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The hippocampus supports high-precision binding in visual working memory

Alyssa A. Borders[1,2] | Charan Ranganath[1,2] | Andrew P. Yonelinas[1,2]

[1]Department of Psychology, University of California, Davis, Davis, California, USA

[2]Center for Neuroscience, University of California, Davis, Davis, California, USA

Correspondence
Alyssa A. Borders, Department of Psychology, University of California, Davis, Davis, CA 95616, USA.
Email: aaborders@ucdavis.edu

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Abstract

It is well established that the hippocampus is critical for long-term episodic memory, but a growing body of research suggests that it also plays a critical role in supporting memory over very brief delays as measured in tests of working memory (WM). However, the circumstances under which the hippocampus is necessary for WM and the specific processes that it supports remain controversial. We propose that the hippocampus supports WM by binding together high-precision properties of an event, and we test this claim by examining the precision of color-location bindings in a visual WM task in which participants report the precise color of studied items using a continuous color wheel. Amnestic patients with hippocampal damage were significantly impaired at retrieving these colors after a 1-s delay, and these impairments reflected a reduction in the precision of those memories rather than increases in total memory failures or binding errors. Moreover, a parallel fMRI study in healthy subjects revealed that neural activity in the head and body of the hippocampus was directly related to the precision of visual WM decisions. Together, these results indicate that the hippocampus is critical in complex high-precision binding that supports memory over brief delays.

KEYWORDS
fMRI, hippocampus, lesions, memory precision, visual working memory

1 | INTRODUCTION

Lesion and neuroimaging studies have shown that the hippocampus is involved in supporting long-term memory for personally experienced events whereas other forms of memory such as short-term or working memory (WM) are subserved by separate neural systems (Alvarez et al., 1994; Baddeley & Warrington, 1970; Scoville & Milner, 1957; Squire & Zola-Morgan, 1991). However, a growing number of studies have challenged this view by showing that the hippocampus can be involved in, and in some cases is critical for, WM as measured on tasks in which subjects are required to maintain a small number of items over a period of a few seconds (Cabeza et al., 2002; Ezzyat & Olson, 2008; Hartley et al., 2007; Olson, Moore, et al., 2006; Ranganath & Blumenfeld, 2005; Stern et al., 2001). The mixed nature of the literature suggests that the question is not whether the hippocampus is involved in WM, but rather when, and thus considerable debate remains regarding the circumstances under which the hippocampus is necessary for successful WM and which processes rely on the hippocampus.

A number of neuropsychological studies have shown that damage to the hippocampus and the surrounding medial temporal lobe (MTL) cortices leads to an impairment in tasks that require associating different aspects of the encoding event such as remembering the color or location of an object compared to tasks that only require memory for individual objects or items (Braun et al., 2008, 2011; Finke et al., 2008, 2013; Hartley et al., 2007; Olson, Page, et al., 2006; Parra et al., 2009; Parra et al., 2015; Pertzov et al., 2013; Van Geldorp et al., 2014). These findings have led to the proposal that the hippocampus is important for binding of associative or relational information in the service of both WM and long-term memory (Cohen &

Eichenbaum, 1993; Graham et al., 2010; LaRocque & Wagner, 2015; Lee et al., 2012; Libby et al., 2014; Olsen et al., 2012; Saksida & Bussey, 2010). Hippocampal involvement in WM binding has remained controversial, however, because a number of studies have reported that hippocampal damage does not always impair WM, even if the tasks require memory for relations or associations (Allen et al., 2014; Baddeley et al., 2010, 2011; Jeneson et al., 2010; Shrager et al., 2008; Squire, 2017). To account for these discrepant findings, we propose that the functional role of the hippocampus is not simply to support binding, as has been previously argued, but to support high-precision memory in the context of complex binding (Yonelinas, 2013). That is, the hippocampus is necessary for the maintenance and retrieval of fine-grained information about prior events with multiple features. Most WM studies in lesioned patients have not assessed high-precision discriminations, and the few that have attempted to have not yet directly linked the hippocampus to memory precision or have only done so indirectly (e.g., Goodrich & Yonelinas, 2016; Koen et al., 2017; Pertzov et al., 2013; Warren et al., 2015). Moreover, although some prior imaging studies observed hippocampal activity during WM tasks (Mitchell et al., 2000; Nee & Jonides, 2011; Piekema et al., 2006; Ranganath & D'Esposito, 2001; Stern et al., 2001), whether hippocampal activity is directly related to the precision of WM remains untested.

To directly determine the role of the hippocampus in supporting WM for high-precision bindings, we conducted complementary patient (Experiment 1) and neuroimaging studies (Experiment 2) using a visual WM paradigm in which subjects are required to recall a color bound to a location and report the precise color using a continuous color wheel (CW; Wilken & Ma, 2004; Zhang & Luck, 2008; Figure 1). This paradigm allowed us to measure the precision of each memory response on a trial-by-trial basis in order to determine whether hippocampal damage reduces WM precision and whether hippocampal activity is directly related to objective measures of precision. We also utilized recently developed computational methods to determine whether a reduction in accuracy was due to reduced memory precision, or an increased likelihood of binding failures, such as misremembering which color was bound to which location or forgetting the color altogether.

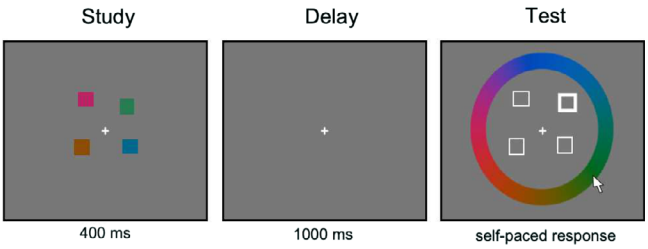

FIGURE 1 Color wheel task design. On each working memory trial, participants studied an array of four colored squares on a gray background and were asked to maintain the information over a 1-s delay. At test, one location of the study array was cued (i.e., the bolded square). Participants reported the exact color of the cued location by selecting the remembered color from a continuous color wheel using the cursor

2 | EXPERIMENT 1: PATIENT STUDY

To determine whether the hippocampus is critical in supporting WM precision, we first tested nine amnestic patients—four with selective hippocampal damage bilaterally and five with damage to the hippocampus and MTL cortex—to determine if they exhibited a selective reduction in the precision of WM judgments compared to controls. The amnestic patients and controls viewed four colored squares and were asked to maintain the colors in each location over a 1-s delay. One of the locations was then cued and the participants reported the remembered color of that square by selecting the exact color hue on a continuous CW using a cursor (Figure 1). For each trial, we calculated the distance between the target color and the selected color to obtain a measure of response error.

