessibility rather than memory fidelity. Supporting this, changes in *d′* were significantly associated with total lesion volume ($\rho = -0.42$, $p = 0.006$, $n = 40$; **Supplementary Figure S2B**), but not with hippocampal lesion size when controlling for total lesion volume (within hippocampal lesion group: partial $\rho = -0.35$, $p = 0.16$, $n = 19$; across all participants: partial $\rho = -0.04$, $p = 0.82$, $n = 40$). Taken together, these results suggest that while total lesion burden impairs VWM accessibility and general task performance, hippocampal lesions selectively impair the precision of VWM representations, as captured by the mixture model[3,24,25].

Lesion-symptom mapping reveals hippocampal contribution to VWM precision

To pinpoint brain regions where lesions disrupt VWM precision, we conducted voxel-based lesion-symptom mapping across all 40 participants. Each participant's binarized lesion mask (0 = intact, 1 = lesioned) was normalized to MNI space. For each voxel, we computed a point-biserial correlation between lesion status and changes in VWM recall variability (*SD*) and probability of recall success (*Pm*) from preOp to postOp testing (**Figure 4A**), controlling for total lesion volume[68]. The analysis was restricted to voxels lesioned in more than five participants to exclude uninformative voxels. Statistical significance was determined using a cluster-based permutation test (see **Materials and methods** for details). This analysis revealed a significant cluster in the left MTL (**Figure 4B**), where voxel-wise lesion status predicted increased recall variability (*SD*) – reflecting reduced VWM precision – after surgery (peak: x = -20, y = 0, z = -28; peak $t = 3.50$, cluster size = 571, cluster-level $\alpha = 0.05$, voxel-level $\alpha = 0.05$).

This cluster overlaps with the entorhinal-hippocampal circuit, a region frequently implicated in pattern separation processes[1,2,4,10–12,70]. In contrast, no voxel cluster was significantly associated with changes in *Pm* (**Figure 4C**). Moreover, memory strength estimates (*d'*) from the unitary process model failed to explain this effect (**Supplementary Figure S5E**), consistent with group-level results.

As this voxel-wise analysis yielded a significant cluster predominantly in the left hemisphere, it raises the question of whether the left hippocampus plays a uniquely important role. To investigate this, we separately analyzed participants with left hippocampal lesions (n = 11) and right hippocampal lesions (n = 8). Both subgroups exhibited significant reductions in VWM precision (hence increased *SD*) after the surgery, with no significant change in *Pm* (**Supplementary Figures S7A** & **S7B**). This suggests that the left-lateralized cluster observed in the lesion-symptom mapping likely reflects sample size asymmetries or lesion overlap – known limitations in lesion-symptom mapping[50,68] – rather than a true functional lateralization of hippocampal contributions.

Supporting this interpretation, and in line with evidence that the hippocampus exhibits retinotopically organized responses to visual inputs[71], we found that VWM precision declined more strongly when the to-be-tested item appeared contralateral to the lesioned hemisphere, regardless of the lesion side (**Supplementary Figures S7C** & **S7D**). These findings further implicate that visual coding properties in the hippocampus may play a role in supporting precise VWM representations[52,71], an intriguing direction for future neural recording studies inspired by the current lesion-based evidence.

Another possibility raised by the lesion-symptom mapping results is that the observed reduction in VWM precision could stem in part from temporal lobe lesions outside the hippocampus, such as the entorhinal cortex or lateral temporal regions along the resection path (**Figure 4B**). This interpretation is conceptually plausible, as pattern separation is thought to involve the broader entorhinal-hippocampal circuit rather than being confined solely to the hippocampus[12,70]. Empirically, however, we found limited support for this account. Among participants with temporal lobe lesions that spared the hippocampus (n = 9), VWM recall precision remained stable (preOp vs. postOp: 30.64 ± 3.09 vs. 28.14 ± 2.02; $t(8) = 0.91$, $p = 0.34$, $r_{equivalent} = 0.31$). In contrast, there was a marginal reduction in recall success rate (preOp vs.

postOp: 0.80 ± 0.03 vs. 0.71 ± 0.05; $t(8) = 2.03$, $p = 0.077$, $r_{equivalent} = 0.31$), suggesting that non-hippocampal temporal lobe lesions may affect cortical mechanisms supporting successful recall, without necessarily degrading the fidelity of recalled content. Taken together, these findings provide converging evidence – at both group and voxel levels – that hippocampal damage primarily impairs the precision, but not the likelihood of successful VWM recall. This anatomical and behavioral dissociation underscores the hippocampus's specific role in maintaining the fidelity, rather than merely the accessibility of VWM content.

Discussion

Classic lesion case-control studies have long suggested minimal involvement of the MTL in VWM[13,16,18–21], particularly for simple visual features such as color and orientation[13]. While several case reports have challenged this view[23,35,42,72,73], the exact nature of MTL involvement remains unresolved. In particular, it is unclear to what extent the MTL contributes to the quantity versus the quality of VWM representations[14,15]. Although MTL lesions typically do not impair overall VWM capacity[18], intracranial recordings have revealed load-dependent increases in MTL activity during VWM tasks[30–32]. Furthermore, prior case-control studies are often limited by potential confounds, such as potential LTM engagement during nominally VWM tasks due to long retention intervals, high memory load, and/or complex stimuli that may trigger LTM associations[13,21,74]. Even for studies using designs similar to our current study, smaller sample sizes, individual differences in case-control designs, and unknown behavioral performance prior to lesions may also contribute to inconsistent conclusions[14,15,49].

