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The medial temporal lobe supports sensing-based visual working memory

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ABSTRACT

It is well established that the medial temporal lobe (MTL), including the hippocampus, is essential for long-term memory. In addition, recent studies suggest that the MTL may also support visual working memory (VWM), but the conditions under which the MTL plays a critical role are not yet clear. To address this issue, we used a color change detection paradigm to examine the effects of MTL damage on VWM by analyzing the receiver operating characteristics of patients with MTL damage and healthy age- and education-matched controls. Compared to controls, patients with MTL damage demonstrated significant reductions in VWM accuracy. Importantly, the patients were not impaired at making accurate high-confidence judgments that a change had occurred; however, they were impaired when making low-confidence responses indicating that they sensed whether or not there had been a visual change. Moreover, these impairments were observed under conditions that emphasized the retrieval of complex bindings or the retrieval of high-resolution bindings. That is, patients with MTL damage exhibited VWM impairments when they were required to remember either a larger number of low-resolution bindings (i.e., set size of 5 and obvious color changes) or a smaller number of high-resolution bindings (i.e., set size of 3 and subtle color changes). The results indicate that only some VWM processes are dependent on the MTL, and are consistent with the proposal that the MTL plays a critical role in forming complex, high-resolution bindings.

1. Introduction

For over a half-century, it has been widely accepted that damage to the hippocampus and surrounding medial temporal lobe (MTL) structures (i.e., perirhinal, parahippocampal, and entorhinal cortices) results in severe long-term memory impairments (Scoville and Milner, 1957). In contrast, whether MTL damage also causes deficits in short-term or working memory has been contentiously debated. Numerous studies have indicated that, in addition to its role in long-term memory, the MTL is critically involved in working memory as well as perception (Aly et al., 2013; Ezzyat and Olson, 2008; Lee and Rudebeck, 2010; Lee et al., 2012; Olson et al., 2006b; Pertzov et al., 2013; Yee et al., 2014). However, other studies have found that patients with MTL damage are unimpaired on similar working memory tasks (Allen et al., 2014; Jeneson et al., 2010; Knutson et al., 2012; Shrager et al., 2006; Shrager et al., 2008). Thus, the conditions under which the MTL is necessary for working memory are still poorly understood, fueling the debate about the specific cognitive processes that are supported by the MTL (Baxter, 2009; Graham et al., 2010; Jeneson and Squire, 2012; Konkel et al., 2008; Ranganath et al., 2014; Yonelinas, 2013).

Early evidence that the MTL was critical for visual working memory (VWM) came from Olson et al. (2006a), who assessed the VWM performance of amnesics with MTL lesions using a color change detection task (Luck and Vogel, 1997). In the change detection task, participants are presented with two arrays of colored squares, separated by a short delay, and have to judge whether a designated square changes color between array presentations. Olson et al. (2006a) found that amnesics showed a VWM deficit compared to controls when they had to remember three colored squares after a delay of either 4 or 8 s. In a separate study using the same paradigm, Jeneson et al. (2012) found a similar patient impairment at delays of 3, 4, and 8 s; however, at a 1 s delay amnesics performed as well as controls for array sizes of up to six colored squares. Because patients were impaired only at delays longer than 1 s, Jeneson et al. (2012) concluded that the poorer patient performance at longer delays actually reflected a long-term memory deficit and that VWM is intact following MTL damage.

However, evidence from studies using a different VWM paradigm known as the color wheel task suggests that amnesics are, in

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fact, impaired at short delays of 1 s or less (Warren et al., 2014; Zhang et al., 2012). 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. Although the color wheel task is similar to the change detection task, it differs in several key aspects. For instance, the color wheel task necessitates the recall of information, whereas the change detection task can be accomplished merely by recognizing that there was, or was not, a change. Therefore, it is possible that such differences in retrieval demands (i.e., recall versus recognition) across tasks have contributed to conflicting results regarding the role of the MTL in working memory. Another potentially important difference is that the color wheel task inherently requires participants to maintain and retrieve highly precise color-location bindings, as opposed to the change detection task which can be accomplished using imprecise color-location bindings. For example, the color wheel task necessitates that participants remember there was an aquamarine square in a particular location, whereas the change detection task used in previous studies of amnesia (i.e., Olson et al. 2006a; Jeneson et al., 2012) could be successfully completed by simply remembering that there was a blue square in a particular location regardless of the exact hue, tint, or shade of blue. That is, studies employing a change detection task have used only a small set of canonical colors (e.g., red, green, blue, yellow, black, and white), rather than testing amnesics' abilities to detect subtle color changes.

The difference in the precision with which representations must be maintained across tasks was the impetus for a recently proposed theory of hippocampal function: The high-resolution binding model (Yonelinas, 2013), which builds 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 Eichenbaum, 2005; Leutgeb and Leutgeb, 2007; Marr, 1971; Norman and O'Reilly, 2003; Rolls, 1996). According to Yonelinas' (2013) model, the hippocampus is critical for integrating, representing, maintaining, and retrieving complex, high-resolution associative information that is used for perception, working memory, and long-term memory. That is, the hippocampus is necessary for linking together – or binding – the various features of an item or event to form a precise and highly-detailed conjunctive representation. Therefore, the high-resolution binding model proposes that damage to the hippocampus and surrounding MTL would be expected to produce VWM impairments under conditions that emphasize the use of high-resolution bindings (e.g., color wheel task) more so than tasks that can be accomplished using imprecise, low-resolution bindings (e.g., change detection). Because this is a key difference between the color wheel and traditional change detection tasks, the high-resolution binding model offers a parsimonious explanation for the discrepant results regarding the role of the MTL in VWM between studies using seemingly similar paradigms.