The average response error distributions of the patients and controls (Figure 2a) showed that a large proportion of responses were clustered near the target color, and that the proportion of trials decreased gradually as error magnitude increased until approximately 60° of error where the distributions then became relatively flat. Importantly, the patients' and controls' distributions were similar except that the patients produced fewer high-precision responses than the controls (i.e., fewer responses that were less than 20° from the correct color). The impairments at each interval of response error (2-degree increments) were quantified using a 2 (group) × 90 (error) linear mixed model ANOVA with participants included as a random effect. This revealed a significant group by error interaction, $F(89,2340) = 1.80$, $p < .001$, indicating that there was a significant difference in response errors in the patients and controls as a function of precision. Follow-up contrasts using least squared means between the two groups at each error interval showed that patients produced significantly fewer high-precision responses (i.e., errors of 4°, $t(2535) = 4.50$, $p < .001$, 8°, $t(2535) = 3.92$, $p = .008$, and 10°, $t(2535) = 3.73$, $p = .018$), compared to controls but the groups did not differ at any other error interval (p's > .2).

The results are consistent with the idea that patients were unable to maintain precise representations in WM, as compared to controls. An alternative explanation for these results, however, is that patients exhibited normal precision but committed more errors because they tended to misremember which color was associated with which location (i.e., "swap errors"). To assess this possibility, we compared the proportion of hits (i.e., responses that were within 20° of the target), and the proportion of swap errors (i.e., the remaining responses that were within 20° of one of the other three colors in the study array) for patients and controls using a 2 (group) × 2 (trial type) linear mixed model ANOVA. There was a significant interaction between group and trial type, $F(1,52) = 7.46$, $p = .009$, which reflected the fact that patients had fewer hits than controls, $t(56.3) = 3.74$, $p < .001$, but the two groups did not differ in proportion of swap errors, $t(56.3) = -0.02$, $p > .99$. The same pattern of significant results was observed when using more conservative scoring methods (i.e., defining hits and swap errors as responses within 15 or 10° of the studied colors). Thus, the reduction in memory precision in the patients cannot be attributed to an increased likelihood of committing

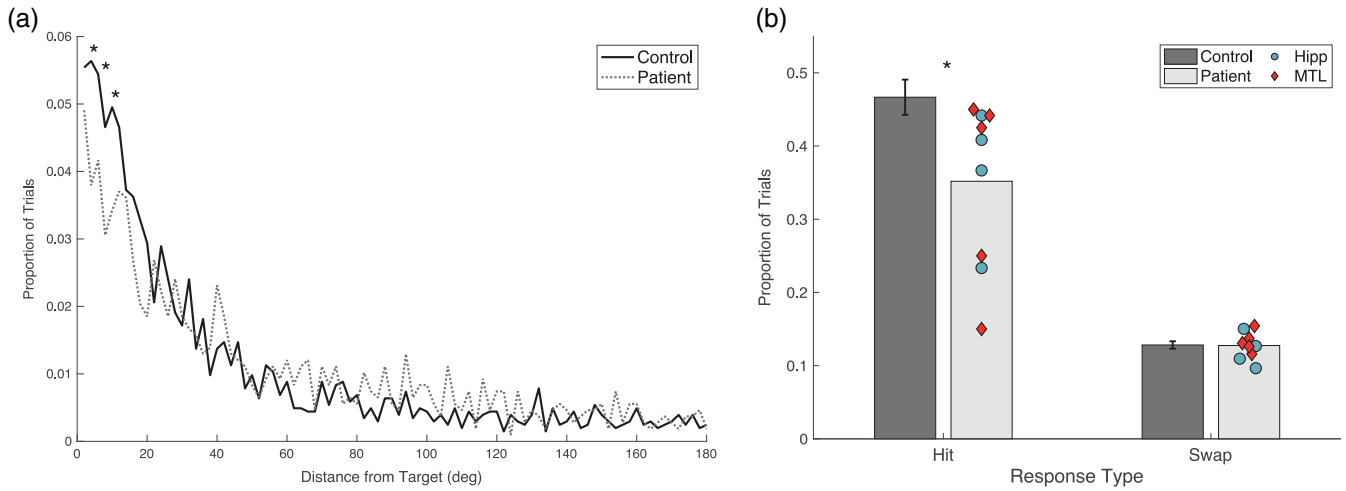

FIGURE 2 Reduced working memory precision in amnesic patients. (a) Proportion of trials related to each interval of response error (i.e., distance in degrees from the target color) for patients (dotted line) and controls (solid). Significance symbols (*) indicate the intervals in which patients and controls differed from one another. (b) Proportion of trials that were within 20° of the target color (hit) or 20° of another studied color (swap). Significance symbols (*) denote a difference in the number of hits for patients and controls, following a significant group × response type interaction. Individual patients are plotted along with the patient group mean. Patients with hippocampal selective lesions are shown in blue circles, while patents with lesions extending into the medial temporal lobe (MTL) are shown in red diamonds

TABLE 1 Parameter estimates of working memory processes

Model	Parameters	*p*-Value	Cohen's *d*	Group	Mean	*SD*
Standard mixture model	Guess	.421	−0.34	Con	0.35	0.14
				PT	0.40	0.17
	Precision (sd)	.003**	−1.39	Con	24.45	3.95
				PT	38.26	16.26
Standard mixture + swap model	Guess	.855	−0.08	Con	0.27	0.16
				PT	0.28	0.21
	Swap	.130	−0.65	Con	0.07	0.07
				PT	0.14	0.16
	Precision (sd)	.008**	−1.20	Con	25.41	4.83
				PT	35.10	12.19
Variable precision model	Guess	.915	0.05	Con	0.28	0.15
				PT	0.27	0.24
	Precision (sd)	.001**	−1.52	Con	28.25	6.56
				PT	59.48	34.29
	Variability	.003**	−1.35	Con	14.04	8.11
				PT	39.46	30.54

Note: Three computational models were used to fit and estimate circular response data. Precision was significantly worse in patients across all three models. Student's *t*-tests results are reported for all parameter comparisons between patients and controls.
** indicates $p \leq 0.01$.

swap errors. Furthermore, when comparing the proportions of trials between the controls and only the subset of patients with hippocampal selective lesions, we still found a significant reduction in hits, $t(46.4) = 2.64$, $p = .022$, but not in swap errors, $t(46.4) = 0.19$, $p > .99$, suggesting that damage to the hippocampus, not the surrounding MTL, is driving this impairment. Data for individual patients are shown along with the group means in Figure 2b.

To further verify that hippocampal damage led to a reduction in memory precision rather than simply reducing the frequency of swap errors or memory failures, we fit three different computational models to quantify the circular response data (Suchow et al., 2013; memtoolbox.org). Despite the different underlying assumptions of each of these models, explained below, they all converged in showing that memory precision was significantly impaired in the patients. For

example, the standard mixture model (Zhang & Luck, 2008) was used to derive estimates of memory precision and the likelihood of random guessing (e.g., memory failure) and showed that hippocampal damage predicted a significant reduction in precision but there was no difference in guess rate between patients and controls (all model parameter estimates and related statistics are presented in Table 1). Next, the standard mixture + swap model (Bays et al., 2009), which adds an additional parameter to account for and estimate the likelihood of swap errors, indicated that hippocampal damage predicted a reduction in precision, and did not impact the rate of guessing or the rate of swap errors. Finally, the variable precision model (Fougnie et al., 2012), which estimates precision and guessing as well as an additional parameter to model variability in precision responses, indicated that patients exhibited a reduction in memory precision and an increase in the variability of precision, but no changes in guess rate. This provides strong evidence that the precision of WM is reduced in patients with damage to the hippocampus. Moreover, this pattern is present even when excluding patients with damage extending into the MTL and comparing parameter estimates between controls and patients with selective hippocampal lesions. That is, we still see a significant patient deficit in precision across all three of the tested models (all p-values < .048, all parameter estimates and statistics in Supplementary Table S1). This again suggests that the hippocampus in particular is critical to supporting precision in WM.