In the present study, we addressed these issues using a mixed-effects design that modeled within-subject changes in VWM performance before and after brain lesion involving or sparing the MTL, particularly the hippocampus. By using simple, repeatedly sampled colors, we minimized the potential for LTM influences while promoting active VWM maintenance[15,22,70]. Across both group-level and voxel-wise lesion-symptom mapping, we found that hippocampal lesions selectively impaired VWM precision, without affecting recall success rates. These findings challenge the classical view that confines hippocampal function to LTM[13], and instead support an important role for the MTL in maintaining precise VWM representations[15].

Of primary theoretical interest, our findings support a unified theoretical framework in which MTL function – centered on hippocampal pattern separation and memory precision – extends across both VWM and LTM[3,48,70]. The selective nature of the lesion effects, which manifested as reduced precision without elevated recall failure, suggests that the hippocampal circuitry preferentially supports the quality rather than quantity of retained VWM content. This interpretation helps reconcile mixed findings in previous lesion studies of MTL involvement in VWM[13,16,18–21,23,35,42,72,73], and aligns with recent human iEEG and fMRI work showing that entorhinal-hippocampal activity associated with pattern separation computation during short retention intervals predicts memory recall fidelity[15,70]. Our findings extend prior work on the role of hippocampal pattern separation in supporting high-fidelity episodic LTM[10,12], and offer a mechanistic account for the observed correlation in recall precision across VWM and LTM tasks[3,48], including enhanced memory precision for objects encoded under a negative emotional context[56,65,75,76] and age-related reductions in memory precision across different timescales[5–9].

Conceptually, the shared role of the MTL in supporting memory precision across timescales is related – but distinct – from the MTL's role in binding items with contextual information in VWM. Prior studies have shown that MTL structures, including the hippocampus, are engaged when VWM tasks requires relational or spatial binding, or the integration of item and context features[27,42–46,55]. These binding mechanisms are theoretically separable from the representational precision of retained VWM content[36,77,78], which is often operationalized as the internal noise within a memory representation that contributes to recall variability[24]. Such noise may reflect degraded representations of items, their contexts, or the binding between them[79]. In our task, the presence of non-target color items at test discouraged misbinding swap errors, and thereby encouraged recall errors that more directly reflected imprecision in the test item's representation[56]. Nevertheless, this design does not entirely rule out elementary feature binding, for example, the spatial binding between color and location during encoding. Because hippocampal representations are retinotopically organized[71], it is plausible that spatial context is automatically bound to nonspatial item features (e.g., color) during encoding[80]. The observed VWM effects may thus reflect degradation in VWM precision for these bound representations (i.e., degraded color at a given location), rather than a noisier or unstable binding process (e.g., confusing colors across different locations). Supporting this idea, we observed greater degradation in VWM precision when the tested item appeared contralateral to the lesioned

hemisphere (**Supplementary Figures S7C & S7D**), consistent with spatially tuned hippocampal coding[52,71]. Future research employing lateralized stimulus presentation designs[33], in combination with intracranial EEG recording and/or eye-tracking, may further illuminate the spatiotemporal dynamics of hippocampal contributions to VWM quality and spatial binding.

Notably, the link between MTL lesions and VWM impairment emerged most clearly when VWM precision was estimated using a mixture model[24,25], which isolates representational variability from overall recall failures. In contrast, a unitary process model that summarizes overall performance with a single continuous memory strength parameter[47] failed to capture the lesion-specific effects observed in this study. This discrepancy calls into questions about the adequacy of unitary process models – particularly those lacking a high-threshold component for recall success[38,39] – in characterizing the underlying structure of VWM representations[3,25]. While the mixture model provides only an approximate characterization of the underlying memory signals, it uniquely captures behavioral variance that maps onto neuroanatomical dissociations predicted by longstanding theories of MTL contributions to memory quality[1,2,10,12]. These findings further highlight the neuropsychological relevance of the mixture model, reinforcing the importance of interpreting model parameters through the lens of neural dissociations rather than relying solely on goodness-of-fit metrics[3,81]. More broadly, our results position VWM precision as a sensitive behavioral marker[82] – one with potential translational value for detecting and tracking functional changes in individuals with memory impairments, including those with focal brain lesions.

Several caveats should be noted to guide interpretation of the present findings. First, lesion overlap across participants can limit precise functional localization[50,68]. We mitigated this by employing both ROI-based and voxel-wise lesion-symptom mapping analyses, which converged on the MTL involving the hippocampus, bolstering the regional specificity of our findings. Yet, variations in lesion extent across individuals makes it hard to assess subfield-specific effects within the hippocampus. Future studies using high-resolution fMRI may be better suited to address this question[70]. Second, post-lesion performance could be influenced by factors such as compensatory plasticity or individual differences in clinical chronicity[49,74]. However, our mix-effects design helps reduce these confounds by capturing within-subject changes across a constrained post-surgical time window. The observed reduction in VWM precision following MTL damage aligns with evidence from transcranial and intracranial electrical stimulation

studies in healthy participants and non-lesion neurological cases[15,52]. This convergence suggests that the MTL's role in VWM quality may generalize beyond the current sample of neurosurgical patients. Third, although general attentional or executive deficits may contribute to reduced global VWM task performance[53,83] – as suggested by the association between total lesion volume and recall success (**Figure 3B** and **Supplementary Figure S2B**) – they do not account for the selective reduction in VWM precision observed following hippocampal lesion, nor the preserved performance on perceptual/motor control tasks. These findings reinforce the distinction between overall recall likelihood and the fidelity of retained VWM content[24–26].