Another potentially important limitation of many previous studies of VWM and the MTL is that they have typically utilized a binary response design (e.g., yes/no or same/different judgments) to compute a single-point measure of performance, such as proportion correct or d' (e.g., Allen et al., 2014; Jeneson et al., 2012; Olson et al., 2006a; Shrager et al., 2008; Yee et al., 2014; but see Pertzov et al., 2013; Warren et al., 2014; Zhang et al., 2012). Procedures that provide more detailed measures of performance, such as receiver operating characteristics (ROCs; Macmillan and Creelman, 2005; Swets, 1973), are able to more thoroughly assess performance and can provide important insights into the underlying cognitive processes that might not be apparent when using single-point measures. Although VWM in MTL patients has not been examined using ROCs before, the utility of this approach is suggested by a recent study of perception. Aly et al. (2013) examined the effects of hippocampal damage on a same/different scene perception task by collecting confidence judgments which were used to plot ROCs. The results showed that hippocampal patients exhibited significant reductions in perceptual sensitivity. Importantly, the ROC analysis demonstrated that the patients were not impaired at making high-confidence discriminations, indicative of a consciously and explicitly perceived difference between stimuli. Rather their impairments were due to a selective reduction in the accuracy of their low-confidence discriminations, which are associated with a general sense of difference between stimuli. These results were taken as evidence that hippocampal damage did not disrupt conscious perception, but rather it reduced the accuracy of low-confidence sensing-based perceptual judgments. Notably, these findings would not have been discovered using only a single-point measure of performance.

In the current study, we examined VWM performance in patients with MTL damage and controls on a color change detection task by collecting confidence judgments and plotting ROCs. Participants studied an array of colored squares then, after a 1 s delay, they were presented with a test array and indicated their level of confidence that a cued square had or had not changed color using a six-point confidence scale (i.e., sure/maybe/guess for each 'same' or 'different' response). This approach allowed us to contrast performance in the patients and controls across levels of response criterion in order to evaluate differences in working memory sensitivity. In addition, it allowed us to assess whether any potential impairments were related to deficits in high-confidence 'perceiving' or low-confidence 'sensing' based responses. Based on the perception results of Aly et al. (2013), we expected that MTL damage would lead to similar results for working memory. That is, we predicted that MTL patients would exhibit reduced VWM accuracy driven specifically by deficits in low-confidence sensing judgments, whereas they would be unimpaired at high-confidence perceiving judgments.

In addition, we explored the influence of two factors thought to be critical for engaging the hippocampus: relational binding complexity and representational resolution. According to relational memory theory, the hippocampus is critical for binding together constituent elements of an event into a coherent representation, but not for representing the individual elements themselves (Cohen and Eichenbaum, 1993; also see Diana et al., 2007). There is substantial evidence that as the complexity of relational binding required by a task increases, the degree to which that task is hippocampally dependent also increases, even at short delays (Hannula et al., 2006; Konkel et al., 2008; Pertzov et al., 2013; Yee et al., 2014). The high-resolution binding model discussed previously extends upon relational theories of the hippocampus by stipulating that hippocampal dependence is also determined by the quality or resolution of the relational bindings that must be maintained (Yonelinas, 2013). Thus, the hippocampus should be necessary for VWM tasks that require the maintenance and retrieval of either highly complex bindings or high-resolution bindings.

Differences in MTL involvement for complex bindings versus high-resolution bindings have, to date, never been directly compared. Thus, it is unknown whether both of these factors are critical for engaging the MTL. To assess this, the current study contrasted the roles of relational binding complexity and representational resolution by examining performance in two conditions that were matched for difficulty. The *complex condition* had a relatively high-complexity demand (i.e., a set size of 5) but required the retrieval of only low-resolution bindings (i.e., when a

color change occurred it switched to an obviously different color). In contrast, the *high-resolution condition* had a relatively low-complexity demand (i.e., a set size of 3) but required the retrieval of high-resolution bindings (i.e., subtle color changes). If complexity and resolution are both critical factors in determining MTL involvement in working memory, as proposed by the high-resolution binding model (Yonelinas, 2013), then the patients should be impaired in both the high-complexity and the high-resolution conditions. Additionally, based on previous ROC results (Aly et al., 2013) we expected that if patients with MTL damage showed reductions in VWM accuracy for either condition, it would be due to selective deficits in low-confidence sensing rather than deficits in high-confidence perceiving.

2. Methods

2.1. Participants

Six neurological amnesic patients (two male, four female, $M=39$ years) with an average of 17 years of education participated. Two patients had damage limited to the hippocampus, and four 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 14th 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. For both subtests of the Controlled Oral Word Association (COWA) test, average patient *z*-scores were within one standard deviation of the average control *z*-scores. Demographics and neuropsychological scores for the patients and controls are shown in Table 1.

