Neuropsychologia 134 (2019) 107227

Contents lists available at ScienceDirect

Neuropsychologia

journal homepage: http://www.elsevier.com/locate/neuropsychologia

Visual working memory impairments for single items following medial temporal lobe damage

Robin I. Goodrich [a,b,*], Trevor L. Baer [b,c], Jörn A. Quent [d], Andrew P. Yonelinas [a,b,c]

[a] Department of Psychology, University of California, Davis, USA
[b] Center for Neuroscience, University of California, Davis, USA
[c] Center for Mind and Brain, University of California, Davis, USA
[d] MRC Cognition and Brain Sciences Unit, University of Cambridge, USA

ARTICLE INFO

Keywords:
Working memory
Medial temporal lobe
Amnesia
Change detection
Receiver operating characteristics

ABSTRACT

A growing body of research indicates that the medial temporal lobe (MTL) is essential not only for long-term episodic memory but also for visual working memory (VWM). In particular, recent work has shown that the MTL is especially important for VWM when complex, high-resolution binding is required. However, all of these studies tested VWM for multiple items which invites the possibility that working memory capacity was exceeded and patient impairments instead reflected deficits in long-term memory. Thus, the precise conditions under which the MTL is critical for VWM and the type of working memory processes that are affected by MTL damage are not yet clear. To address these issues, we examined the effects of MTL damage on VWM for a single item (i.e., a square that contained color, location, and orientation information) using confidence-based receiver operating characteristic methods to assess VWM discriminability and to separate perceiving- and sensing-based memory judgments. This approach was motivated by dual-process theories of cognition that posit distinct subprocesses underlie performance across perception, working memory, and long-term memory. The results indicated that MTL patients were significantly impaired in VWM for a single item. Interestingly, the patients were not impaired at making accurate high-confidence judgments that a change had occurred (i.e., perceiving), rather they were impaired at making low-confidence judgments that they sensed whether or not there had been a change in the absence of identifying the exact change. These results demonstrate that the MTL is critical in supporting working memory even for a single item, and that it contributes selectively to sensing-based discriminations.

1. Introduction

Historically, the medial temporal lobes (MTL) have been characterized as a dedicated, long-term, declarative memory system (Scoville and Milner, 1957; Squire and Zola-Morgan, 1991), but more recent models have expanded to include other possible cognitive processes, such as perception and working memory (Aly et al., 2013; Lee and Rudebeck, 2010; Lee et al., 2012; McCormick et al., 2017; Sadil and Cowell, 2016; Yonelinas, 2013). However, previous studies examining the involvement of the MTL in visual working memory (VWM) have found conflicting results leaving ambiguity about the exact conditions under which the MTL is necessary for VWM (Allen et al., 2014; Axmacher et al., 2007; Baddeley et al., 2010; Jeneson et al., 2010; Jeneson et al., 2012; Jeneson and Squire, 2012; Olson, 2006; Olson et al., 2006; Pertzov et al., 2013; Warren et al., 2015; Yee et al., 2014). Moreover, evidence suggesting that the MTL is critical for VWM largely comes from studies which utilized complex materials (e.g., scenes) or larger sets of simple items (e.g., four colored squares) that may have exceeded patients' working memory capacity and so may have required hippocampally-dependent long-term memory mechanisms.

Single-item representations are assumed to have a privileged status in working memory (Cowan, 1988, 2008; Oberauer, 2009). When only a single object needs to be held in VWM there is no competition for the focus of attention and working memory capacity limits should not be exceeded. However, when multiple items must be held in VWM there becomes an inherent competition for the focus of attention, and the likelihood of exceeding working memory capacity grows with each additional item needing to be maintained. It has been proposed that, when VWM capacity limits are surpassed, long-term episodic memory supported by the MTL is needed (Jeneson et al., 2012). While this would

* Corresponding author. Department of Psychology, University of California, Davis, One Shields Avenue, Davis, CA 95616, USA
E-mail address: rigoodrich@ucdavis.edu (R.I. Goodrich).

https://doi.org/10.1016/j.neuropsychologia.2019.107227
Received 18 May 2019; Received in revised form 25 August 2019; Accepted 9 October 2019
Available online 12 October 2019
0028-3932/

be expected to help support the performance of healthy controls with intact MTLs and normal long-term memory, it would likely produce performance impairments in patients with long-term memory deficits due to MTL damage. Thus, VWM studies that find patient deficits may actually reflect long-term memory deficits because the task or materials exceeded the limits of working memory. Whether task materials inadvertently overtax working memory processes may be a key factor in explaining discrepant results regarding the role of the MTL in VWM.

Another important difference between studies which do and do not find evidence for MTL involvement in VWM is the degree to which precise, high-resolution bindings are required. Building on earlier relational and binding models (Cohen et al., 1997; Diana et al., 2007; Shimamura, 2010; Sutherland and Rudy, 1989), representational-hierarchical models (Bussey and Saksida, 2007; Cowell et al., 2010; Graham et al., 2010; see Baxter, 2009 for a review), and neurobiological and computational models of hippocampal function (Hasselmo and Howard, 2005; Leutgeb and Leutgeb, 2007; Marr, 1971; Norman & O'Reilly, 2003; Rolls, 1996), Yonelinas (2013) proposed a 'complex high-resolution binding model' that assumes the hippocampus is critical for binding together the various high-resolution features that make up an event. For example, it is expected to be important in forming precise and highly detailed conjunctive representations such as linking the precise color and precise location of a specific studied object (e.g., the aquamarine square was in a specific location on the computer screen). Consistent with this approach, there is evidence that damage to the hippocampus and surrounding MTL produces impairments under conditions that emphasize the use of complex, high-resolution bindings more so than tasks that can be accomplished using simple, low-resolution bindings. For example, Koen et al. (2017) found that MTL patients were significantly impaired in VWM for high-resolution object-location and object-color bindings (i.e., subtle changes in object color or location), but performed similarly to controls for equally difficult low-resolution object-location and object-color bindings (i.e., larger, more obvious changes in object color or location). Similarly, Goodrich and Yonelinas (2016) observed VWM deficits in MTL patients for both complex color-location bindings (i.e., a large set size of 5 squares) and equally difficult high-resolution color-location bindings (i.e., smaller, more subtle changes in square color).