In sum, this study contributes to a growing body of evidence implicating the MTL – particularly the hippocampus – in VWM[29], especially in maintaining fine-grained, high-fidelity VWM representations of simple visual features over short delays[15,70]. Our findings demonstrate that the hippocampus is necessary for preserving precise VWM. These results challenge strict compartmentalizations of memory systems[13,21], and call for revisions to existing neurocognitive models of VWM[17], incorporating the hippocampus and broader MTL as core substrates supporting the quality of VWM representations.

Data availability

Processed data used in this study can be found at: https://osf.io/eup85/. Custom MATLAB analysis code is available upon request.

Acknowledgements

We thank Weiwei Zhang, Julio I. Chapeton, and John Wittig Jr. for their insightful comments on the project. We also thank Kelsey Sundby, Uma Mohan, Ryan Kirkpatrick, Ian Bright, Rachael Volkman, Maxwell Lichtenfeld, Elizabeth Jitendran, Audrey Phan and Molly Baumhauer for assistance in data collection. We are deeply appreciative of all patients who have selflessly volunteered their time to participate in this study.

Funding

The funding of this work comes from the National Institute of Neurological Disorders and Stroke (ZIA-NS003144 to K.A.Z; R00NS126492 to W.X.).

Competing interests

The authors report no competing interests.

Supplementary material

Supplementary material is available at *Brain* online.

References

1. Marr D. Simple Memory: A Theory for Archicortex. *Philosophical Transactions of the Royal Society of London B: Biological Sciences*. 1971;262(841):23-81.
2. Aimone JB, Deng W, Gage FH. Resolving new memories: A critical look at the dentate gyrus, adult neurogenesis, and pattern separation. *Neuron*. 2011;70(4):589-596.
3. Xie W, Ma T, Thakurdesai S, Kim I, Zhang W. Discrimination of mnemonic similarity is associated with short-term and long-term memory precision. *Mem Cogn*. 2025;53(4):1259-1271. doi:10.3758/s13421-024-01648-y
4. Stark SM, Yassa MA, Lacy JW, Stark CEL. A task to assess behavioral pattern separation (BPS) in humans: Data from healthy aging and mild cognitive impairment. *Neuropsychologia*. 2013;51(12):2442-2449.
5. Korkki SM, Richter FR, Jeyarathnarajah P, Simons JS. Healthy ageing reduces the precision of episodic memory retrieval. *Psychology and Aging*. 2020;35(1):124-142. doi:10.1037/pag0000432

6. Xie W, Berry A, Lustig C, Deldin P, Zhang W. Poor sleep quality and compromised visual working memory capacity. *Journal of the International Neuropsychological Society*. 2019;25(6):583-594. doi:10.1017/S1355617719000183

7. Peich MC, Husain M, Bays PM. Age-related decline of precision and binding in visual working memory. *Psychology and Aging*. 2013;28(3):729-743. doi:10.1037/a0033236

8. Rhodes S, Abbene EE, Meierhofer AM, Naveh-Benjamin M. Age differences in the precision of memory at short and long delays. *Psychology and Aging*. 2020;35(8):1073-1089. doi:10.1037/pag0000565

9. Gellersen HM, McMaster J, Abdurahman A, Simons JS. Demands on Perceptual and Mnemonic Fidelity Are a Key Determinant of Age-Related Cognitive Decline Throughout the Lifespan. *Journal of Experimental Psychology: General*. 2024;153(1):200-223. doi:10.1037/xge0001476

10. Yassa MA, Stark CEL. Pattern separation in the hippocampus. *Trends in Neurosciences*. 2011;34(10):515-525.

11. Rolls ET. Pattern separation, completion, and categorisation in the hippocampus and neocortex. *Neurobiology of Learning and Memory*. 2016;129(C):4-28.

12. Leal SL, Yassa MA. Integrating new findings and examining clinical applications of pattern separation. *Nature Neuroscience*. 2018;21(2):163-173. doi:10.1038/s41593-017-0065-1

13. Jeneson A, Squire LR. Working memory, long-term memory, and medial temporal lobe function. *Learning and Memory*. 2012;19(1):15-25. doi:10.1101/lm.024018.111

14. Warren DE, Duff MC, Cohen NJ, Tranel D. Hippocampus contributes to the maintenance but not the quality of visual information over time. *Learning & memory*. 2014;22(1):6-10.

15. Xie W, Chapeton JI, Bhasin S, et al. The medial temporal lobe supports the quality of visual short-term memory representation. *Nature Human Behaviour*. 2023;7(4):627-641. doi:10.1038/s41562-023-01529-5

16. Scoville WB, Milner B. Loss of recent memory after bilateral hippocampal lesions. *Journal of Neurology, Neurosurgery, and Psychiatry*. 1957;20(1):11-21.

17. Christophel TB, Klink PC, Spitzer B, Roelfsema PR, Haynes JD. The distributed nature of working memory. *Trends in Cognitive Sciences*. 2017;21(2):111-124.

18. Jeneson A., Wixted JT, Hopkins RO, Squire LR. Visual working memory capacity and the medial temporal lobe. *Journal of Neuroscience*. 2012;32(10):3584-3589. doi:10.1523/jneurosci.6444-11.2012

19. Milner B. Visual recognition and recall after right temporal-lobe excision in man. *Neuropsychologia*. 1968;6(3):191-209.