To gauge whether the observed patient deficits in memory precision may have been related to underlying deficits in color perception or difficulties with the continuous CW task, a subset of patients ($n = 5$) and controls ($n = 11$) performed a perceptual task that was analogous to the WM task except that only one color was presented on each trial, the CW was visible for the entire duration of the trial, and a response was made on the CW immediately after the target disappeared, without a delay. Analysis of the perceptual response errors using the standard mixture model and variable precision model as described above showed no differences between patients and controls in any parameters, with precision estimate p's > .49, indicating that the patients performed normally on the perceptual task (response error distributions and parameter estimates for perceptual errors can be found in the supplemental information Figure S1 and Table S2, respectively). Note that the standard mixture + swap model was not used because, with only a single item, there was no possible swap location. These results suggest that the observed WM deficits cannot be attributed to an inability to make precise color discriminations or difficulty using the CW to respond.

The finding that the WM memory precision impairments were observed in patients with selective hippocampal damage suggests that the hippocampus rather than the surrounding MTL cortex plays a critical role in WM. However, it is possible that these patients may have suffered from subtle damage to surrounding MTL cortex that was undetected. Although the patients with observable damage to the hippocampus and those with varying damage to the MTL cortex including the hippocampus showed similar impairments, suggesting that the hippocampus in particular was critical for WM precision, we sought additional evidence for hippocampal involvement in WM precision by examining fMRI activation in healthy subjects.

3 | EXPERIMENT 2: fMRI

To determine whether the hippocampus is directly related to the precision of WM, we conducted an fMRI study with healthy subjects, which allowed us to determine if the level of neural activity in the hippocampus was related to an objective measure of memory precision. Subjects were scanned while they completed a visual WM CW task similar to that in the patient study described above (Figure 1), except that the number of items in each study trial was increased from 4 to 6 to increase difficulty for younger adults, and the nontarget color squares were represented at test, with only the target square empty. Behavioral results, shown in Figure 3a revealed that, as in the previous experiment, a large proportion of responses were near the target color and the proportion of response errors decreased gradually until approximately 60° of error (see supplementary information Table S3 for model estimates of behavioral data).

We examined how WM precision was related to BOLD activity in the head, body and posterior portions of the hippocampus and secondary analyses explored activity in the MTL cortex, specifically the perirhinal (PRc), entorhinal (ERc), and parahippocampal (PHc) cortices. Regions of interest (ROIs) were selected based on previous studies implicating these regions in functions ranging from perception to memory (Ritchey et al., 2015), and were anatomically defined for each participant (see Figure 3b for ROI examples).

If the hippocampus supports the varying precision of WM representations, then during successful memory (i.e., trials in which the participant likely had some information about the target color and reported a color near the target), then activity should be directly related to the precision of the behavioral responses on a trial-by-trial basis, whereas during unsuccessful memory (i.e., trials in which the participant likely had no information about the target color and guessed at random) there should be no relationship between activity and precision. Alternatively, hippocampal activity might reflect general memory success and show greater activation during remembered compared to forgotten items, but no direct relationship with precision.

For each participant, event-related precision regressors—a regressor that modeled the parametric effect of error on each trial—modeled Hits (error < 60) and Guess (error > 60) trials separately. Precision regressors were given a negative sign so that positive activity would be expected for a positive relationship between neural activity and *smaller error*. Non-parametric regressors for Hits and Guesses were also included in the model to account for the average activity level of each type of trial before correlating degree of error with amplitude of the neural signal in the precision regressors. Parameter estimates indexing activation for the parametric Hit and Guess contrasts were then extracted from each subject's individual ROIs. In order to compare activity across subregions, we conducted all analyses using linear mixed model ANOVAs on parameter estimates with accuracy and ROI as fixed effects and participant as a random effect.

The average parameter estimates for each hippocampal ROI are shown in Figure 3c and indicate that hippocampal activity was directly related to memory precision for Hits but not for random Guesses, particularly in the head and body of the hippocampus. There was a