Patient 1002 suffered from adult onset pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS) encephalopathy, and exhibited abnormally necrotic cavities on the left and right hippocampi (Fig. 1). The cavities had a rounded shape and resembled pathologic cavities described in specimens of hypoxia-related CA1 necrosis (Nakada et al., 2005). The extent of damage was determined from the patient's MRI scan, and there was no apparent damage in the surrounding parahippocampal gyrus. 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 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. Patient 1085 had a right temporal lobectomy to treat epilepsy. The surgery was a standard right 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 clinical MRI scan.

Twelve healthy controls (five male, seven female, $M=39$ years) with an average of 17 years of education participated. None of the controls had any history of psychological or neuropsychological

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	COWA z-score (Letter/Category)	WAIS-R IQ
1002	Bilateral HC	33	F	18	−1.5/−1.1/−1.5/−0.9/−0.9	10	n/a	110
1003	Bilateral HC	62	F	12	−1.8/−0.3/−1.5/0.1/−2.2	1	−1.1/−0.3	112
1005	Bilateral MTL	30	F	19	−0.1/1.1/0.3/0.3/−0.4	5	0.2/−0.5	110
1007	R MTL	42	M	18	0.9/−0.9/0.1/1.2/−0.1	10	−0.4/0.6	106
1009	L MTL	40	M	17	−1.6/0.4/−1.1/−0.7/−0.6	50	0.5/−1.2	97
1085	R MTL	25	F	15	−1.1/1.3/−0.6/0.3/−0.5	10	n/a	104
Amnesics ($N=6$)	–	38.7	4F	16.5	−0.9/0.1/−0.7/0.0/−0.8	14.3	−0.2/−0.4	106.5
		(13.0)	2M	(2.6)	(1.0/1.0/0.8/0.7/0.7)	(17.9)	(0.7/0.7)	(5.5)
Controls ($N=12$)	–	38.6 (14.0)	7F 5M	16.9	0.4/1.5/0.8/0.6/1.0	78.3	0.2/0.3	111.5
				(1.8)	(1.1/0.7/1.1/0.8/1.0)	(19.0)	(0.6/0.8)	(4.4)

Note. Individual scores are presented for each patient, followed by patient and control group means (standard deviations in parentheses). HC=hippocampus; MTL=medial temporal lobe; n/a=score not available.

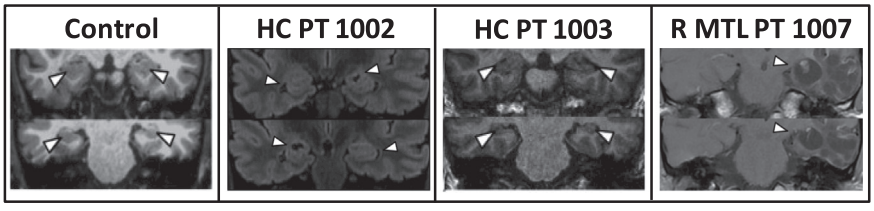

Fig. 1. Coronal MRI scans for a healthy control, two patients with selective hippocampal damage bilaterally, and a patient with more extensive right MTL damage. Images for the control and patients 1003 and 1007 are T2 weighted, and for patient 1002 are fluid-attenuated inversion recovery (FLAIR).

disorders and all performed normally on neuropsychological tests. The average control IQ was 112, and controls scored, on average, in the 78th percentile on the Doors and People memory battery. The patient and control groups were matched with respect to age, education, and estimated IQ. All participants reported normal or corrected-to-normal vision and exhibited normal color vision (Ishihara, 2000; Patients: $M=14.00$ plates, $SD=0.00$; Controls: $M=13.58$ plates, $SD=0.51$). 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

In the current study, VWM was assessed in two different conditions that were matched for difficulty. In the high-complexity condition, participants were required to remember a relatively large number (i.e., set size=5) of low-resolution bindings (i.e., obvious color changes). In the high-resolution condition, participants were required to remember a relatively small number (i.e., set size=3) of high-resolution bindings (i.e., subtle color changes). Prior to testing patients and controls, VWM accuracy was matched across the complex and high-resolution conditions ($p=.161$) in a pilot experiment that used an independent healthy sample ($N=26$) to ensure that any observed patient impairments were not due to differences in task difficulty.