20. Shrager Y, Levy DA, Hopkins RO, Squire LR. Working memory and the organization of brain systems. *Journal of Neuroscience*. 2008;28(18):4818-4822. doi:10.1523/JNEUROSCI.0710-08.2008

21. Jeneson A, Mauldin KN, Hopkins RO, Squire LR. The role of the hippocampus in retaining relational information across short delays: The importance of memory load. *Learning and Memory*. 2011;18(5):301-305. doi:10.1101/lm.2010711

22. Cowan N. The magical number 4 in short-term memory: A reconsideration of mental storage capacity. *Behavioral and Brain Sciences*. 2001;24(1):87-185.

23. Goodrich RI, Baer TL, Quent JA, Yonelinas AP. Visual working memory impairments for single items following medial temporal lobe damage. *Neuropsychologia*. 2019;134(May). doi:10.1016/j.neuropsychologia.2019.107227

24. Zhang W, Luck SJ. Discrete fixed-resolution representations in visual working memory. *Nature*. 2008;453(7192):233-235.

25. Xie W, Zhang W. Dissociations of the number and precision of visual short-term memory representations in change detection. *Memory and Cognition*. 2017;45(8):1423-1437. doi:10.3758/s13421-017-0739-7

26. Adam KCS, Vogel EK, Awh E. Clear evidence for item limits in visual working memory. *Cognitive Psychology*. 2017;97:79-97.

27. Yonelinas AP. The hippocampus supports high-resolution binding in the service of perception, working memory and long-term memory. *Behavioural Brain Research*. 2013;254:34-44.

28. Newmark RE, Schon K, Ross RS, Stern CE. Contributions of the hippocampal subfields and entorhinal cortex to disambiguation during working memory. *Hippocampus*. 2013;23(6):467-475. doi:10.1002/hipo.22106

29. Li J, Cao D, Li W, Sarnthein J, Jiang T. Re-evaluating human MTL in working memory: insights from intracranial recordings. *Trends in Cognitive Sciences*. 2024;28(12):1132-1144. doi:10.1016/j.tics.2024.07.008

30. Axmacher N, Schmitz DP, Wagner T, Elger CE, Fell J. Interactions between medial temporal lobe, prefrontal cortex, and inferior temporal regions during visual working memory: a combined intracranial EEG and functional magnetic resonance imaging study. *Journal of Neuroscience*. 2008;28(29):7304-7312.

31. Boran E, Hilfiker P, Stieglitz L, Sarnthein J, Klaver P. Persistent neuronal firing in the medial temporal lobe supports performance and workload of visual working memory in humans. *NeuroImage*. Published online 2022:119123. doi:10.1016/j.neuroimage.2022.119123

32. Boran E, Fedele T, Klaver P, et al. Persistent hippocampal neural firing and hippocampal-cortical coupling predict verbal working memory load. *Science Advances*. 2019;5(3):eaav3687. doi:10.1126/sciadv.aav3687

33. Vogel EK, Machizawa MG. Neural activity predicts individual differences in visual working memory capacity. *Nature*. 2004;428(6984):748-751.

34. Lisman JE, Idiart MA. Storage of 7+/-2 short-term memories in oscillatory subcycles. *Science*. 1995;267(5203):1512-1515.

35. Pertzov Y, Miller TD, Gorgoraptis N, et al. Binding deficits in memory following medial temporal lobe damage in patients with voltage-gated potassium channel complex antibody-associated limbic encephalitis. *Brain*. 2013;136(8):2474-2485.

36. Wheeler ME, Treisman AM. Binding in short-term visual memory. *Journal of Experimental Psychology: General*. 2002;131(1):48-64. doi:10.1037//0096-3445.131.1.48

37. Bays P, Wu E, Husain M. Storage and binding of object features in visual working memory. *Neuropsychologia*. 2011;49:1622-1631.

38. Bays PM, Husain M. Dynamic shifts of limited working memory resources in human vision. *Science*. 2008;321(5890):851-854. doi:10.1126/science.1158023

39. van den Berg R, Shin H, Chou WC, George R, Ma WJ. Variability in encoding precision accounts for visual short-term memory limitations. *Proceedings of the National Academy of Sciences*. 2012;109(22):8780-8785. doi:10.1073/pnas.1117465109

40. Emrich SM, Riggall AC, LaRocque JJ, Postle BR. Distributed patterns of activity in sensory cortex reflect the precision of multiple items maintained in visual short-term memory. *Journal of Neuroscience*. 2013;33(15):6516-6523.

41. Galeano Weber EM, Hahn T, Hilger K, Fiebach CJ. Distributed patterns of occipito-parietal functional connectivity predict the precision of visual working memory. *NeuroImage*. 2017;146:404-418.

42. Olson IR, Page K, Moore KS, Chatterjee A, Verfaellie M. Working memory for conjunctions relies on the medial temporal lobe. *Journal of Neuroscience*. 2006;26(17):4596-4601. doi:10.1523/JNEUROSCI.1923-05.2006

43. Hannula DE, Tranel D, Cohen NJ. The long and the short of it: Relational memory impairments in amnesia, even at short lags. *Journal of Neuroscience*. 2006;26(32):8352-8359.