Interestingly, Goodrich and Yonelinas (2016) found that patients' VWM deficits were selectively driven by one of two known perceptual/working memory subprocesses: *sensing*-based discrimination. Sensing refers to the detection of change between two images in the absence of specific identification of what exactly has changed, and is a strength-based process associated with low levels of response confidence (Aly and Yonelinas, 2012; Elfman et al., 2014). Conversely, patients were just as proficient as controls at *perceiving*-based discrimination, which is a state-based process. That is, MTL damage had no influence on high-confidence responses that corresponded to trials in which they could identify specific, discrete changes between images. A selective sensing-based impairment in MTL patients has also been observed in perceptual change-detection tasks using complex scene stimuli (Aly et al., 2013, Experiment 1). Moreover, in healthy individuals, hippocampal activity is directly related to the level of confidence associated with participants' sensing responses (Aly et al., 2013, Experiment 2).

In the current experiment, we examined whether the MTL is necessary for VWM for a single object (i.e., a square containing color, location, and orientation information). Based on previous studies showing that VWM impairments are limited primarily to tasks that require high-resolution discriminations, the current VWM task required participants to detect subtle changes in color, location, and/or orientation. If the MTL is critical for VWM, we expected that patients with MTL damage would be impaired compared to controls on this task. In addition, we expected that these deficits would be specific to reductions in sensing-based rather than perceiving-based working memory responses. In contrast, if the previously reported deficits were not due to a reduction in VWM, per se, but rather arose because the tasks required memory for more items than the participants could hold in working memory (i.e., Jeneson et al., 2012), then the patients should be unimpaired in the current study because it required memory for only a single object and so should not require the MTL.

We were also interested in determining whether MTL patients would be differentially impacted by the type and number of features that changed. That is, on each trial a colored square was studied then, following a brief delay, a test item was presented that was either identical to the study item or that differed very slightly from the study item. Some of the change trials consisted of a 'single feature' change whereby either the color, the location, or the orientation changed, whereas other change trials consisted of a 'multiple feature' change whereby the color, location, and orientation all changed together but by a smaller degree than any one change in the single-feature trials. The degree that each feature changed was selected such that overall difficulty was roughly matched in the different types of trials in order to minimize potential confounds related to differing levels of difficulty. Importantly, the participants did not know which type of change would occur on any given trial so they should attend to all three of the critical object features.

To date and to our knowledge, no study has directly assessed the effects of MTL damage on perceiving- and sensing-based VWM for a single object, or for different types of object features. One possibility is that the MTL may be particularly important for detecting simultaneous changes to multiple item features due to enhanced binding requirements compared to changes in one item feature alone (Cohen et al., 1997; Diana et al., 2007). In addition, the MTL may play a greater role for certain types of item features over others. For example, VWM for location feature changes may be predominantly impaired given previous work suggesting that the hippocampus is especially important for spatial information (Bird and Burgess, 2008; Hartley, Lever, Burgess, & O'Keefe, 2014; Kolarik et al., 2018; Kolarik et al., 2016; Lee et al., 2012; Moser et al., 2017). However, if VWM impairments in MTL patients instead reflect long-term memory deficits due to exceeding working memory capacity limits, then we would not expect to see any differences between patients and controls for either the single-feature or multi-feature change condition.

2. Methods

2.1. Participants

Five neurological amnesic patients (two male, $M = 49.80$ years) with an average of 16.20 years of education participated in the study. Two patients had damage limited to the hippocampus, and three patients had damage to the hippocampus and the surrounding MTL cortex. The average patient IQ was 107, as measured by the Wechsler Adult Intelligence Scale-Revised (WAIS-R), and patients scored, on average, in the 18th percentile on the Doors and People memory battery. Average patient *z*-scores for all subtests, except the attention index, of the Wechsler Memory Scale-Revised (WMS-R) were more than one standard deviation below the average control *z*-scores. Demographics and neuropsychological scores for the patients and controls are shown in Table 1.

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 suggested damage was limited to the hippocampus bilaterally with no damage apparent in the surrounding parahippocampal gyrus (Fig. 1). Patient 1003 had limbic encephalitis, and MRI scans suggested damage limited to the hippocampus bilaterally with no damage apparent in the surrounding parahippocampal gyrus (Fig. 1). Grey matter volume estimates indicated that the left and right hippocampi were reduced in volume, but no other MTL structure showed significant volume reduction. See Aly et al. (2013) for estimates of grey matter volume for this patient (referenced as Patient

Table 1
Participant demographics and neuropsychological test scores.

Patient ID	Damage	Age	Sex	Education	WMS-R z-score (Ver/Vis/Gen/Att/Del)	Doors & People %ile	WAIS-R IQ
1001 ●	Bilateral HC	60	F	16	−0.9/-1.0/-1.0/1.3/-0.5	25	110
1003 ■	Bilateral HC	66	F	12	−1.8/-0.3/-1.5/0.1/-2.2	1	112
1005 □	Bilateral MTL	34	F	19	−0.1/1.1/0.3/0.3/-0.4	5	110
1007 ⬦	R MTL	46	M	18	0.8/-0.9/0.1/1.2/-0.1	10	106
1009 ○	L MTL	43	M	16	−1.6/0.4/-1.1/-0.7/-0.6	50	97
Amnesics	–	49.8	3 F 2 M	16.2	−0.7/-0.1/-0.6/0.4/-0.7	18.2	107.0
($N = 5$)		(13.0)		(2.7)	(1.1/0.9/0.8/0.8/0.8)	(20.0)	(6.0)
Controls	–	56.0 (11.3)	8 F 3 M	16.7	0.6/1.6/1.1/1.1/1.3	68.8	113.7
($N = 11$)				(2.5)	(0.6/0.8/0.8/0.6/0.9)	(27.5)	(8.2)

Note. Individual scores are presented for each patient, followed by patient and control group means (standard deviations in parentheses). Symbols next to patient IDs correspond to their representative symbols in Figs. 4 and 5. Abbreviations: HC = hippocampus; MTL = medial temporal lobe.

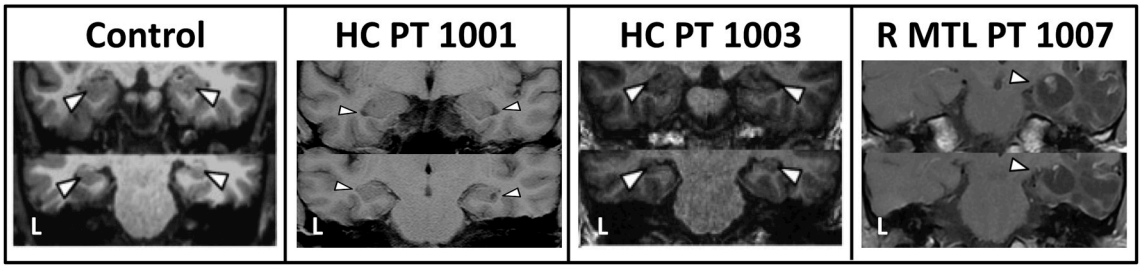

Fig. 1. Coronal T2-weighted MRI scans for a healthy control, two patients with selective bilateral hippocampal damage, and a patient with more extensive right MTL damage.