The low-resolution color stimuli comprised seven base category colors which were similar to the canonical colors used in previous studies (e.g., Olson et al., 2006a; Jeneson et al., 2012). The high-resolution color stimuli comprised the same seven base colors plus 14 modified colors. This resulted in seven low-resolution stimuli and 21 high-resolution stimuli. The color stimuli were created by selecting seven equidistant and dissimilar base colors from the Netscape ($6\times6\times6$) Color Palette Map. Red, green, and blue (RGB) intensity values, which range from 0 to 255, were extracted from each of the seven base colors using Adobe Photoshop CS5 v.12.1. Intensity values of 77 were then added to or subtracted from one of the RGB dimensions in order to create two modified versions of each of the original seven base category colors. For example, the base color green had RGB values of 0, 255, 51. An intensity value of 77 was subtracted from the G dimension, but the R and B dimensions were left unchanged, in order to create green1 (RGB: 0, 178, 51). To create green2 (RGB: 0, 255, 128), the R and G dimensions were left unchanged and an intensity value of 77 was added to the B dimension. Together these three similar colors (i.e., green, green1, and green2) formed a color group which was distinct from all of the other created color groups. This procedure was repeated for each base color, although whether the addition/subtraction of an intensity value of 77 was applied to the R, G, or B dimension for any particular modification varied. Table 2 shows the RGB values for each of the 21 color stimuli that resulted from this process: seven base category colors (green, yellow, red, pink, purple, blue, and cyan) and 14 modified colors (green1, green2, yellow1, yellow2, red1, red2, pink1, pink2, purple1, purple2, blue1, blue2, cyan1, and cyan2).

Table 2
RGB intensity values of color stimuli.

	Base color			Modification 1			Modification 2		
	R	G	B	R	G	B	R	G	B
Green	0	255	51	0	178	51	0	255	128
Yellow	255	255	0	255	178	0	178	255	0
Red	255	51	0	178	51	0	255	128	0
Pink	255	0	153	255	0	230	255	0	76
Purple	153	0	255	76	0	255	230	0	255
Blue	0	51	255	0	128	255	0	51	178
Cyan	0	255	255	0	255	178	0	178	255

Note. Modifications 1 and 2 were created from the base color within the same row by adding or subtracting an intensity value of 77 from one of the RGB dimensions. R=red; G=green; B=blue.

For the complex condition, sample array colors were randomly selected without replacement from the low-resolution stimulus set. For the high-resolution condition, sample array colors were randomly selected without replacement from the high-resolution stimulus set with the constraint that only one stimulus per color group could be presented in the sample array on any given trial. For 'same' trials in either condition, the sample array was re-presented as the test array. For complex 'change' trials, the new test color was randomly selected from among the remaining low-resolution stimuli not used for that particular trial's sample array. For example, in a complex 'change' trial that presents a sample array of red, green, blue, yellow, and pink squares the cued square at test could change to either purple or cyan. For high-resolution 'change' trials, the new test color was randomly selected from among the unused colors belonging to the cued square's color group. In a high-resolution 'change' trial that presents a sample array of red, green2, and blue1 squares, the green2 square, for instance, could change to either green or green1. In other words, complex 'change' trials involved a change from one base color to another base color, whereas high-resolution 'change' trials involved a change within a color group.

2.3. Procedure

The experiment involved a color change detection task modeled after the paradigm of Luck and Vogel (1997), followed by a perceptual control task (Zhang et al., 2012). For each participant, all testing was completed in a single 60 min session.

2.3.1. Change detection task

The stimuli were presented on a grey background that, when viewed at a distance of 50 cm, subtended 1° of visual angle horizontally and vertically. During presentation, the colored squares were separated by at least 3° of visual angle and appeared in pseudorandom locations within an invisible, centered rectangle that subtended $17.6°\times13.2°$ of visual angle. All experimental procedures were identical for the complex and high-resolution conditions aside from the differences in stimuli and set size discussed previously. Each trial began with a centrally-presented fixation cross (+) which remained continuously visible throughout the trial. The sample array appeared for 300 ms, followed by a 1 s delay, and then a test array was presented for 2 s. In the test array, one square was cued (i.e., surrounded by a thick black border) and participants had to indicate whether that particular square had changed color or not between the sample and test arrays. Participants were required to respond within a 4 s window following the test array onset, which consisted of the 2 s test array presentation and an additional 2 s period following test array offset. Participants made same/different judgments using a 6-point confidence scale which was visible at the bottom of the screen throughout the response window. Specifically, participants indicated their level of confidence that the cued square had changed color (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, or after 4 s had elapsed, the next trial would initiate. Examples of 'change' trials for both the complex and high-resolution conditions are illustrated in Fig. 2.

Participants completed a total of 240 trials across two blocks (one high-complexity and one high-resolution; order counterbalanced across participants). Each block consisted of 120 trials