44. Ezzyat Y, Olson IR. The medial temporal lobe and visual working memory: Comparisons across tasks, delays, and visual similarity. *Cognitive, Affective, & Behavioral Neuroscience*. 2008;8(1):32-40. doi:10.3758/cabn.8.1.32

45. Barense MD, Henson RNA, Lee ACH, Graham KS. Medial temporal lobe activity during complex discrimination of faces, objects, and scenes: Effects of viewpoint. *Hippocampus*. 2010;20(3):389-401. doi:10.1002/hipo.20641

46. Barense MD, Gaffan D, Graham KS. The human medial temporal lobe processes online representations of complex objects. *Neuropsychologia*. 2007;45(13):2963-2974. doi:10.1016/j.neuropsychologia.2007.05.023

47. Schurgin MW, Wixted JT, Brady TF. Psychophysical scaling reveals a unified theory of visual memory strength. *Nature Human Behaviour*. 2020;4(11):1156-1172. doi:10.1038/s41562-020-00938-0

48. Xie W, Park HB, Zaghloul KA, Zhang W. Correlated Individual Differences in the Estimated Precision of Working Memory and Long-Term Memory: Commentary on the Study by Biderman, Luria, Teodorescu, Hajaj, and Goshen-Gottstein (2019). *Psychological Science*. 2020;31(3):345-348. doi:10.1177/0956797620903718

49. Vaidya AR, Pujara MS, Petrides M, Murray EA, Fellows LK. Lesion Studies in Contemporary Neuroscience. *Trends in Cognitive Sciences*. 2019;23(8):653-671. doi:10.1016/j.tics.2019.05.009

50. Moore MJ, Demeyere N, Rorden C, Mattingley JB. Lesion mapping in neuropsychological research: A practical and conceptual guide. *Cortex*. 2024;170:38-52. doi:10.1016/j.cortex.2023.10.001

51. Wilken P, Ma WJ. A detection theory account of change detection. *Journal of Vision*. 2005;4(12):11. doi:10.1167/4.12.11

52. Xie W, Thakurdesai S, Varastegan S, Zhang W. Transcranial Direct Current Stimulation Over Bilateral Temporal Lobes Modulates Hippocampal-Occipital Functional Connectivity and Visual Short-Term Memory Precision. *Hippocampus*. 2025;35(1):e23678. doi:10.1002/hipo.23678

53. Adam KCS, Mance I, Fukuda K, Vogel EK. The Contribution of Attentional Lapses to Individual Differences in Visual Working Memory Capacity. *Journal of Cognitive Neuroscience*. 2015;27(8):1601-1616.

54. Dockree PM, Bellgrove MA, O'Keeffe FM, et al. Sustained attention in traumatic brain injury (tbi) and healthy controls: enhanced sensitivity with dual-task load. *Exp Brain Res*. 2006;168(1-2):218-229. doi:10.1007/s00221-005-0079-x

55. Borders AA, Ranganath C, Yonelinas AP. The hippocampus supports high-precision binding in visual working memory. *Hippocampus*. Published online December 27, 2021:1-14. doi:10.1002/hipo.23401

56. Xie W, Zhang W. Negative emotion boosts quality of visual working memory representation. *Emotion*. 2016;16(5):760-774. doi:10.1037/emo0000159

57. Grange JA, Moore SB. mixtur: An R package for designing, analysing, and modelling continuous report visual short-term memory studies. *Behav Res*. 2022;54(5):2071-2100. doi:10.3758/s13428-021-01688-1

58. Lo BP, Donnelly MR, Barisano G, Liew SL. A standardized protocol for manually segmenting stroke lesions on high-resolution T1-weighted MR images. *Front Neuroimaging*. 2023;1:1098604. doi:10.3389/fnimg.2022.1098604

59. Cox RW. AFNI: Software for analysis and visualization of functional magnetic resonance neuroimages. *Computers and biomedical research, an international journal*. 1996;29(3):162-173.

60. Yushkevich PA, Piven J, Hazlett HC, et al. User-guided 3D active contour segmentation of anatomical structures: Significantly improved efficiency and reliability. *NeuroImage*. 2006;31(3):1116-1128. doi:10.1016/j.neuroimage.2006.01.015

61. Tzourio-Mazoyer N, Landeau B, Papathanassiou D, et al. Automated Anatomical Labeling of Activations in SPM Using a Macroscopic Anatomical Parcellation of the MNI MRI Single-Subject Brain. *NeuroImage*. 2002;15(1):273-289. doi:10.1006/nimg.2001.0978

62. Good P. *Permutation Tests: A Practical Guide to Resampling Methods for Testing Hypotheses*. Springer Science & Business Media; 2013.

63. Hardman KO, Vergauwe E, Ricker TJ. Categorical working memory representations are used in delayed estimation of continuous colors. *Journal of Experimental Psychology: Human Perception and Performance*. 2017;43(1):30-54.

64. Sutterer D, Rosca CG, Woodman GF. Does motor noise contaminate estimates of the precision of visual working memory? *Visual Cognition*. 2022;30(3):195-201. doi:10.1080/13506285.2022.2044947

65. Xie W, Zhang W. Negative emotion enhances mnemonic precision and subjective feelings of remembering in visual long-term memory. *Cognition*. 2017;166:73-83. doi:10.1016/j.cognition.2017.05.025

66. Zhang W, Luck SJ. Sudden death and gradual decay in visual working memory. *Psychological Science*. 2009;20(4):423-428.

67. Cappiello M, Zhang W. A dual-trace model for visual sensory memory. *Journal of Experimental Psychology: Human Perception and Performance*. 2016;42(11):1903-1922.