2). Patient 1005 had damage to the hippocampus and surrounding parahippocampal gyrus bilaterally following a traumatic brain injury due to a car accident. The extent of damage was determined from the patient's high-resolution MRI scan. See Kolarik et al. (2016) for estimates of grey matter volume for this patient. Patient 1007 had viral encephalitis, resulting in encephalomalacia and extensive volume loss in the right temporal lobe, right hippocampus and surrounding parahippocampal gyrus, and right orbitofrontal cortex (Fig. 1). The extent of damage was determined from the patient's MRI scan. Patient 1009 had a left temporal lobectomy to treat epilepsy. The surgery was a standard left anterior temporal lobe resection, in which approximately 4 cm of the anterior lobe, including the anterior half of the hippocampus, the amygdala, and the anterior third of the parahippocampal gyrus, were removed. The rest of the brain appeared to be normal on a high-resolution MRI scan.

Eleven healthy controls (three male, $M = 56.00$ years) with an average of 16.73 years of education also participated in the study. None of the controls had any history of psychological or neuropsychological disorders and all performed normally on neuropsychological tests. The average control IQ was 114, and controls scored, on average, in the 69th percentile on the Doors and People memory battery. The patient and control groups were matched with respect to age, education, and estimated IQ (all $ps > .10$). All participants reported normal or corrected-to-normal vision and exhibited normal color vision (Ishihara, 2000; Patients: $M = 13.00$ plates, $SD = 0.00$; Controls: $M = 13.64$ plates, $SD = 0.50$). The study was approved by the University of California, Davis Institutional Review Board and informed consent was obtained from all participants prior to testing. Participants were compensated $15/hr for their time.

2.2. Materials

The current study used a change detection paradigm to assess VWM for a single item. The single item was a square that possessed three relevant features: color, location, and orientation (Fig. 2). Orientation refers to the angle of an internal Gabor patch with a Gaussian envelope that was 20% of the size of the square. For each participant, parameter matrices were randomly created at the start of the experiment to determine the color, location, and orientation of the squares for each trial. Color was determined by randomly selecting values between 3% and 97% (RGB decimal values of 8 and 247, respectively) for each of the three dimensions in RGB color space. Location was determined by randomly selecting coordinates within 40%–60% of the screen's x-axis and 45%–55% of the screen's y-axis. Orientation, as a feature, was determined by randomly selecting a degree of orientation for the Gabor patch between 1° and 360°. Additionally, the size of the squares, as well as the frequency and contrast of the Gabor patch, were randomly determined for each trial to ensure that each trial was distinct. The size of the squares could range from 201 to 440 pixels. The spatial frequency of the Gabor patch could range from 0.02 to 0.1 cycles per pixel and in luminance contrast from 0.1 to 0.9 pixel intensities. However, the square size and the spatial frequency and contrast of the Gabor patch did not change between study and test within a trial and so were not considered relevant features.

VWM performance for two types of changes was assessed: single-feature changes and multi-feature changes. In the single-feature condition, only one of the three relevant features of the square changed on a given trial. For color 'different' trials, the study and test squares differed in color by 40% (RGB decimal value of 102) on one of the three dimensions in RGB color space. For location 'different' trials, the study and test squares differed in their location by 45 pixels on either the x or y coordinate. For orientation 'different' trials, the study and test squares differed by 50°. In the multi-feature condition, all three relevant features changed simultaneously but by a smaller degree than any one change in the single-feature condition. That is, multi-feature 'different' trials involved a change in color by 15% (RGB decimal value of 38), a change in location by 25 pixels, and a change in orientation by 15°. For 'same' trials, the study square was re-presented as the test square.

In order to control for overall task difficulty in the single-feature and the multi-feature conditions, pilot studies were conducted to identify differences that led to comparable levels of discrimination across each condition. This was done to ensure that any deficits we might observe for any one condition would not be attributed to differences in overall performance (i.e., patients might simply be more impaired on more

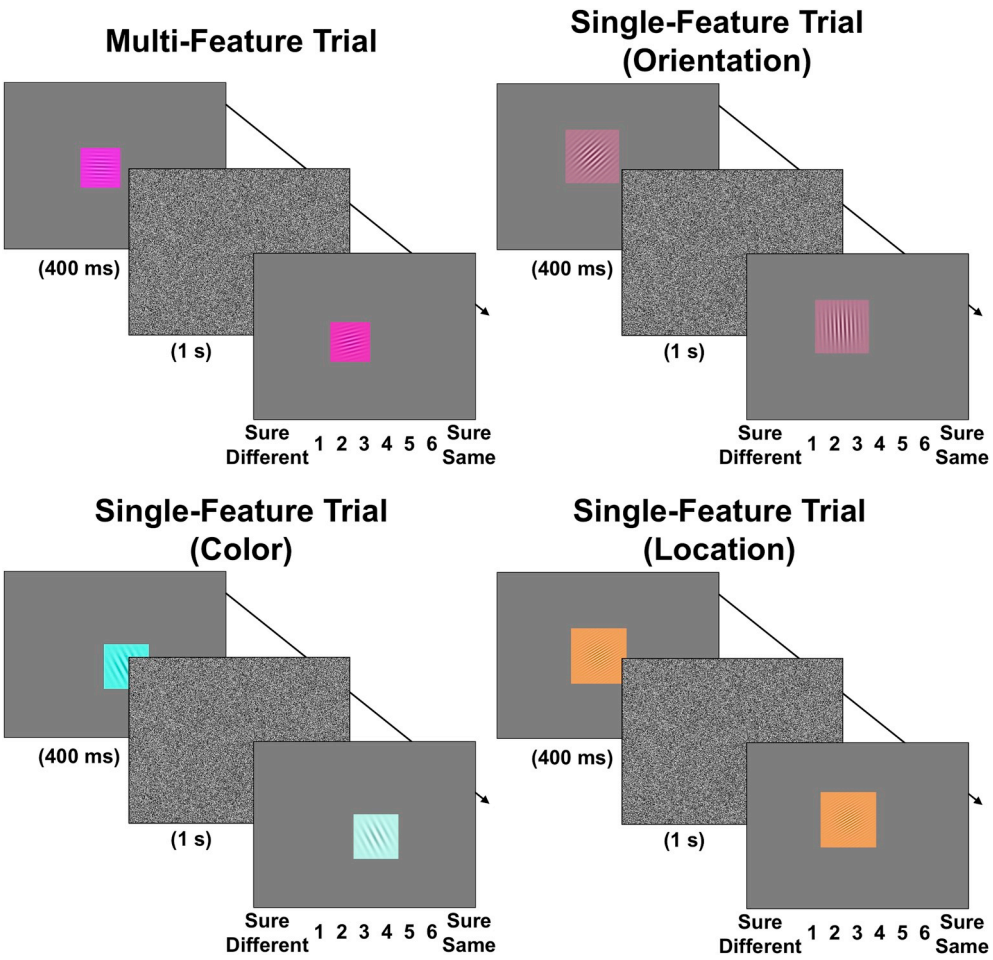

Fig. 2. Change detection task trial sequence examples for 'different' trials from the multi-feature change condition (top left), the orientation single-feature change condition (top right), the color single-feature change condition (bottom left), and the location single-feature change condition (bottom right). Trial examples are not drawn to scale. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