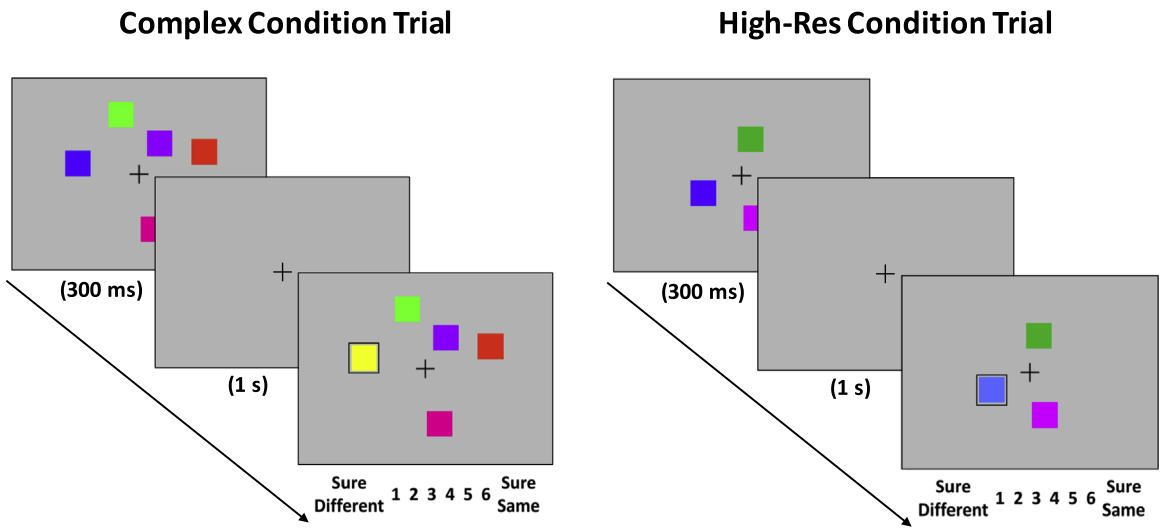

Fig. 2. Change detection task trial sequence for the complex and high-resolution conditions. In the complex condition participants were required to remember a larger number of low-resolution bindings (i.e., set size of 5 and obvious color changes). In the high-resolution condition participants were required to remember a smaller number of high-resolution bindings (i.e., set size of 3 and subtle color changes). For each condition, a 'change' trial is depicted. 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.

presented in random order – half 'same' trials (no color change) and half 'different' trials (color change). Each block was preceded by 16 practice trials consistent with the condition of that particular block.

2.3.2. Perceptual control task

Upon completing the change detection task, participants performed a control task in order to establish that their perceptual resolution was intact and that they could distinguish between the color stimuli used in the current study. Participants had to discern which of two sequentially presented pairs of colored bars consisted of a heterogeneous color pair. For every trial, one pair of bars was always the same color and the other pair was always different colors. All pairs of bars were presented on a grey background as two identically-sized adjacent rectangles that, when viewed at a distance of 50 cm, each subtended 0.5° of visual angle horizontally and 2° of visual angle vertically. The pairs of bars were presented in random locations within an invisible, centered rectangle that subtended 17.6° × 13.2° of visual angle. Each trial began with a centrally-presented fixation cross (+) which remained visible throughout the trial. The first pair of colored bars appeared in a random location for 200 ms, followed by a 400 ms delay, and then a second pair of colored bars appeared in a different random location for 200 ms. Finally, the fixation cross was replaced with a prompt asking "Which pair was different? 1 or 2? ". Participants had 4 s to indicate whether the first pair (1) or second pair (2) of colored bars consisted of a heterogeneous color pair. Responses were input using the numbers 1 and 2 on a keyboard. The perceptual control task was completed in a single block of 84 trials.

2.4. Data analysis

Same/different confidence ratings from the change detection task were used to plot ROCs for each participant, and aggregate ROCs were plotted for group comparisons. This is done by plotting hits (y-axis) and false alarms (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. The rightmost point of the ROC represents the highest confidence 'different' response. 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. Overall VWM accuracy (i.e., sensitivity) was measured as d' calculated at the midpoint of the ROC (i.e., using the proportion of hits and false alarms, regardless of confidence). ROCs were fit to the Dual Process Signal Detection (DPSD) model using maximum likelihood estimation in order to estimate two free memory parameters (i.e., perceiving 'different' and sensing) (Aly and Yonelinas, 2012; Yonelinas, 1994, 2001). According to the DPSD model, perceiving and sensing make independent contributions to working memory (and perception) and they differentially contribute to the shape of the resulting ROC. The probability of perceiving 'different' is reflected by the upper x-intercept of the ROC – the further left it is shifted, the higher the obtained estimate of perceiving-based VWM. On the other hand, the estimate of sensing 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 VWM, it is expected that subjects will correctly identify a change trial if they perceive that one of the study colors has changed (P_d for perceive different). However, even if they fail to perceive a specific color change (i.e., $1-P_d$), they may still make a correct response on the basis that they sense there was a change (S_d, which reflects the proportion of different trials that exceed the sensing response criterion). Thus, P('different'|different)$= P_d+(1-P_d)*(S_d)$. It is also expected that subjects will incorrectly identify some proportion of no-change trials as being different (S_s, which reflects the proportion of same trials that exceed the sensing response criterion). Thus, P('different'|same)$=S_s$. Sensing is assumed to reflect an equal-variance signal-detection process and, hence, S_d and S_s will be a function of the distance between the means of the same and different item distributions (d') and the response criterion (c).

A more generalized form of the DPSD model allows subjects to also perceive that the test array is identical to the study array (P_s for perceive same), in which case one would add another free parameter. However, determining that there was absolutely no change between the study and test arrays would require perfect memory for the study array which is unlikely given the set size and the subtlety of the perceptual changes that were examined. Moreover, when it has been estimated in tests of working memory and perception it tends to approach zero (Aly and Yonelinas, 2012). For these reasons we did not include this additional parameter in

the analyses described below. However, when the perceiving 'same' parameter was included, it approached zero and its inclusion did not alter the main results or conclusions.