68. DeMarco AT, Turkeltaub PE. A multivariate lesion symptom mapping toolbox and examination of lesion-volume biases and correction methods in lesion-symptom mapping. *Human Brain Mapping*. 2018;39(11):4169-4182. doi:10.1002/hbm.24289

69. Meng XL, Rosenthal R, Rubin DB. Comparing correlated correlation coefficients. *Psychological Bulletin*. 1992;111(1):172-175.

70. Xie W, Cappiello M, Yassa MA, Ester E, Zaghloul KA, Zhang W. The entorhinal-DG/CA3 pathway in the medial temporal lobe retains visual working memory of a simple surface feature. *eLife*. 2023;12:e83365. doi:10.7554/eLife.83365

71. Silson EH, Zeidman P, Knapen T, Baker CI. Representation of Contralateral Visual Space in the Human Hippocampus. *J Neurosci*. 2021;41(11):2382-2392. doi:10.1523/JNEUROSCI.1990-20.2020

72. Olson IR, Moore KS, Stark M, Chatterjee A. Visual Working Memory Is Impaired when the Medial Temporal Lobe Is Damaged. *Journal of Cognitive Neuroscience*. 2006;18(7):1087-1097. doi:10.1162/jocn.2006.18.7.1087

73. Goodrich RI, Yonelinas AP. The medial temporal lobe supports sensing-based visual working memory. *Neuropsychologia*. 2016;89:485-494. doi:10.1016/j.neuropsychologia.2016.07.011

74. Xie W, Wardle SG, Langbein J, et al. The role of the parahippocampal cortex in memory consolidation for scenes. *Learning & Memory*. 2025;32(4):a054053.124.

75. Xie W, Ye C, Zhang W. Negative emotion reduces visual working memory recall variability: A meta-analytical review. *Emotion*. 2023;23(3):859-871. doi:10.1037/emo0001139

76. Xie W, Zhang W. Mood-dependent retrieval in visual long-term memory: dissociable effects on retrieval probability and mnemonic precision. *Cognition and Emotion*. 2018;32(4):674-690. doi:10.1080/02699931.2017.1340261

77. Baddeley AD, Allen RJ, Hitch GJ. Binding in visual working memory: The role of the episodic buffer. *Neuropsychologia*. 2011;49(6):1393-1400. doi:10.1016/j.neuropsychologia.2010.12.042

78. Treisman A, Zhang W. Location and binding in visual working memory. *Memory & Cognition*. 2006;34(8):1704-1719. doi:10.3758/BF03195932

79. Ekstrom AD, Yonelinas AP. Precision, binding, and the hippocampus: Precisely what are we talking about? *Neuropsychologia*. 2020;138(June 2019):107341. doi:10.1016/j.neuropsychologia.2020.107341

80. Pertzov Y, Husain M. The privileged role of location in visual working memory. *Attention, Perception, & Psychophysics*. 2014;76(7):1914-1924. doi:10.3758/s13414-013-0541-y

81. Pitt MA, Myung IJ. When a good fit can be bad. *Trends in Cognitive Sciences*. 2002;6(10):421-425.

82. Zokaei N, Burnett Heyes S, Gorgoraptis N, Budhdeo S, Husain M. Working memory recall precision is a more sensitive index than span. *Journal of Neuropsychology*. 2015;9(2):319-329. doi:10.1111/jnp.12052

83. deBettencourt MT, Keene PA, Awh E, Vogel EK. Real-time triggering reveals concurrent lapses of attention and working memory. *Nature Human Behaviour*. 2019;3(8):808-816. doi:10.1038/s41562-019-0606-6

Figure legends

Figure 1 Study design and lesion distribution in the current sample. (**A**) In the VWM color recall task, participants were asked to remember and report the color of one of three randomly cued colored squares following a 1000 ms retention interval. Participants completed the color recall task and a perceptual/motor control task both before and after neurosurgical intervention (referred to as preOp and postOp, respectively). (**B**) Group-level lesion overlaps across all participants (n = 40). Red lines indicate the slices used for the sagittal and axial views.

Figure 2 Lesions affecting the hippocampus selectively reduce VWM recall precision. Among the 40 participants, (**A**) 19 had lesions involving the hippocampus, while (**B**) the remaining 21 had lesions outside the hippocampus or no detectable lesions. Binary lesion maps illustrate the extent of damage across individuals (marked in cyan). (**C**) In the hippocampal lesion group, recall errors became more variable postoperatively, as reflected by a broader central peak in the error distribution, without pronounced changes in the tails. (**D**) In contrast, the recall error distributions in the non-hippocampal lesion group remained consistent across preOp and postOp sessions. (**E**) Planned comparisons of task performance revealed a significant postoperative increase in recall variability in the hippocampal lesion group, indicating reduced VWM precision. However, the probability of successful recall did not significantly change. (**F**) No reliable changes in VWM performance metrics were observed in the non-hippocampal lesion group. The connected lines with dots in (**E**) and (**F**) represent individual best-fit parameters for each participant. The error bars represent standard error of the mean.

Figure 3 Lesion volumes and their associations with changes in VWM task performance across preOp and postOp sessions. (**A**) Recall variability (*SD*), estimated from a mixture model as an inverse index of VWM precision, was significantly correlated with hippocampal lesion volume – both within the hippocampal lesion group and across all participants – but not with total lesion volume. (**B**) In contrast, the probability of recall success (*Pm*), estimated as one minus the proportion of failed responses, was significantly correlated only with total lesion volume. These findings suggest a dose-dependent relationship between hippocampal damage and reductions in VWM precision, distinct from broader task impairments potentially driven by diffuse damage or attentional lapses[54]. Each dot represents one participant. Light blue dots and dashed lines indicate non-significant associations; solid blue dots and lines indicate significant associations. Lines show linear best-fit estimates for visualization. Partial ρ values reflect correlations between hippocampal lesion volume and VWM performance after controlling for total lesion volume. Directional comparison of correlational strength after taking into account the correlation between hippocampal lesion size and overall lesion size: $^{*}p < 0.05$, $^{**}p < 0.01$ (one-tailed). Each voxel is $2 \times 2 \times 2$ mm^3 in size.