difficult working memory tasks). The reported feature manipulations above led to matched VWM accuracy – measured as area under the ROC curve (A_g; Macmillan and Creelman, 2005; Pollack and Hsieh, 1969) – across the single- and multi-feature conditions ($p = .628$) in a pilot experiment that used an independent healthy sample ($N = 6$). In addition, as reported below in the results section of the current study, controls also performed similarly for both types of trials indicating that the conditions were indeed matched for difficulty.

2.3. Procedure

The current study utilized a color change detection task modeled after the paradigm of Luck and Vogel (1997). All stimuli were presented on a grey background and each trial began with a centrally presented fixation cross (+) for 400 ms, followed by a 100 ms blank screen. The study square was then presented for 400 ms, followed by a 1 s delay filled with a dynamic white noise mask to prevent any retina-based image effects. Finally, the test square was presented, along with the response scale at the bottom of the screen; both remained on the screen for as long as participants needed to make a response. Participants made same/different judgments using a 6-point confidence scale. Specifically, participants indicated their level of confidence that the square had changed (1 = *sure different*, 2 = *maybe different*, 3 = *guess different*) or stayed the same (6 = *sure same*, 5 = *maybe same*, 4 = *guess same*). Responses were input using the numbers 1 through 6 on a keyboard. After a response was made the next trial would initiate. See Fig. 2 for examples of 'different' trials for the single-feature and multi-feature change conditions.

Participants completed a total of 270 randomized trials: 90 single-feature 'different' trials, 90 multi-feature 'different' trials, and 90 'same' trials. Because the trials were randomized participants were unaware which feature(s) would change on any given trial. Following trials 70, 140, and 210, participants were given the opportunity to take a short break (e.g., 1–2 min). Prior to testing, participants were familiarized with the types of changes to expect and performed ten practice trials: two 'different' trials per type of change and two 'same' trials. For the practice trials only, participants were given feedback and asked to explain their responses to ensure they understood the task and were using the response scale correctly. If the task or scale was not fully understood, the instructions and/or practice trials were repeated.

2.4. Data analysis

Same/different confidence ratings from the change detection task were used to generate receiver operating characteristics (ROCs) for each participant, and aggregate ROCs were generated for group comparisons. This is done by plotting the hit rate (i.e., the probability of correctly responding 'same' when the two squares were the same) on the y-axis, against the false alarm rate (i.e., the probability of incorrectly responding 'same' when the two squares were different) on the x-axis, across varying levels of response confidence. The leftmost point of the ROC represents the highest confidence 'same' response and points extending rightward represent cumulative hit and false alarm rate probabilities as each consecutive level of response confidence is

included. Intermediate points of the ROC represent lower confidence 'same' (from left) and 'different' (from right) responses, with decreasing confidence as the midpoint of the ROC is approached. VWM accuracy was measured as the area under the ROC curve (A_g) which is a nonparametric measure of discrimination sensitivity used for multipoint ROCs (Macmillan and Creelman, 2005; Pollack and Hsieh, 1969).

In order to separate perceiving- and sensing-based discriminations we utilized a signal detection based model of ROCs (Macmillan and Creelman, 2005; Swets, 1973; Yonelinas, 1994, 2001; Yonelinas and Parks, 2007). The observed ROCs were fit to the Dual Process Signal Detection (DPSD) model using maximum likelihood estimation in order to estimate the free parameters of perceiving and sensing (for additional details on how these ROC parameter estimates are obtained see Aly and Yonelinas, 2012; Goodrich and Yonelinas, 2016, 2019; Yonelinas, 1994, 2001). According to the DPSD model, perceiving and sensing make independent, yet joint, contributions to working memory and they differentially influence the shape of the ROC. Sensing is assumed to reflect the classic signal detection process underlying the common *d'* sensitivity metric and is reflected by the degree of ROC curvilinearity – the further the ROC curves away from the chance diagonal, the greater the obtained estimate of sensing-based responding. In addition to sensing, however, if the participant can identify some qualitative difference between the two squares then these trials are assumed to be consciously perceived as different and so are expected to result in high confidence 'different' responses as high, or higher, than the highest confidence 'different' responses based on sensing. The probability of perceiving is reflected by the upper x-intercept of the ROC – the further left it is shifted, the higher the obtained estimate of perceiving-based responding.

To examine whether MTL patients exhibited VWM impairments for a single item, we conducted 2 (group: patient/control) × 2 (condition: single-feature change/multi-feature change) mixed-model ANOVAs. These were used to compare patient and control VWM accuracy, perceiving, and sensing for the single-feature and the multi-feature change conditions. We also conducted 2 (group: patient/control) × 3 (single-feature change type: color/location/orientation) mixed-model ANOVAs to assess VWM accuracy, perceiving, and sensing for the three different types of single-feature changes. All error bars depict ±1 S E.

3. Results

Visual examination of the aggregate ROCs (Fig. 3a) shows that the patient ROCs were closer to the chance diagonal than the control ROCs, indicating that the patients performed more poorly overall. Moreover, the same pattern was apparent for both the single-feature and the multi-feature change conditions. In addition, the VWM impairments appeared to be most pronounced at the midpoints of the ROCs, which suggests the impairments were based largely on a reduction in the accuracy of patients' low-confidence sensing responses rather than high-confidence perceiving responses. As described next, formal analysis of individual participant ROCs confirmed each of these observations.

Overall VWM accuracy (Fig. 4), measured using the area under the ROC curve (A_g), was significantly lower for patients ($M = 0.72$, $SE = 0.04$) than for controls ($M = 0.82$, $SE = 0.02$), as shown by a main effect of group, $F(1,14) = 8.52$, $p = .011$, $\eta_p^2 = 0.38$. There was neither a main effect of the change condition ($p = .181$) nor a group × condition interaction ($p = .890$), suggesting that patients were comparably impaired at detecting single-feature and multi-feature changes. Additionally, control performance was not significantly different between conditions ($p = .321$) suggesting that task difficulty was matched for the single- and multi-feature change conditions.