Absent trials, in which participants did not respond within the 4 s response window, were uncommon (patients: 0.1% of trials; controls: 0.7% of trials). These trials were not included in the analyses.

To examine whether patients exhibited VWM impairments, we conducted 2 (group: patient/control) × 2 (condition: complex/high-resolution) mixed-model ANOVAs. These were used to compare patient and control accuracy, perceiving, and sensing between the complex condition and the high-resolution condition on the VWM task. All analyses were performed using IBM SPSS v.23.

3. Results

3.1. Perceptual control task

Performance on a perceptual control task was assessed to ensure that any observed patient deficits were not due to an inability to perceive differences between the color stimuli used in the current study. There was no difference in performance between patients (M=89.83%, SD=5.63%) and controls (M=91.27%, SD=5.43%) on this task, $t(16)=0.52$, $p=.608$. Therefore, we can be confident that any potential VWM impairments exhibited by patients cannot be attributed to an inability to accurately perceive the color stimuli used in the current paradigm.

3.2. Change detection task

To assess whether MTL damage causes VWM impairments, and to characterize the nature of any such impairments, we examined change detection ROCs for patients and controls for the complex condition and the high-resolution condition. Visual examination of the aggregate ROCs (Fig. 3a) shows that the patients' ROCs were lower than those of the control participants, indicating that the patients performed more poorly overall. Moreover, the same pattern was apparent for both the complex and high-resolution conditions. In addition, the VWM impairments were most pronounced at the midpoints of the ROCs, which indicates that 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 subject ROCs confirmed each of these observations.

We first examined overall VWM performance (Fig. 3b) by calculating d' at the ROC midpoint. There was a significant main effect of group, $F(1,16)=4.97$, $p=.041$, $\eta_p^2=0.24$, indicating that the patients (M=1.00, SE=0.17) were impaired relative to controls (M=1.48, SE=0.12). There was neither a significant main effect of condition ($p=.088$) nor a group × condition interaction ($p=.359$), suggesting that the patient impairments were comparable in the