Figure 4 Lesion-symptom mapping confirms a significant hippocampal contribution to lesion-induced reductions in VWM precision. (**A**) We performed a between-subject lesion-symptom mapping analysis by correlating lesion status at each normalized brain voxel with participants' behavioral (beh.) changes in the VWM task from preOp to postOp, controlling for individual differences in total lesion volume. (**B**) Using cluster-wise correction, we identified a significant cluster in the left MTL, including the hippocampus and adjacent regions such as the amygdala and entorhinal cortex, that reliably predicted increased VWM recall variability (i.e., reduced VWM precision) following the lesion. (**C**) In contrast, no significant cluster was found to reliably predict changes in participants' overall probability of recall success.

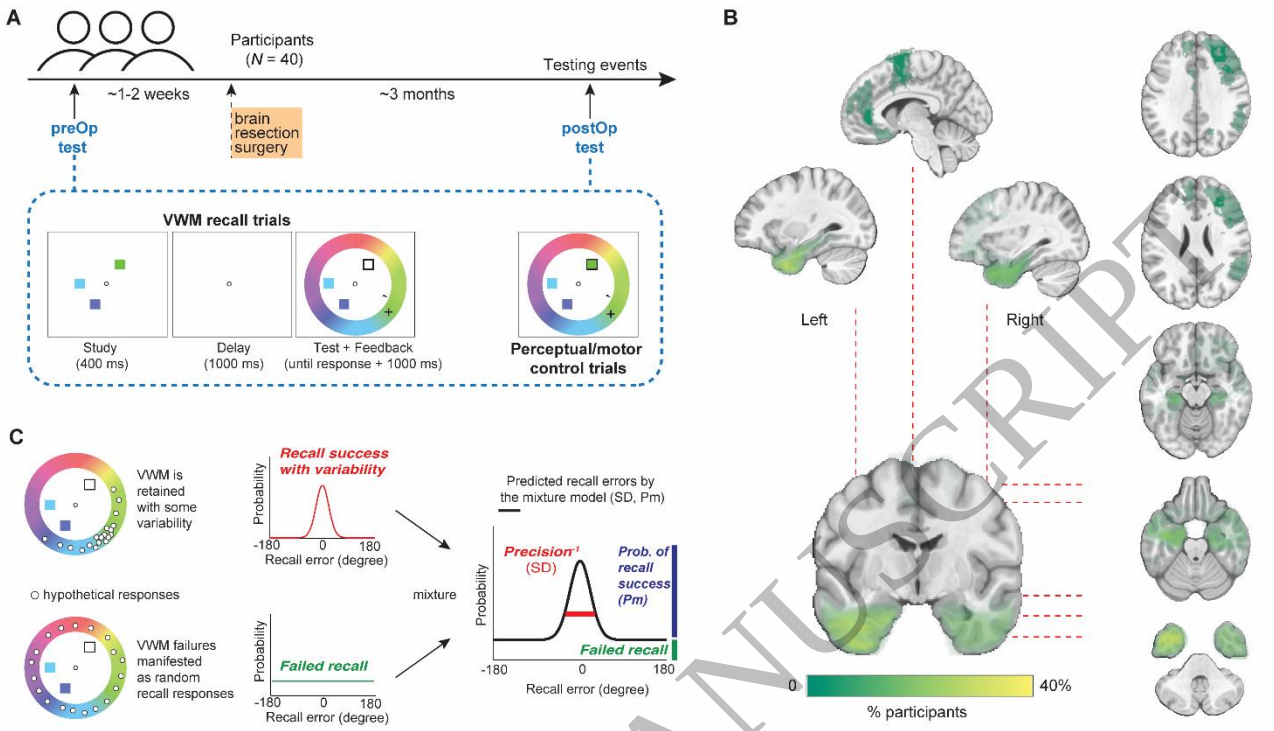

Figure 1
168x99 mm (x DPI)