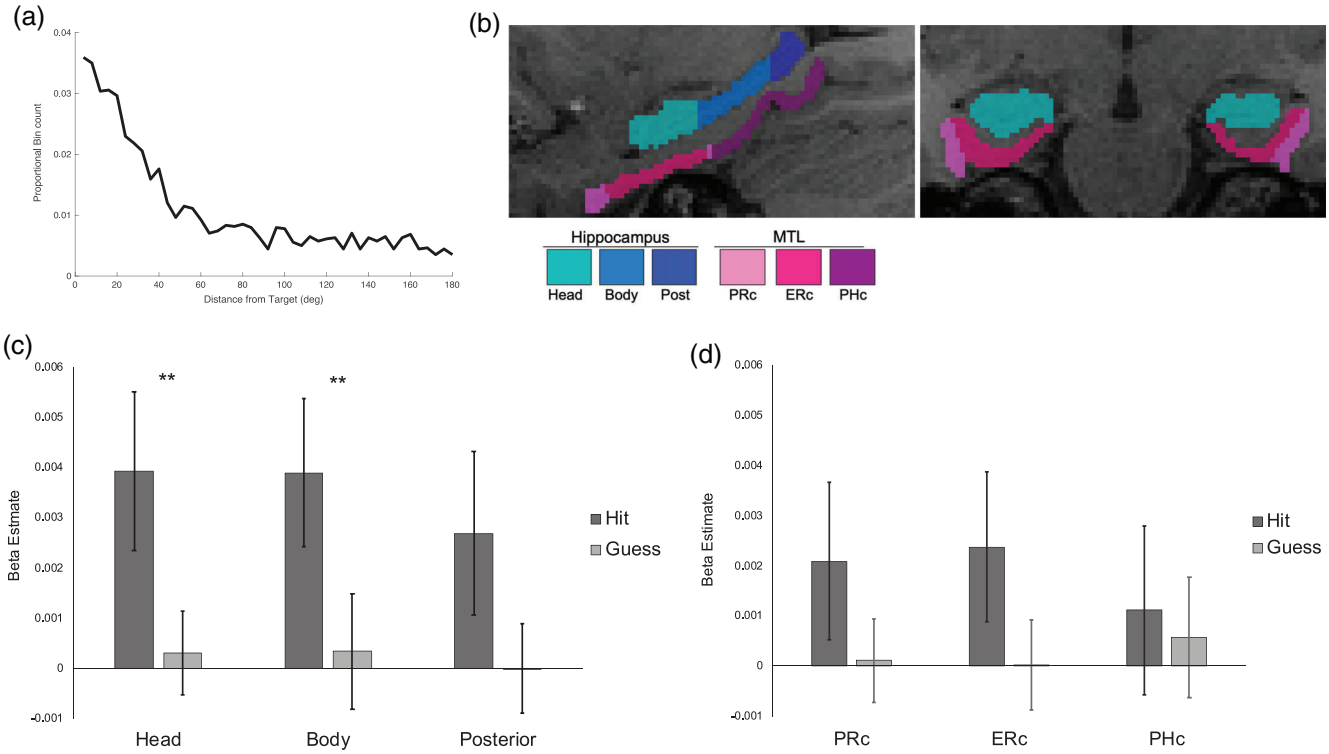

FIGURE 3 Medial temporal lobe modulation of memory precision in the color wheel task. (a) Distribution of errors aggregated across all subjects for the working memory (WM) color wheel task. (b) Sample region of interest (ROI) tracing of the head, body, and posterior portions of the hippocampus and the perirhinal cortex (PRc), entorhinal cortex (ERc), and parahippocampal cortex (PHc). (c) Precision-related activity in each hippocampal ROI. Activity in the head and body of the hippocampus was directly related to the degree of WM precision for hits but not for guesses. (d) Precision-related activity for hits and guesses in each medial temporal lobe (MTL) cortical subregion ROI. None of the MTL cortical regions were significantly related to WM precision. Significance indicators reflect *p*-values from an accuracy × ROI pairwise comparison using Bonferroni correction and Kenward–roger approximation estimation of degrees of freedom

significant main effect of accuracy, $F(1,90) = 18.73$, $p < .001$, reflecting the fact that hippocampal activity increased with memory precision for the Hits, but not for the Guesses. There was no effect of ROI, $F(2,90) = 0.54$, $p = .574$, nor a significant interaction, $F(2,90) = 0.23$, $p = .80$, suggesting that the effects were not significantly different across the long axis of the hippocampus. However, we conducted planned comparisons between Hit and Guess parametric activity for each ROI to find which hippocampal regions contributed to the main effect. Activity in the hippocampal head and body was significantly higher for Hits than Guesses (head: $t(90) = 2.69$, $p = .024$; body: $t(90) = 2.70$, $p = .024$) while activity in the posterior hippocampus did not differ between the two response types (posterior: $t(90) = 1.89$, $p = .186$). Thus, the results provide evidence that the hippocampus is indeed directly involved in visual WM precision and these effects were robust across the head and body of the hippocampus.

A secondary analysis examined activity related to precision within MTL cortex ROIs including the PRc, ERc, and PHc (see Figure 3d), but did not find a strong relationship between neural activity and precision. The analysis of these ROIs revealed a marginal, nonsignificant main effect of accuracy, $F(1,90) = 3.93$, $p = .051$, weakly suggesting that the Hits were modulated by memory precision more than Guesses. There was neither a main effect of ROI, $F(2,90) = 0.12$, $p = .889$, nor a significant interaction, $F(2,90) = 0.68$, $p = .508$. In follow-up comparisons conducted to mirror the hippocampal ROI analysis, none of the MTL subregions showed a significant difference between parametric activity in Hits and Guesses (PRc: $t(95.3) = 1.41$, $p = .49$; ERc: $t(95.3) = 1.73$, $p = .26$; PHc: $t(95.3) = 0.21$, $p = .99$.).

To determine whether the observed hippocampus involvement in WM was limited to the CW WM task, we assessed memory success effects in a standard change detection (CD) WM task that has been used in a number of neuropsychological studies (Goodrich & Yonelinas, 2016; Jeneson et al., 2012). This CD task was the same as the CW task except that when a square was cued at test, it was either the same color as at study (i.e., same trials) or a new color not present in the original array (i.e., different trials), and participants indicated whether the square was the same or different from study. The colors were selected from a set of seven canonical colors rather than the entire color space. We contrasted Correct and Incorrect change trials and extracted beta parameter estimates from each subject's ROIs. The average parameter estimates for each ROI (supplementary information Figure S2a) were compared to zero in a one-sample *t* test and showed that MTL activity across all subregions, both in the

hippocampus and the MTL cortex, predicted WM success (all *p*'s < .002). Thus, activity in each of the hippocampal and MTL cortical regions was related to WM success in the CD task.

As a final control, to determine whether the hippocampal activity we observed in the WM CW task reflected the requirement to maintain precise visual information over a delay, or the requirement to make fine-grained discriminations using a continuous response paradigm in general, we examined activity in a perceptual control (PC) task. The perception task was identical to the WM task except that participants only studied a single item in each trial and there was no delay between the study item and the test. The functional data from this task were analyzed similarly to the CW task with regressors for Hits (error < 30) and Guesses (error > 30) plus a negative parametric regressor scaled to the degree of response error on Hit trials. A parametric regressor was omitted for Guess trials because there were very few responses further than 30° from the target color. Parameter estimates related to parametric activity in Hits were extracted from each of the hippocampal and MTL cortex ROIs (supplementary information Figure S2b). Because we could not compare parametrically modulated activity for Hits and Guesses, activity from each ROI was compared to zero in a one-sample *t* test. The analysis indicated that perceptual precision was not significantly related to activity in any of the ROIs (*p*'s > .25), suggesting that the parametric relationship between WM precision and hippocampal activity cannot be attributed to perceptual discrimination or demands of the continuous response paradigm. To assess that the failure to find a correlation between precision and activity in the PC task was due to the reduced range of the observed precision errors, we used the same analyses described above to examine other regions outside of the MTL known to be involved in visual WM. Parametric modulation activity in the parietal lobe, specifically the inferior parietal gyrus (IPG; defined in automated anatomical atlas 2; Rolls et al., 2015) was significantly greater than zero, $t(17) = -4.30$, $p < .001$, suggesting that the limited range of errors in the control condition was not a limiting factor in detecting parametric effects between precision and activity.

4 | DISCUSSION

The aim of the current study was to test the hypothesis that the hippocampus plays a role in WM by supporting complex high-precision binding. To test this, we used an associative visual WM task that allowed us to quantify the precision of each memory response in parallel patient and neuroimaging experiments. Amnestic patients with damage to the hippocampus, whether that included the hippocampus and the surrounding MTL or was selective to the hippocampus, were significantly impaired on the WM task. Importantly, patients were not more likely to forget the color completely or misremember the color-location binding but were specifically impaired in their ability to maintain and retrieve the precise color of the bound items. This precision impairment was seen regardless of the method or theoretical model used to quantify the memory responses and was not observed in an analogous color perception task that did not require WM maintenance of the information or binding of the color to a location. In healthy participants, we found that neural activity in the head and body of the hippocampus was directly related to the degree of WM precision such that greater color memory precision was related to increased hippocampal activation. This hippocampal activation was specific to visual WM precision, and it was not observed in an analogous color perception task in which there was no requirement to maintain that information over a delay period or to bind the color with a location. Together, these studies provide strong evidence in support of the idea that the hippocampus is involved in processes that require the binding of high-precision information in WM.