Subsequently, we examined the ROC parameter estimates to determine whether perceiving and sensing differentially contributed to VWM performance between patients and controls for the single- and multi-feature change conditions (Fig. 5). For sensing, there was a significant main effect of group, $F(1,14) = 5.19$, $p = .039$, $\eta_p^2 = 0.27$, indicating a deficit in sensing-based VWM for patients ($M = 0.45$, $SE = 0.19$) compared to controls ($M = 1.02$, $SE = 0.14$). There was also a significant main effect of condition, $F(1,14) = 8.95$, $p = .010$, $\eta_p^2 = 0.39$, such that estimates of sensing were higher for multi-feature changes ($M = 1.11$, $SE = 0.11$) than for single-feature changes ($M = 0.84$, $SE = 0.13$). There

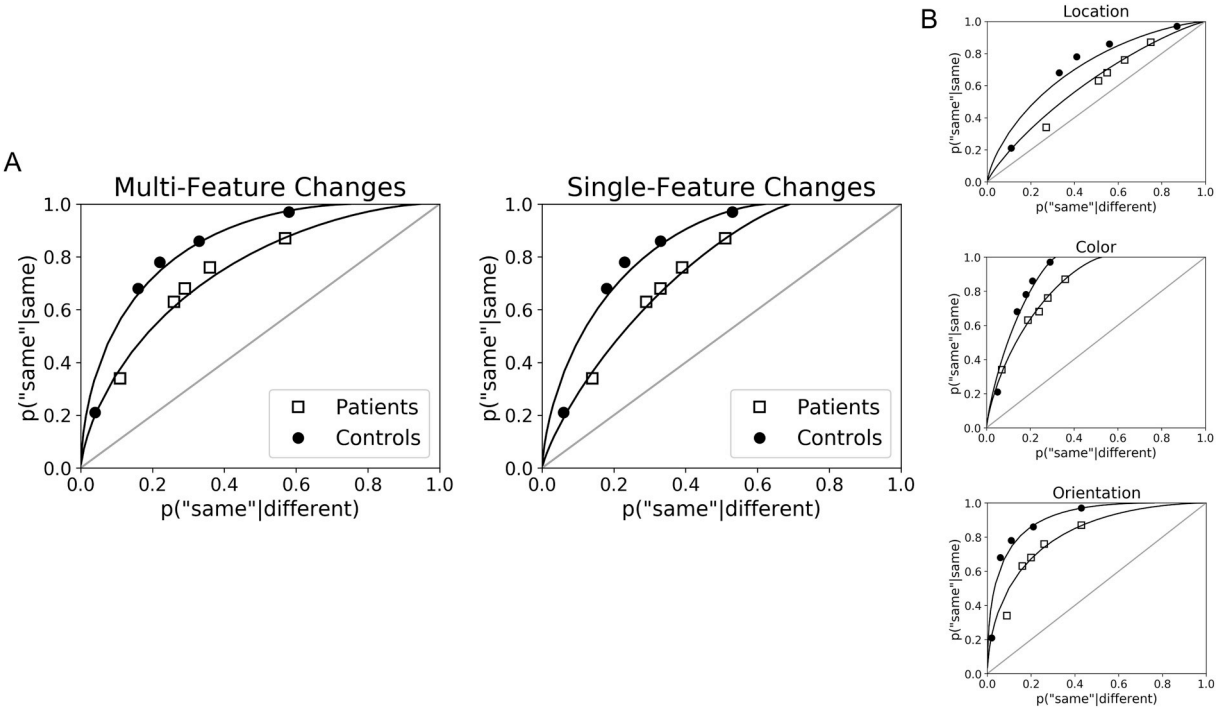

Fig. 3. (A) Aggregate ROCs for the multi-feature and single-feature change conditions, for patients and controls. (B) Aggregate ROCs for the separate single-feature changes: Location, Color, and Orientation. Filled circles = controls; empty squares = patients.

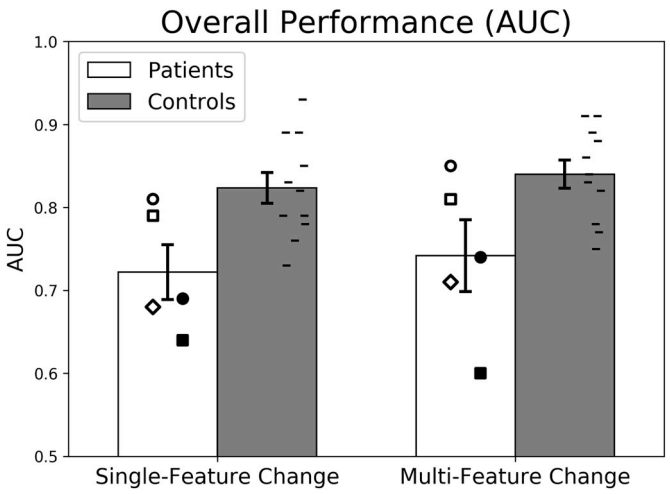

Fig. 4. Overall visual working memory performance, measured as area under the curve (*Ag*), for the single-feature and multi-feature change conditions, for patients and controls. Filled symbols = bilateral hippocampal patients; empty symbols = MTL patients; dashes = controls.

was no significant group × condition interaction ($p = .445$), suggesting a comparable sensing-based deficit for single-feature and multi-feature changes following MTL damage.

For perceiving, there was no significant effect of group ($p = .391$), nor a group × condition interaction ($p = .352$), implying that MTL damage did not impair perceiving-based VWM for single items. There was a significant main effect of condition, $F(1,14) = 6.13$, $p = .027$, $\eta_p^2 = 0.31$, such that estimates of perceiving were higher for single-feature changes ($M = 0.32$, $SE = 0.04$) than for multi-feature changes ($M = 0.24$, $SE = 0.04$).