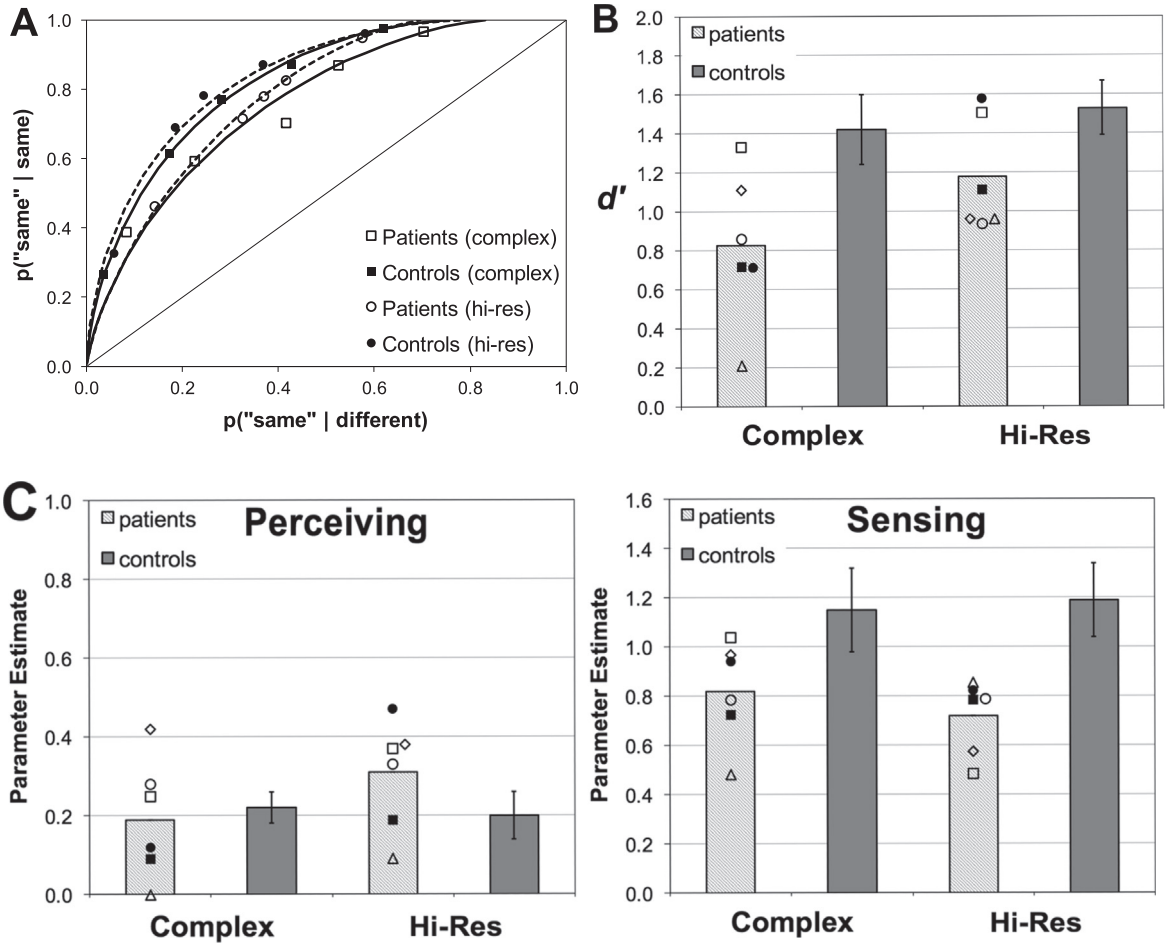

Fig. 3. Patient and control VWM performance results for the complex and high-resolution conditions. (A) Aggregate ROCs. Filled symbols=controls; open symbols=patients; solid lines=complex condition; dashed lines=high-resolution condition. (B) Overall VWM accuracy. (C) Parameter estimates for perceiving and sensing, which are on different scales (probability and d', respectively). For (B) and (C), filled symbols=hippocampal patients and open symbols=MTL patients; Error bars depict ±1 standard error.

two test conditions. Also, note that controls displayed matched VWM accuracy across the complex and high-resolution conditions ($p=.503$), which is consistent with our prior efforts to ensure that any patient impairments were not the result of differences in difficulty across conditions.

Next, we examined the ROC parameter estimates to assess differences in the contributions of perceiving and sensing to VWM performance for the complex and high-resolution conditions (Fig. 3c). For sensing, there was a significant main effect of group, $F(1,16)=5.34$, $p=.034$, $\eta_p^2=0.25$, indicating a deficit in sensing-based VWM for patients ($M=0.77$ $SE=0.14$) compared to controls ($M=1.17$, $SE=0.10$). There was neither a significant main effect of condition ($p=.846$) nor a group × condition interaction ($p=.667$), suggesting that the patient sensing deficits were similar for both test conditions. In contrast, for perceiving, there was no significant effect of group ($p=.538$) or condition ($p=.377$), nor a group × condition interaction ($p=.279$), suggesting that perceiving-based VWM was not reduced in the patients.

All of the above results were consistent for patients with selective hippocampal damage as well as for patients with more extensive MTL damage. Given the small sample sizes that resulted from dividing the patients into subgroups (hippocampal: $n=2$; MTL: $n=4$), we lacked the statistical power to uncover any significant differences between these subgroups and the controls. However, Fig. 3b and c illustrate that the scores for hippocampal patients (filled symbols) and MTL patients (open symbols) are intermixed. 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, suggesting that hippocampal damage alone is sufficient to produce the observed deficits in VWM.

3.3. VWM performance across levels of response criteria

An examination of the ROCs in Fig. 3a indicates that the patients' VWM impairments were most pronounced in the middle of the ROC. This suggests that the extent to which we are able to detect a VWM impairment in patients might depend on the particular response criterion that participants adopt. To further assess this possibility, we calculated d' at the leftmost (strict response criterion), middle (moderate response criterion), and rightmost (lax response criterion) points of the ROC (see Fig. 4). Strikingly, patients exhibited a significant VWM impairment compared to controls only at a moderate level of response criterion ($p=.041$). In contrast, at the other response criteria there was no evidence of a patient deficit (strict criterion $p=.678$; lax criterion $p=.937$). In fact, numerically the patients appeared to be doing slightly better than the controls at these extreme criteria. This finding illustrates the utility of examining ROCs rather than simply collecting binary responses, and may explain why results from prior studies examining the effects of MTL damage on working memory have been mixed. That is, had we collected only binary same/different responses and had participants adopted a moderate response criterion, we would have detected a working memory impairment. However, if participants had adopted either a more or less strict response criterion, we would have failed to detect a working memory impairment.

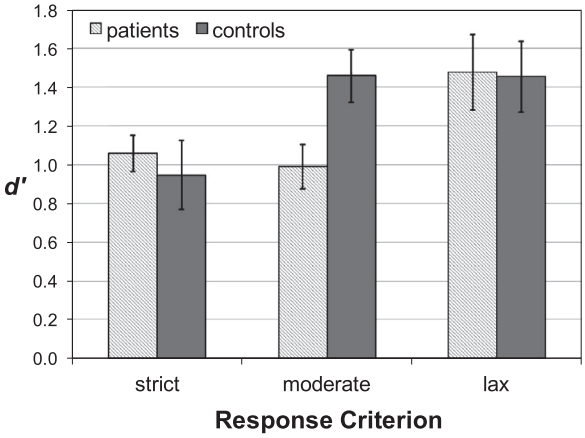

Fig. 4. Comparison of VWM performance, collapsed across conditions, as a function of response criterion. Performance is measured as d' at the leftmost (strict criterion), middle (moderate criterion), and rightmost (lax criterion) points of the ROC. Error bars depict ±1 standard error.

The ROC analysis reported above focused on assessing changes in VWM sensitivity across levels of response criteria, but we also examined the ROCs for evidence of differences in response bias. Overall, the patients and controls appeared to exhibit similar patterns of response bias in the sense that the ROC points for the patients and controls were similarly spread across the full range of the scale (see Fig. 3a). However, there was a tendency for the patients to adopt a more lax criterion and accept more trials as 'same' (i.e., the patients' ROC points are shifted slightly rightward compared to the controls), and this appeared to be most pronounced for the leftmost and middle points of the ROCs. Given that these are the points which reflected the contribution of lower confidence sensing responses, rather than perceiving responses, this finding is consistent with the parameter estimates in indicating that MTL damage seemed to selectively alter sensing- rather than perceiving-based VWM.