The findings are consistent with prior patient and neuroimaging work indicating that the hippocampus is involved in WM tasks (Braun et al., 2008, 2011; Finke et al., 2008, 2013; Hartley et al., 2007; Parra et al., 2009, 2015; Pertzov et al., 2013; Van Geldorp et al., 2014). However, patients in our study were able to remember the general color of target items and did not report the color of other nontargeted item any more than controls did, indicating that they retained some ability to bind locations to their respective colors. The patients were only impaired in retrieving the precise colors of the studied item, illustrating that the hippocampus is particularly critical in supporting high-precision binding.

Thus, one potential reason that some prior studies (Allen et al., 2014; Baddeley et al., 2010, 2011; Jeneson et al., 2010, 2012; Shrager et al., 2008; Squire, 2017) have failed to detect WM impairments in hippocampal patients is that they may not have evaluated or required high-precision memory information or processing. Consistent with this account, patients with hippocampal damage were found to be impaired at making WM judgments in a forced-choice test when high-precision discriminations were required (i.e., lures or nontarget items are highly similar to the studied item), but they were not impaired in equally difficult tasks that required less precise discriminations (Koen et al., 2017). Similarly, hippocampal lesioned patients were significantly impaired at a visual WM CD task that required high-precision information to detect subtle color differences (Goodrich & Yonelinas, 2016).

While the current results showed that hippocampal damage predicted a pronounced reduction in WM precision and was not directly related to a significant increase in binding errors or memory failures, the results of our study should not be interpreted to imply that hippocampal damage cannot lead to an increase in binding errors or memory failures. For example, prior studies have indicated that hippocampal damage can lead to an increase in binding errors in some cases (Pertzov et al., 2013; Watson et al., 2013) and memory failures rather than reduced precision in others (Warren et al., 2015). It is not yet clear why hippocampal damage does not always produce a consistent pattern of impairment, but it could be related to the extent to which different items occur in close spatial proximity (Czoschke et al., 2019; Fougnie et al., 2012), the number of objects that are maintained (Oberauer & Lin, 2017; Vellage et al., 2019), or the duration of the study or maintenance period (Bays et al., 2011).

One underlying process of WM that, to our knowledge, has not been explored in the neuropsychological literature is the variability of

precision. Using the variable precision model to interpret the continuous response data, patients showed reduced precision ability and greater variability of that precision ability from trial to trial. The root of this variability has yet to be established even in healthy participants, but some have proposed it is related to interference from other studied items, both items from previous trials and other items in the study array (Czoschke et al., 2019; Fougnie et al., 2012). Given that this interference may reflect the ability to separate or integrate information across time and space, a well-documented function of the hippocampus in other domains, the integrity of the hippocampus' functionality could very well influence the variability of precision. Future work employing the variable precision model in a variety of patient populations could prove valuable in delineating factors that influence this variability and understanding WM more broadly.

Although we did not explicitly control for verbal coding or direct participants not to generate verbal labels for each color, we do not think that verbalization strategies could explain the current hippocampal effects observed in WM. First, the rapid encoding duration we used (i.e., the four-item array was presented for 400 ms) should limit verbalization. Moreover, the usefulness of any color naming should be made difficult given the continuous color stimuli used. In addition to not providing precise information about a color, items within a single array could differ by as little as 12°, and so a verbal label would not be reliable in distinguishing between colors. Secondly, if participants did attempt to generate descriptive labels, they would likely be unable to encode all four colors before the array disappeared and show an increase in memory failure rather than the observed decrease in precision. Finally, in a prior study examining visual WM in amnesics using colored squares, a secondary verbalization task to explicitly limit color naming did not affect the patient's impairments (Jeneson et al., 2012) suggesting that verbal strategies, even if they are being used, are not particularly useful in this task.

The current findings may help explain some of the broader cognitive impairments often observed in patients with hippocampal damage. For example, it is well documented that patients exhibit pronounced impairments on memory and perception tasks that involve complex spatial scenes (Graham et al., 2010). One critical role of visual WM is to integrate visual information across visual saccades to form abstract representations of visual scenes (Luck & Vogel, 2013; Nau et al., 2018). In this way, deficits in both the perception and memory of complex scenes could be due to impaired WM binding. In addition, the current finding that hippocampal damage disrupts memory for precise bindings is useful in understanding the navigational deficits sometimes observed in amnesic patients. For example, recent work has indicated that hippocampal patients can remember general location information very well, such as remembering which quadrant of a room an object was earlier located in, but they are severely impaired at identifying precisely where in the room the object was located (Kolarik et al., 2016, 2018). We believe that viewing the hippocampus not simply as supporting binding but as specifically supporting high-precision binding, may be useful in revealing other cognitive deficits as well.

It is important to note that it is possible that the subset of patients with selective bilateral hippocampus lesions may have had additional damage to the surrounding MTL cortex that was undetectable using our current MRI methods. Although this does not detract from the findings that the MTL is critical for WM, it does somewhat weaken the interpretation of results from Experiment 1 that the hippocampus, specifically, is critical for normal WM precision. However, the hippocampus is the only common structure with confirmed damage across all of the patients across a range of etiologies. There is no evidence to suggest that the different etiologies of the four hippocampal-selective patients would all produce the same undetectable damage, and that this extrahippocampal profile of damage would be the true cause of the precision impairments. In addition, the important role of the hippocampus in complex WM precision is consistent with the neuroimaging results of the hippocampus and surrounding MTL cortices.

The current neuroimaging results support several previous studies that have reported hippocampal activation during WM tasks (Mitchell et al., 2000; Nee & Jonides, 2011; Newmark et al., 2013; Piekema et al., 2006; Ranganath & D'Esposito, 2001; Stern et al., 2001) but they further revealed that on a trial-by-trial basis hippocampal activity is directly related to WM precision. Other fMRI studies have found cortical areas that support WM precision, including the parietal lobe (Galeano Weber et al., 2016) and low-level sensory regions in the occipital lobe (Emrich et al., 2013; Ester et al., 2013), but no study we are aware of has focused on the hippocampus or MTL cortex. In the current study, in trials where the participant remembered some information about the cued color, the magnitude of neural activity in the hippocampus increased as the recalled color was closer to the target color. Importantly, this modulation of precision was greater than chance, as modeled with random guessing. This novel finding further provides support to the hypothesis that the hippocampus plays a fundamental role in the precision of WM, especially given that activity in the MTL, which robustly predicted WM success in the control task, was only marginally related to precision and no subregion appeared to significantly contribute to the effect.