Lastly, we conducted secondary analyses to separately examine the effects of the three different types of single-feature changes. As illustrated in Fig. 3b, the patient ROCs were closer to the chance diagonal compared to the control ROCs suggesting the MTL patients were impaired for location, color, and orientation changes. It should be noted that separating the single-feature change trials in this manner resulted in only 30 'different' trials per change type which is considered insufficient for properly fitting ROCs and estimating parameters, and produces a nontrivial drop in statistical power (Yonelinas, 1994, 2001; Yonelinas and Parks, 2007). Thus, the following results should be contemplated with these caveats in mind. For overall VWM accuracy (A_g), there was no significant group × change type interaction for the different single-feature changes ($p = .867$) but, as indicated by a main effect above, the patients exhibited a significant decrease in accuracy compared to the controls for the single-feature change trials ($p = .011$). These results indicate that the MTL patients were similarly impaired for all types of single-feature changes used in the current study. In addition, there was a main effect of type of feature, $F(2,28) = 20.78$, $p < .001$, $\eta_p^2 = 0.60$, reflecting the fact that participants performed significantly worse for location changes than for either color or orientation changes ($ps < .001$). Subsequent analyses examining estimates of sensing and perceiving revealed that neither of the group × change type interactions for the single-feature changes were significant (sensing $p = .533$; perceiving $p = .286$), suggesting MTL patients were impaired in similar ways across each type of single-feature change used in the current study.

Altogether, these results provide evidence for a sensing-based VWM impairment for a single item following damage to the MTL. Moreover, all of the above results were consistent for patients with selective hippocampal damage as well as for patients with more extensive MTL damage. Although we lacked statistical power to reveal any significant differences between the patient groups due to small subgroup sample sizes (hippocampal: $n = 2$; MTL: $n = 3$), there is no evidence that the observed deficits are notably less pronounced in the patients with selective hippocampal damage than in those with more extensive MTL damage. This is reflected by the intermixed data points for hippocampal patients (filled symbols) and MTL patients (open symbols) in Figs. 4 and 5. Therefore, it appears that selective hippocampal damage is sufficient to impair sensing-based VWM for a single item.

4. Discussion

The medial temporal lobe has historically been characterized as supporting long-term declarative memory, while playing little or no role in other cognitive processes such as working memory (Scoville and Milner, 1957; Squire and Zola-Morgan, 1991). Nevertheless, a growing body of literature has indicated that patients with MTL damage sometimes do exhibit deficits in working memory, but these deficits have often been attributed to the fact that studies used complex materials or a larger number of objects than participants could maintain in working memory (Allen et al., 2014; Baddeley et al., 2010; Jeneson et al., 2012; Jeneson and Squire, 2012). Here we asked whether the MTL is, in fact, important for VWM of a single item. Using an ROC analysis in conjunction with a change detection paradigm that required the maintenance and retrieval of high-resolution visual changes, we provide novel evidence that VWM for a single item (i.e., a square containing color, location, and orientation information) is dependent on the MTL. Specifically, we showed that patients with MTL damage exhibited

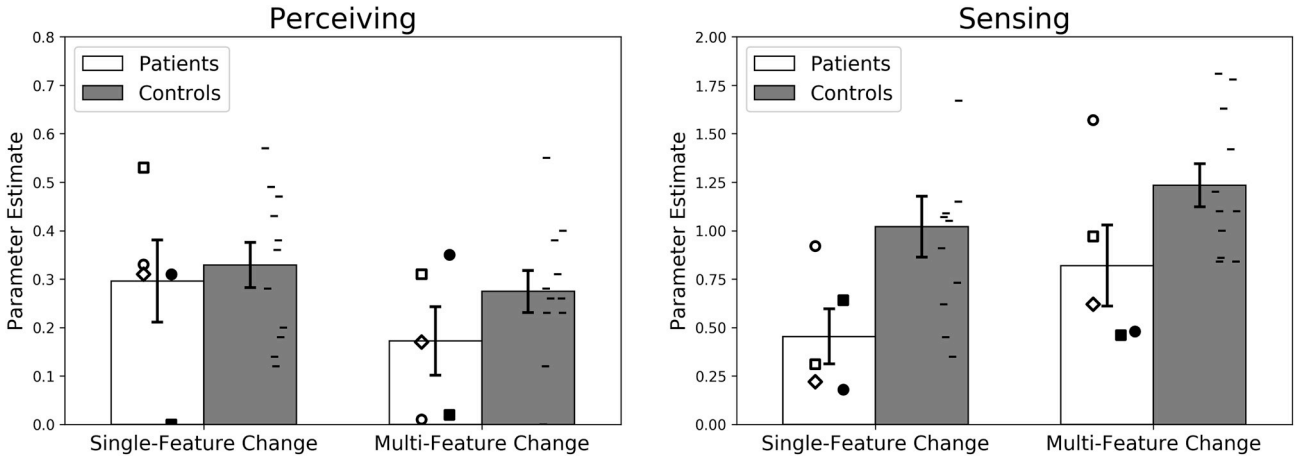

Fig. 5. ROC parameter estimates of perceiving and sensing, measured as probability and *d*', respectively, for the single-feature and multi-feature change conditions, for patients and controls. Filled symbols = bilateral hippocampal patients; empty symbols = MTL patients; dashes = controls.

significant VWM impairments for a single item and that these impairments were driven by selective deficits in sensing-based rather than perceiving-based VWM. That is, compared to controls, patients were impaired at making low-confidence sensing judgments that a single item had changed. Conversely, the ability to make high-confidence perceiving judgments that a single item had changed was comparable between patients and controls. These results not only add to the growing body of work showing that the MTL is important for VWM (Axmacher et al., 2007; Koen et al., 2017; Olson, 2006; Olson et al., 2006; Pertzov et al., 2013; Warren et al., 2015; Yee et al., 2014), but also bolster recent findings suggesting it is important only for sensing-based VWM responses (Aly et al., 2013; Goodrich and Yonelinas, 2016).

The finding that MTL patients exhibited a selective sensing-based VWM deficit parallels results from previous studies that have examined perception and VWM using the same dual-process analytic approach to separate perceiving and sensing contributions to overall performance. Aly et al. (2013) found that patients with hippocampal damage were impaired on a scene discrimination task due to selective reductions in low-confidence sensing-based perception. There was no difference in high-confidence perceiving-based perception between patients and controls. Moreover, a follow-up neuroimaging study in an independent healthy sample showed that activity in the hippocampus linearly tracked the confidence of sensing responses based on a graded strength signal, whereas hippocampal activity was not associated with perceiving responses (Aly et al., 2013). Similarly, Goodrich and Yonelinas (2016) found that patients with damage to the MTL exhibited VWM impairments in a standard multiple-item color change detection paradigm and these impairments were driven by reductions in estimates of sensing, but not perceiving. This was true when either high-resolution bindings (i.e., subtle changes in color) or high-complexity bindings (i.e., larger set sizes) were required. One potential concern with these prior studies was that they employed complex scenes or a large number of simple items (e.g., five colored squares) which may have exceeded working memory capacity, leading to the involvement of hippocampally-dependent long-term memory mechanisms. However, the current findings indicate that the same pattern of results, with respect to perceiving and sensing, is obtained when there is only one item to maintain in VWM, arguing against the capacity account of earlier results.