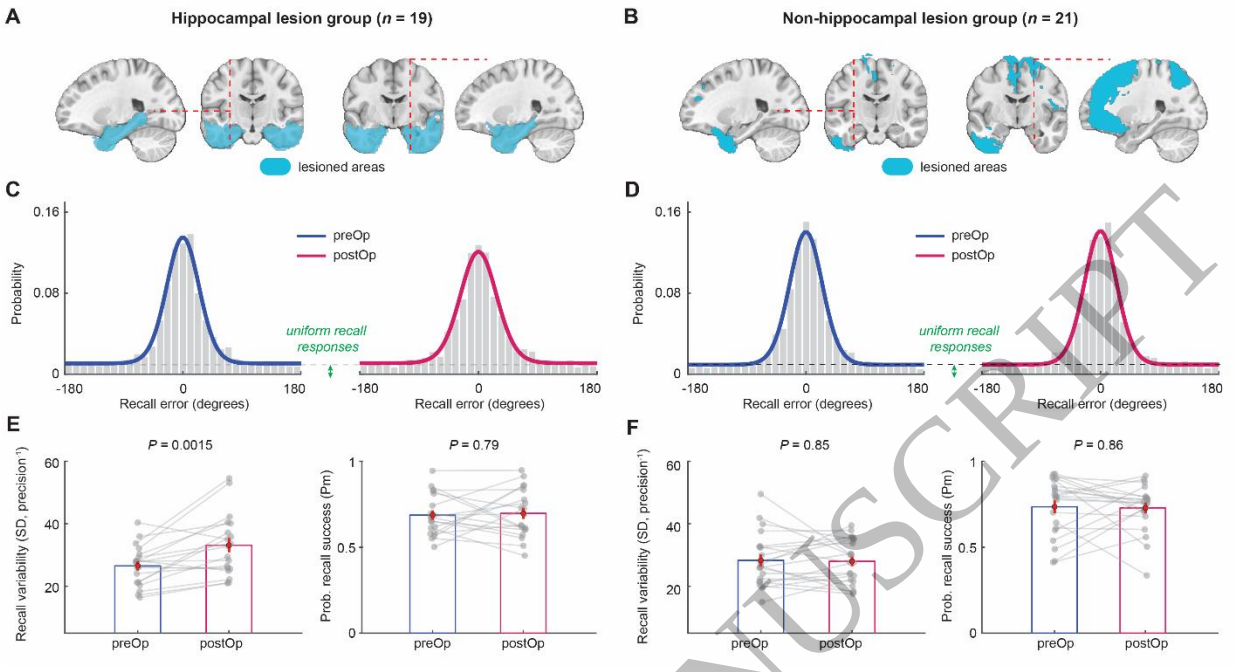

Figure 2
163x88 mm (x DPI)

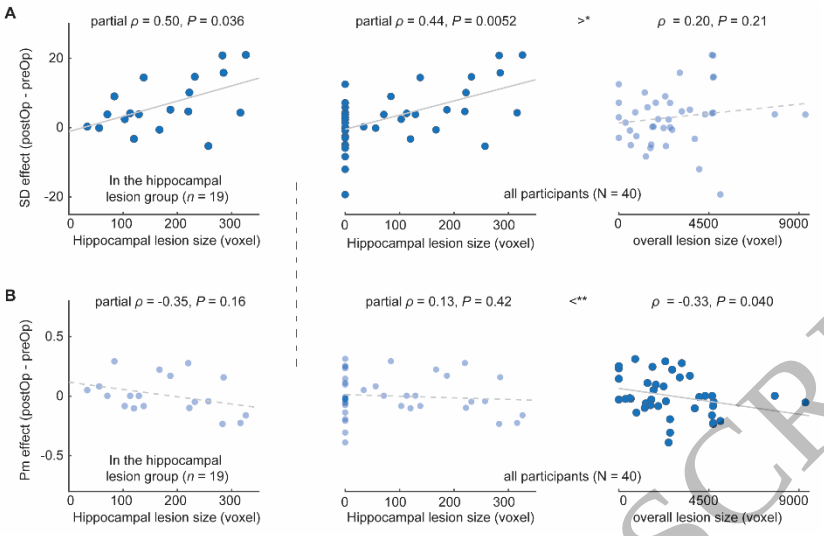

Figure 3
109x70 mm (x DPI)

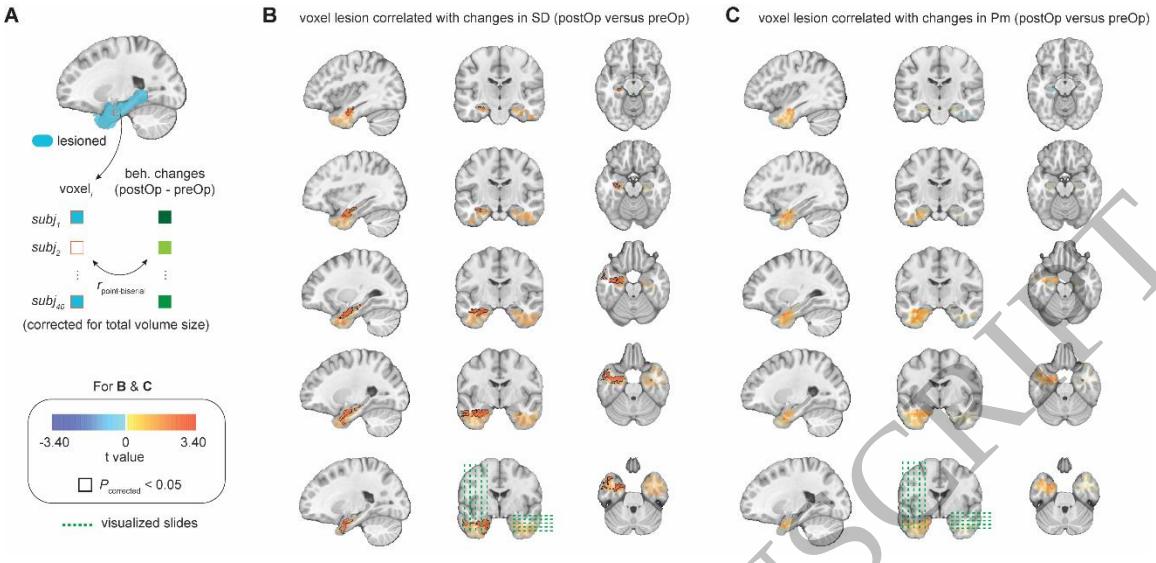

Figure 4
152x73 mm (x DPI)