Interestingly, the posterior hippocampus and the parahippocampal cortex were not significantly related to memory precision, which is surprising given work suggesting that these more posterior MTL regions may be related to precise spatial information (Brunec et al., 2018; Poppenk et al., 2013). This work characterizing potential differences across the long axis of the hippocampus and extending MTL has come primarily from studies of long-term memory and so whether differences in precision can be observed across the long axis in WM tasks is currently unknown. Unfortunately, there were not enough patients with damage localized to either the anterior or posterior hippocampus in Experiment 1 to make any meaningful comparisons and address this question. It is also possible that the more anterior precision-related activity that we observed reflects the retrieval of color information rather than spatial location information. Future studies examining the role of different hippocampal subregions in precision across WM tasks and materials will be critical in further understanding the functional role of the hippocampus in WM.

Recent fMRI studies of visual WM precision have focused on a network of regions including the prefrontal cortex, the inferior parietal sulcus, and various visual regions (Emrich et al., 2013; Ester et al., 2013; Galeano Weber et al., 2016, 2017). The current results add to this literature by indicating that the hippocampus also plays a critical role in WM, and that it is particularly useful in binding items to precise color information. However, it is not known how the hippocampus interacts with these other regions to support WM precision. One dominant view of WM is that frontal–parietal attentional mechanisms interact with the visual regions involved in processing the sensory characteristics of the maintained items to keep those representations in an active state, possibly via recurrent oscillatory activity (for review see Luck & Vogel, 2013). Along these lines then, the hippocampus may become temporally synchronized with these attentional and visual processing areas, and so may provide additional mnemonic activation information for the maintained items. Another possibility is that the hippocampus may not be directly involved in maintaining continuous activation per se, but rather it may form a representation of the study event through synaptic weight changes within the hippocampus, and this hippocampal representation can then be compared to the test probe in visual and parietal regions to derive a memory match signal (Elfman et al., 2014).

In Experiment 1, hippocampal patients were impaired when they were required to maintain the colors of four simple items across a 1 s delay, but they were not impaired in a PC condition in which they indicated the color of a single item. The PC task was designed to verify that the patients were not visually impaired at discriminating between the colors that were used in the WM task. That is, if patients could not perceive those colors normally then they could not be expected to be able to bind those colors to the item locations. The results thus show that the WM impairments seen in the patients cannot be attributed to impairments in detecting precise color information. Moreover, the finding that hippocampal activity in the fMRI study was directly related to WM precision but was not related to precision in the control condition indicates that the hippocampus is related specifically to WM precision, not to making precise color judgments per se. These results, however, should not be interpreted as indicating that the hippocampus plays no role in perception. For example, if we had included more complex materials in the perception task, such as simultaneously presenting multiple colored squares to compare that could differ in small increments; the patients may have been impaired in the perception task as well as the WM task. In fact, prior work has indicated that these types of patients can be impaired at making perceptual discriminations for complex materials even when there is no memory delay period (Aly et al., 2013; Barense et al., 2007; Graham et al., 2010). Moreover, other work has indicated that the patient's WM deficits can be observed either when the materials are complex or when the task requires memory for precise information (Goodrich & Yonelinas, 2016; Koen et al., 2017). These results suggest that the hippocampus is critical in forming complex high-precision representations that support both WM and perception (Yonelinas, 2013).

In summary, the neuropsychological and imaging studies reported here converge in suggesting that the hippocampus plays a critical role in WM precision, whereas there was limited evidence for a similar role of regions in the surrounding MTL cortex. Specifically, damage to the hippocampus predicts a reduction in visual WM precision and hippocampal activity is directly related to the objective precision of those memories, providing further evidence for the hippocampus' role maintaining and retrieving the high-precision features that make up complex events, even in WM.

5 | METHODS

5.1 | Experiment 1: Methods

5.1.1 | Participants

Nine amnestic patients and seventeen healthy age- and education-matched controls participated in exchange for monetary compensation. Four of the patients had selective hippocampal damage and five had lesions that included the hippocampus and extended into surrounding MTL cortex. Each patient was administered a battery of neuropsychological tests including the WMS-R (Wechsler, 1987), the Doors and Peoples test (Baddeley et al., 1994), and the Shipley Institute of Living Scale (SILS) (Shipley, 1940). The SILS was used to estimate WAIS-R IQ (Zachary et al., 1985). All participants reported normal or corrected-to-normal vision and were screened for normal color vision with the 24-plate Ishihara Color Blindness Test (Ishihara, 2000). All controls scored within the normal range on all tests. Patient descriptions and neuropsychological test scores are shown in Table 2 and the etiology and lesion descriptions are listed in detail below.

Patient 1001 suffered from Hashimoto encephalopathy and exhibited abnormal necrotic cavities on the left hippocampus and similar but less pronounced cavities on the right hippocampus. This patient's cavities had a rounded shape and resembled the pathologic cavities consistent with individuals who have suffered hypoxia-related CA1 necrosis (Nakada et al., 2005). MRI scans were assessed by a neurologist and suggested damage was limited to the hippocampus bilaterally with no damage apparent in the surrounding parahippocampal gyrus. Patient 1003 had limbic encephalitis that resulted in bilateral hippocampal damage with no apparent damage to the surrounding MTL cortex (see Figure 4). Gray matter volume estimates indicated that the left and right hippocampi were reduced in volume, but no other MTL structures showed significant volume reduction. See Aly et al. (2013) for estimates of gray matter volume for this patient (referenced as Patient 2 in that study). Patient 1005 had a traumatic brain injury due to a car accident and suffered bilateral damage to the MTL, including hippocampus. The extent of damage was assessed from the patient's high-resolution MRI scan (see Figure 4). For specific estimates of gray matter loss in the hippocampus and surrounding parahippocampal gyrus, see Kolarik et al. (2016). Patient 1008 suffered a prenatal right posterior cerebral artery infarct

TABLE 2 Patient descriptions and neuropsychological scores

Patient	Damage	Age	Ed	Sex	WAIS-R Est IQ	WMS-R (z score)					D&P (%tile)
						Verbal	Visual	Gen	Attn	Delay	
1001	Bilateral HC	56	16	F	110	−0.87	−1.00	−1.00	1.33	−0.47	25%
1003	Bilateral HC	60	12	F	112	−1.80	−0.27	−1.53	0.07	−2.20	1%
1005	Bilateral MTL	30	19	F	110	−0.07	1.07	0.33	0.27	−0.40	5%
1008	R MTL	72	12	F	83	0.07	−1.53	0.40	0.00	−0.27	5%
1009	L MTL	37	17	M	97	−1.60	0.40	−1.13	−0.67	−0.60	50%
1010	L MTL	64	12	M	na	−2.93	−1.07	−3.20	−0.87	−1.73	5%
1011	Bilateral HC[a]	52	16	M	96	−2.53	2.00	−1.40	−0.20	−1.13	1%
1012	L MTL	56	21	M	112	−1.40	0.93	−0.80	1.67	−0.40	na
1032	Bilateral HC	49	18	F	95	−0.33	1.47	0.13	−0.20	−0.07	25%

Note: The Shipley Institute of Living Scale was used to estimate WAIS-R IQ. The Doors and People test is based on recognition and recall; the generalized memory percentile is reported.