In the current study we focused on examining VWM for a single relatively simple object because this was expected to be well within the capacity of working memory, which is thought to be able to maintain roughly three independent objects (Luck and Vogel, 1997). The objects in the current study consisted of a number of simple features including color, orientation, and location – any or all of which could change on a given trial. The extent to which the current results generalize to other types of materials or test conditions will need to be assessed in future studies. For example, whether these results are also observed for different types of visual materials such as faces is not yet known. Previous work has shown that damage to the MTL does impair working memory for faces (Olson et al., 2006; Rose et al., 2012). Additionally, face perception in healthy individuals relies on a combination of perceiving- and sensing-based processing such that global facial information relies more heavily on sensing and local facial information relies more heavily on perceiving (Goodrich and Yonelinas, 2019). We anticipate that employing a dual-process approach would reveal that the VWM deficits for faces exhibited by MTL patients are driven by reductions in sensing. However, future work will be necessary to confirm this prediction.

It will also be important to determine whether MTL patients would show VWM deficits under conditions in which they know in advance which object feature was likely to change. In the current design, participants had to encode color, orientation, and location because any one, or all three, of these features could change. In contrast, if they only have to focus on a single feature it is possible that the conjunctive representations supported by the hippocampus may no longer be utilized. A number of studies have suggested that one object with multiple features taxes VWM capacity to the same extent as one object with one feature (Luck and Vogel, 1997, 2013; Zhang and Luck, 2011; although also see Bays and Husain, 2008) suggesting that similar results might be obtained regardless of the number of relevant object features. However, other studies have suggested that VWM can be sensitive to the number of object features. For example, Wilson et al. (2012) found greater contralateral delay activity (CDA; an electrophysiological index of VWM) when one object with three features (shape, color, and orientation) had to remembered compared to when one object with one feature had to be remembered, but less CDA than when three separate single-feature objects had to remembered.

In addition, visual examination of Fig. 5 suggests that perceiving-based working memory may behave somewhat differently for single- vs. multi-feature changes. Patients and controls alike exhibited increased, albeit nonsignificant, estimates of perceiving, on average, for single-feature compared to multi-feature change trials. This is consistent with previous work showing that perceiving contributes more to performance for localized, discrete changes than for more widespread, relational changes (Aly and Yonelinas, 2012; Goodrich and Yonelinas, 2019). Visual examination of the separate single-feature ROCs (Fig. 3b), also suggests that perceiving and sensing may differentially contribute to different types of feature changes. These differences may be due to disparities in difficulty between the separate types of single-feature changes in the current study or it could be that certain object features are inherently easier to detect. For example, color tends to be given attentional and perceptual processing priority over other features, such as shape (Lee et al., 2018; Rentzeperis et al., 2014). It will be important for future research to determine whether different object features rely more heavily on perceiving- or sensing-based working memory.

The MTL patients in the current study included individuals with extensive lesions, making it challenging to determine exactly which regions are critical for the observed deficits. In addition, limitations of human lesion studies make it difficult to rule out the possibility that there may be influential damage that is not detectable with current imaging methods. Thus, future studies of animals in which lesions can be carefully controlled will be crucial in determining the precise MTL regions involved in the sensing process. For instance, previous studies have successfully used an ROC approach to separate the dual processes underlying long-term episodic memory in rats (Fortin et al., 2004), indicating that it is feasible to examine perceiving- and sensing-based processes in rats as well. Importantly, the two patients in the current study with seemingly selective hippocampal lesions exhibited deficits that were comparable to the patients with more extensive MTL lesions. Thus, the current results suggest that hippocampal damage is sufficient to lead to the observed sensing-based VWM impairment. Future work will need to more closely examine the role of different subfields within the hippocampus to determine whether different regions are especially important for VWM. Neurocomputational work has suggested that the CA1 subfield may be particularly sensitive to high-resolution changes like those used in the current paradigm (Elfman et al., 2014). Neuroimaging studies are currently underway to determine if VWM is particularly reliant on specific hippocampal subfields. One possibility is that the extent to which the hippocampus plays a role in working memory may depend on the precise location of the hippocampal damage.

Among the MTL patients, there was some potentially informative variability with respect to performance. For example, patient 1009's (empty circle in Figs. 4 and 5) estimates of sensing were both more similar to controls than the other patients. Interestingly, this is the only patient in our sample without any known damage to the right MTL. Previous neuropsychological and neuroimaging research has found that spatial memory tends to be strongly lateralized to the right MTL (Smith and Milner, 1981). Patients with right hippocampal damage show a greater deficit (Stepankova et al., 2004), and the right hippocampus of healthy individuals shows increased activity (Piekema et al., 2006),

when tasks require representations containing spatial information. Thus, it is possible that sensing relies more heavily on right MTL function than on left, especially when spatial information is a relevant factor. Future studies directly contrasting larger groups of patients with selective right compared to left MTL lesions will be useful in assessing this possibility.

Our results align with previous studies which have found a double dissociation between perceiving and sensing, in healthy samples. Aly and Yonelinas (Experiment 3A; 2012) tested participants' ability to discriminate between scenes that had been manipulated such that differences consisted of either widespread, configural, global changes (i.e., pinching or spherizing across the extent of the scene) or detailed, discrete local changes (i.e., addition or deletion of a feature). Goodrich and Yonelinas (Experiment 1; 2019) conducted a similar study that tested participants' ability to discriminate between faces that differed either globally or locally in the same manner. These two experiments yielded converging results in that estimates of perceiving were greater for local than for global changes and estimates of sensing were greater for global than for local changes. The current study observed a similar dissociative pattern. For patients and controls alike, single-feature changes were associated with a greater contribution of perceiving and multi-feature changes were associated with a greater contribution of sensing. Thus, our findings fit well with previous work which has also produced a double dissociation between perceiving and sensing and reinforces the assumption that they are functionally independent processes.

The fact that perceiving and sensing are two distinct, separable processes underlying perception and working memory is consistent with dual-process theories of cognition. For example, Tulving (1989) proposed that functionally distinct processes, termed remembering and knowing, underlie long-term memory. Moreover, he found that these long-term memory processes are associated with different states of conscious awareness and subjective experience (Tulving, 1985), just as perceiving and sensing are associated with different states of conscious awareness and subjective experience (Aly and Yonelinas, 2012; Goodrich and Yonelinas, 2019). In addition to functional independence, neuropsychological, neuroimaging, and neurocomputational studies converge in showing that the dual processes underlying perception, working memory, and long-term memory are also anatomically distinct. For instance, in perception and working memory, sensing relies on the hippocampus but perceiving does not (Aly et al., 2013; Aly et al., 2014; Aly et al., 2014; Goodrich and Yonelinas, 2016). Similarly, in long-term memory, remembering is hippocampally dependent but knowing is not (Düzel et al., 2001; Duzel et al., 1997; Eichenbaum et al., 2007; Elfman et al., 2014). Thus, collectively, our findings fit well with dual-process theories of cognition and add to the large body of work emphasizing the importance of taking into account the subjective experiences of participants in addition to objective measures which allow for process dissociation within and across tasks.