Abbreviations: D&P, Doors and People Test; HC, hippocampus; MTL, medial temporal lobe; na, score not available; OFC, orbitofrontal cortex; WAIS-R, Wechsler Adult Intelligence Scale-Revised; WMS-R, Wechsler Memory Scale-Revised.

[a]This patient suffered a mild hypoxic episode as a result of a cardiac arrest and has presumed selective hippocampal damage. He is unable to undergo structural MRI scanning to confirm the extent and selectivity of the damage due to an implanted defibrillator.

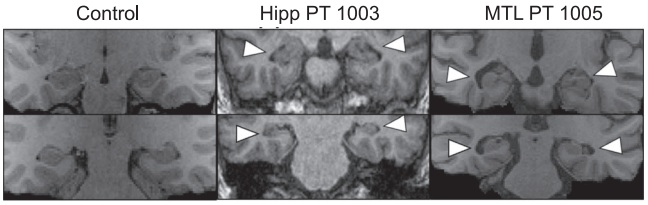

FIGURE 4 Patient lesion images. Sample MRI images for a control participant, a patient with selective hippocampal damage (1003) and one patient with damage extending into the medial temporal lobe (MTL) (1005). All images are of coronal slices in the head and body of the hippocampus

resulting in damage to the right occipital-temporal cortex. An MRI taken as an adult revealed significant damage to the posterior hippocampus and parahippocampal gyrus, as well as the fusiform and lingual gyri. The patient also has left hemianopsia. Patients 1009 and 1012 had left temporal lobectomies to treat intractable epilepsy. The surgeries were standard temporal lobe resections, in which approximately 4 cm of the anterior temporal lobe, including the anterior half of the hippocampus, the amygdala, and the anterior third of the parahippocampal gyrus, were removed. Patient 1009 underwent a high-resolution MRI scan and the rest of the brain appeared to be normal post-surgery as assessed by a neurologist. Patient 1010 had a craniotomy in the left temporal region to remove an astrocytoma and an arachnoid cyst. The surgery was a standard left anterior temporal lobe resection, in which approximately 4 cm of the anterior temporal lobe, including the anterior third of the hippocampus and the amygdala, were removed. The rest of the brain appeared normal on a clinical MRI scan as assessed by a neurologist. Patient 1011 suffered a mild hypoxic episode as a result of a cardiac arrest and has presumed selective hippocampal damage due to oxygen deprivation under 8 min (Gadian et al., 2000; Hopkins et al., 1995; Kono et al., 1983; Rempel-Clower et al., 1996; Smith et al., 1984). This patient has a defibrillator and is unable to undergo structural MRI scanning to confirm the extent and selectivity of the damage. Patient 1032 had viral encephalitis resulting in atrophy in both hippocampi, with loss of the internal hippocampal architecture on the left side. Clinical MRI scans assessed by a neurologist showed no additional damage to the surrounding area or cortex.

5.1.2 | Task design

Participants performed a WM CW task (Figure 1) followed by a PC CW task. All trials were presented on a gray background with a fixation cross appearing in the center of the screen. Participants were told to focus on the fixation cross between trials and during the delay periods. The stimuli were 50 × 50-pixel colored squares with a 2-pixel white border. All color stimuli were selected from a set of 180 colors that comprised the CW. These 180 colors were evenly distributed along a continuous color circle with equal luminance derived from CIE $L^*a^*b^*$ space. The color circle had a radius of 60 and $L = 60$, $a = 20$, $b = 38$. The colors presented on each trial were constrained to be at least 12° apart to reduce the similarity between studied items. The presentation locations for the colored squares were selected from a set of 12 start positions centered around an invisible circle that, when viewed at 50 cm, subtended 12° of visual angle (diameter 400 pixels). To prevent the squares from repeating in predictable locations, the locations varied randomly from the start position by up to 90 pixels in the horizontal and vertical directions. On each WM trial, participants studied an array of four colored squares for 400 ms and were then asked to maintain the information over a 1-s delay. At test, empty squares reappeared in the same locations and one square of the array was cued with a bolded border. Participants were given an unlimited amount of time to report the

remembered color of the cued square on a continuous CW using a mouse. Once participants made a response, on-screen feedback showed an "X" at the correct target color for 1000 ms.

The PC task was also given to assess whether the perceptual abilities of patients and controls differed. The task was identical to the WM task except only a single colored square appeared in each trial while the CW was displayed, and there was no delay between the study and the test. That is, participants were presented with a single colored square and the CW for 400 ms and reported the color on the CW using a mouse immediately after the square disappeared. On-screen feedback again appeared at the end of the trial. The task required that participants report the precise color of the square, but they did not have to bind a color to each location or maintain the information over a delay. This task was added after 10 subjects had been run, and thus we only have data for 5 patients and 11 controls.

5.1.3 | Statistical analyses

We fit three different computational models to quantify the circular response data and estimate parameters of different WM processes using Memtoolbox (Suchow et al., 2013) in MATLAB 2018a. All subsequent statistical analyses were conducted in R version 3.5.1. To compare parameter estimates from each model, Student's *t* tests were used to compare patients and controls. Samples were tested for equal variance and normality using Levene's test and Shapiro–Wilk test, respectively. Some samples violated the assumption of equal variance and so a Welch test supplemented the Student's *t* test. The pattern of significant comparisons was identical to the original Student's *t* test. All samples met the assumption of normality.

We used linear mixed effects models to assess differences between patients and controls in the types of responses. These models included group and either the response error interval or the trial type (i.e., hits and swap errors) as fixed effects, and participant as a random effect. All linear mixed models were analyzed in R using the lmerTest package to fit the models and the eemeans package to estimate least squared means for follow-up comparisons with Bonferroni multiple comparisons correction and Kenward–Roger approximation estimation of degrees of freedom.

5.2 | Experiment 2: Methods

5.2.1 | Participants

Nineteen healthy young adults (mean age = 24.44, female = 12) participated in Experiment 2. Participants were self-reported to have normal color vision and screened to exclude contraindications for fMRI such as non-MR compatible implants. One participant was excluded because of technical issues with the scanner that resulted in unusable structural data. No participants were excluded due to excessive movement (more than 3 mm of head motion in any direction) or abnormalities in the MR scan. This resulted in 18 participants with useable data.

5.2.2 | Task design

Participants performed three tasks throughout the experiment. First, participants completed three blocks of a CD WM task, followed by three blocks of the CW WM task, and finally two blocks of a PC task. The CW task was used to assess whether hippocampal activity was directly related to visual WM color precision. The CD task served as a control to assess hippocampal activation in a standard visual WM task in which subjects were not explicitly required or directed to attend to high-precision color information. The PC task required participants to make color discriminations using a continuous CW but there was no WM requirement (i.e., only a single item and no WM delay) and served as a perceptual-motor control. Behavioral piloting of the two WM tasks was conducted to balance difficulty. Pilot studies indicated that a set size of six items led to similar levels of performance (approximately 70%) in the two tasks and that task order did not affect performance. The CD task always preceded the CW task because the requirement to focus on color precision that is involved in the CW task could carry over to the CD task even though the latter task does not explicitly require precise color memory to succeed. Each block included 50 trials. At the beginning of each new task, participants were given written and oral instructions followed by 16 practice trials that were not scanned. Structural scans were collected immediately before the CW task. The CW stimuli set and array locations were selected in the same manner described in Experiment 1. The colors used in the CD tasks were green, yellow, red, pink, purple, blue, and cyan.