That hippocampal damage leads to a reduction in the accuracy of low-confidence, strength-based sensing judgments in the current working memory study, as well as in other perception and working memory studies (Aly et al., 2013; Goodrich and Yonelinas, 2016), is striking given it is well established that hippocampal damage impairs high-confidence, recollection-based recognition in studies of long-term memory (Eichenbaum et al., 2007; Fortin et al., 2004; Koen and Yonelinas, 2014; Quamme et al., 2004; Yonelinas, 2005; Yonelinas et al., 2002). Why does the hippocampus contribute to perception and working memory in such a different way? Recent computational work has suggested that this difference arises because of the differential likelihood of pattern completion in long-term recognition tasks, on the one hand, and perception and working memory tasks on the other. Elfman et al. (2014) examined the output of a hippocampal model based on the complementary learning systems framework (Norman & O'Reilly, 2003) in a simulated long-term recognition memory task and in a simulated perception task and found that these two tasks naturally produced distinct hippocampal signals. For recognition memory, a thresholded pattern of activity emerged such that hippocampal activity exhibited a bimodal distribution for studied items, indicating discrete states of retrieval success (strong activity) and retrieval failure (weak activity); nonstudied lures always led to retrieval failure (weak activity). Thus, a proportion of the studied items led to pattern completion and the retrieval of detailed study information (presumably leading to high-confidence responses), whereas other studied items did not lead to pattern completion and were effectively indistinguishable from non-studied lures (presumably leading to low-confidence responses). However, when the same model was applied to perception it produced overlapping Gaussian distributions of activity which were predictive of image match/mismatch. That is, because the second image was presented immediately after the first, the second image invariably led to pattern completion and the strength distribution was no longer bimodal. Instead, it produced a pattern of activity consistent with the graded strength signal associated with sensing. Specifically, as the degree of relational match between two sequentially presented images increased, mean hippocampal activity increased. The results indicate that the hippocampus naturally produces a high-confidence, state-based recollection signal in recognition memory and a lower-confidence, strength-based sensing signal in perception and working memory.

Given that VWM deficits are most often found in tasks that require processing of complex relational information, we anticipated that multi-feature changes might be more dependent on the MTL than single-feature changes and, in turn, produce greater reductions in patient performance. However, we found significant VWM impairments for both types of changes. We believe that deficits were observed in the single and multi-feature trials because participants did not know in advance which feature on a given trial would change and, thus, they had to encode all three of the relevant features. However, as described above, future studies that directly manipulate whether participants know which features will be relevant on a given trial will be needed to test this possibility. It is also possible that interference buildup over many trials led to the observed patient deficits for the single-feature change trials as a result of degraded working memory representations of objects in the MTL (Barense et al., 2012) – a notion that comes from representational-hierarchical models (Bussey and Saksida, 2002, 2007). Additional evidence from eye-tracking further suggests that VWM representations of single-feature objects are degraded, rather than absent, following MTL damage as indicated by shorter patient fixations directed at the lures most similar to a target (Warren et al., 2010).

The current results appear inconsistent with those from another MTL patient study that used a similar color change detection task with set sizes that varied from one to eight items (Jeneson et al., 2012). In that study, patients were unimpaired even when the set size was one item. Although there are several potentially important differences across these studies, we believe that the key difference is whether or not successful performance required highly precise VWM representations. Jeneson et al.'s (2012) task necessitated detection of change to a single feature (i.e., color) and they used only a small set of canonical colors (e.g., red, green, blue, yellow, black, and white). Thus, their task could be successfully completed by simply remembering that the square was blue regardless of the exact hue, tint, or shade of blue because the changes were always between color categories (e.g., from blue to red). However, our task necessitated detection of change to multiple features (i.e., color, location, orientation) and we employed more subtle changes. Meaning, our task could not be successfully completed by simply remembering, for example, that the square was blue because the change could occur within a color category (e.g., from sky blue to cornflower blue). Given that the hippocampus is necessary for binding the various features of an item or event into a coherent and conjunctive representation (Cohen and Eichenbaum, 1993; Konkel and Cohen, 2009), and the hippocampus becomes increasingly involved as representational bindings become more precise (Goodrich and Yonelinas, 2016; Koen et al., 2017; Yonelinas, 2013), it is possible that the changes utilized by Jeneson et al.

(2012) required only imprecise, low-resolution bindings that would not be hippocampally dependent.

Our results also appear to be in partial conflict with those from a study that examined VWM in MTL patients, using a color wheel task, in which patient deficits were observed for three and six items, but not for one item (Warren et al., 2015). In the color wheel task, participants are presented with an array of colored squares and, following a brief delay, must indicate the precise color a cued square had been in the initial array by choosing a color on a continuous color wheel. The color wheel task inherently requires participants to maintain and retrieve highly precise color-location bindings, so the finding that the patients were impaired for larger set sizes is consistent with the current findings of VWM impairments in MTL patients. But, why did MTL damage produce VWM impairments for a single object in our study but not in Warren et al.'s (2015) study? One possibility, as suggested by the authors, is that significant VWM deficits in the single-object condition in the latter study were not detected because of ceiling levels of performance (i.e., the probability of an item being in VWM was near 1 for all groups). Another possibility is that because the task only required working memory for color, rather than testing memory for multiple features of the object, the task may have been supported by the cortex.

In summary, the current neuropsychological findings indicate that the MTL is critically involved in VWM discriminations based on low-confidence sensing judgments, but not high-confidence perceiving judgments. This was true when only a single item needed to be maintained in VWM. Thus, our results cannot be explained as reflecting long-term memory impairments because one item is well within the VWM capacity limits of MTL patients. We argue that, aside from capacity limits, high-resolution binding plays a critical role in determining the extent of MTL involvement in VWM and should be considered as a key factor in future studies of working memory.

Acknowledgements

We thank all of our participants and their families for their time and patience. We also thank the members of the Human Memory Lab for valuable feedback on the manuscript. JAQ received travel funds from the Hans Böckler Foundation. Research reported in this publication was supported by the National Eye Institute of the National Institutes of Health under Award Number R01EY025999. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

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