On each WM, trial participants studied an array of six colored squares on a gray background for 400 ms and were asked to maintain the information over a 1-s delay. At test, the study array reappeared and one location of the study array was cued. Participants had 2000 ms to respond on CD trials and 3000 ms to respond on CW and PC trials. In the CD task, participants reported whether the color in the cued square changed or remained the same. In the changed trials, the square changed from one distinct color to another (e.g., red to green) and did not require precise color information to successfully detect a change. In contrast, the cued square was blank in the CW task and participants reported the exact remembered color of the cued location using the continuous CW. Mouse responses in Experiment 2 were made with a scanner-safe trackball mouse to reduce movement in the scanner. To encourage a precise response under a time constraint, participants were encouraged to use the entire 3000 ms response period to refine their color choice. Feedback was given after every trial; correct/incorrect for CD trials and an "X" at the correct target color for trials using the CW.

In the perception task, participants were presented with a single colored square and asked to report the exact color using the continuous CW immediately after the square disappeared. The task required that participants report the precise color of the square, but they did not have to bind each color to a location or maintain the information over a delay.

5.2.3 | fMRI acquisition and preprocessing

Scanning was done on a Siemens Skyra 3 T scanner system with a 32-channel phased array head coil. Functional images were collected of the whole brain using a multiband EPI sequence with 3 mm isotropic resolution (TR = 1220 ms, TE = 24 ms, 38 interleaved slices, FOV = 192 mm, flip angle = 67°, multi-band acceleration factor = 2, bandwidth = 2442 Hz/Px). High-resolution T1-weighted structural images (1.0 mm isotropic) were collected for each participant using an MPRAGE sequence (FOV 256 mm, TR 1800 ms, TE 2.96 ms, T1 1060ms, GRAPPA, slices 208, flip angle = 7 , bandwidth = 240 Hz/Px). These scans were collected between the first and second task. Each functional run began and ended with 10 s of blank screen to allow for signal normalization and full signal capture for the final trial.

All preprocessing of fMRI data was conducted using Statistical Parametric Mapping software (SPM8, RRID:SCR_007037). Implicit masking was disabled by setting the default mask threshold to negative infinity and a whole brain explicit mask was used instead. Functional EPI images were spatially realigned to the first image of the second block and resliced. The structural MPRAGE image was co-registered to the mean EPI image. The structural and functional images were normalized to the Montreal Neurological Institute (MNI) EPI template brain using segmentation parameters of the co-registered MPRAGE image. Functional images were then resliced to 3 mm^3 isotropic resolution and smoothed with a 6 mm FWHM Gaussian kernel. Slice timing correction was not implemented because there were multiple slices acquired at each time point with the multiband sequence and a short TR should remain robust against timing issues.

The EPI time series were checked for excessive motion (>3 mm in any direction) and rapid changes in signal (>1.5% sudden change in global mean signal) using Artifact Detection Tools (RRID:SCR_005994). Two subjects had excessive movement isolated to a single run (one CW run, one PC run). These runs were excluded from preprocessing, behavioral analysis, and functional MR data analyses.

All analyses used structural ROIs of the hippocampus, further divided into head, body, and posterior, as well as PRc, ERc, and PHc. These ROIs were selected based on previous studies implicating these regions in functions ranging from perception to memory and anatomically defined with boundaries described according in Ritchey et al. (2015). Individual ROIs for each participant were traced on each MPRAGE structural scan in subject-native space using the ITK-SNAP software (ITK-SNAP, RRID:SCR_00201) then warped to the MNI template using the same normalization parameters generated for each participant in preprocessing. If a voxel had functional activity <5% the global signal, it was omitted from that subject's analysis. Because we had no predictions about laterality, ROIs were collapsed across hemisphere for analyses.

5.2.4 | fMRI data analyses

We used a separate general linear model to model the functional data for each task and all first level models included run regressors and six motion regressors in addition to the event-related regressors for each task. Activity in each trial was modeled at the onset of the test display.

All CW trials with a response error greater than 60° were categorized as "Guesses" because the distribution of errors was consistently flattened to the uniform distribution at that point and responses were likely made at random without information about the target color. Trials with a response error less than the 60-degree threshold likely occurred when the participant had some information about the target color and so categorized as "Hits." Event-related precision regressors—a regressor that modeled the parametric effect of error on each trial—modeled Hits and Guess trials separately. Non-parametric stick function regressors for Hits and Guesses were also included in the model to account for the average activity level of each type of trial before correlating degree of error with amplitude of the neural signal in the precision regressors. Parameter estimates indexing activation for the parametric Hit and Guess contrasts were then extracted from each subject's individual ROIs using the SPM toolbox, MARSBAR (Brett et al., 2002; marsbar.sourceforge.net).

Using similar logic, PC trials were categorized as Hits (error < 30) and Guesses (error > 30) based on the shape of the distribution of response errors. The functional data from this task were analyzed similarly to the CW task with regressors for Hits and Guesses plus a parametric regressor scaled to the degree of response error on Hit trials. A parametric regressor was omitted for Guess trials because there were very few responses further than 30° from the target color. Parameter estimates related to parametric activity in Hits were then extracted from each of the hippocampal and MTL ROIs.

In the CD task, trials were sorted as either a hit, miss, correct rejection, or false alarm and a regressor was included for each type. We were interested in the detection of color differences so in our analyses, we contrasted correct and incorrect change trials only and extracted beta parameter estimates related to accuracy from each subject's ROIs.

5.2.5 | Statistical analyses

We used linear mixed effects models to compare precision-related neural activity across ROIs. Accuracy and ROI were included as fixed effects with participants as a random effect. All linear mixed models were analyzed in R 3.5.1 using the lmerTest package to fit the models and the eemeans package to estimate least squared means for follow-up comparisons with Bonferroni multiple comparisons correction and Kenward–Roger approximation estimation of degrees of freedom.

The CD analysis consisted of a measure of accuracy from each participant's first-level contrasts. Given the extremely high performance in the PC task, we could not estimate parametrically modulated activity for Guesses and only used a precision-related measure in Hits. Thus, each task yielded a single measure of activity related to accuracy and we could not conduct analyses analogous to the CW task (i.e., linear mixed effects models.) Instead, we used one-sample *t* tests to compare neural activity from each ROI to zero.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ORCID

Alyssa A. Borders https://orcid.org/0000-0001-7699-5399
Charan Ranganath https://orcid.org/0000-0001-5835-6091

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