3.4. Examination of alternative ROC models

3.4.1. The unequal variance signal detection model

In order to assess the extent to which the current conclusions rest on the specific model used to the examine the ROCs (i.e., the DPSD model), and to evaluate the robustness of the dissociation observed in the sensing- and perceiving-based VWM parameters, we reanalyzed the data using the most common alternative ROC model: The Unequal Variance Signal Detection (UVSD) model (Swets, 1973; Yonelinas and Parks, 2007). The UVSD model assumes the two parameters that describe the shape of the ROC are strength/discriminability (d') and variance ratio (V_S). Strength represents the discriminability of same and different items, as measured by the distance between the means of the same and different item strength distributions, and is reflected by the degree of ROC curvilinearity. The variance ratio represents the ratio of the variance for the same item distribution relative to the variance for the different item distribution, and the estimate of variance ratio is reflected by the degree and direction of ROC asymmetry. If the variances of the same and different item distributions are similar, then the ROC will be symmetrical. If the variance of the same item distribution is greater than or less than that of the different item distribution, then the ROC will be asymmetrically pushed up on the left or right side, respectively.

The results from fitting the UVSD model paralleled our primary conclusions in showing that MTL damage significantly and selectively reduced VWM strength, $t(16)=2.18$, $p=.045$, while having no effect on the process or processes that influence variance ratio, $t(16)=-0.12$, $p=.909$. As expected, estimates of strength were reduced in patients ($M=1.00$, $SD=0.18$) compared to controls ($M=1.29$, $SD=0.29$), whereas estimates of variance ratio were similar in patients ($M=0.84$, $SD=0.09$) and controls ($M=0.83$, $SD=0.14$).

We also contrasted the fit of the DPSD and UVSD models using (Dunning's) log-likelihood ratio G^2 test as a goodness-of-fit index, and found that the two models fit the data equally well. The G^2 values were 96.25 and 105.82 for the DPSD and UVSD models,

respectively (smaller values indicate better fit). This corresponds to Bayesian Information Criteria (BIC) of −711.89 and −713.89 for the DPSD and UVSD models, respectively, which are not meaningfully different BICs (Kass and Raftery, 1995). In addition, assessment of the G^2 test statistic for each participant showed that the UVSD model significantly deviated ($p < 0.05$) from the observed data in 6 out of 18 participants, whereas the DPSD model deviated from the observed data in only 3 out of 18 participants.

3.4.2. The equal variance signal detection model

Both the DPSD and UVSD models assume that there are two separable components underlying performance, whereas the Equal Variance Signal Detection (EVSD) model assumes that the strength/discriminability (d') parameter alone describes the shape of the ROC (Swets, 1973; Yonelinas and Parks, 2007). To assess whether the results could be accounted for using the simpler, single-parameter EVSD model, we directly compared it to the other models using the change in log-likelihood ratio G^2 test for nested models as a comparative fit index. Because the additional parameter (i.e., perceiving for DPSD and variance ratio for UVSD) in the more complex models can vary between participants, G^2 test statistics were calculated separately for each participant and then summed, for each model.

Both the DPSD model, $G^2(18) = 54.49$, $p < 0.001$, and the UVSD model, $G^2(18) = 44.92$, $p < 0.001$, provided a significantly better fit to the observed data than the EVSD model. In addition, assessment of the G^2 test statistic for each participant showed that the EVSD model significantly deviated ($p < 0.05$) from the observed data in 7 out of 18 participants. These results are important in supporting the use of two-parameter models when interpreting the results from working memory. In addition, they indicate that single parameter estimates of discrimination, such as d', are not entirely appropriate for assessing VWM performance. This converges with the findings from the response criteria analysis, such that when a single-parameter index of discrimination was used to assess performance the effects of amnesia were found to be dependent on the specific response criterion that the participants happened to adopt.

4. Discussion

The current study examined the effects of MTL damage on visual working memory using an ROC analysis in conjunction with a color change detection paradigm, and showed that MTL patients exhibited significant VWM impairments compared to age- and education-matched controls. Moreover, the VWM deficit observed in patients was selectively driven by reductions in the accuracy of low-confidence sensing judgments of change, whereas high-confidence perceiving judgments were similar between patients and controls. These results add to the growing consensus that the MTL is critically involved in working memory, but additionally illustrate why such deficits have not always been detected (e.g., Allen et al., 2014; Jeneson et al., 2010; 2012; Shrager et al., 2008). That is, only by examining performance across a range of response confidence did it become apparent that the patient deficits were limited to low-confidence memory responses. Had we collected only binary responses (e.g., yes/no or same/different) in the current study, and had participants adopted a strict or lax response criterion, we would have failed to find evidence for a VWM impairment.

The results further showed that the patients were impaired when the working memory task required either high-resolution bindings or high-complexity bindings. Even with a small set size of 3 items, patients exhibited VWM impairments when required to maintain and retrieve highly precise color information. Moreover, similar deficits were observed when the task required only low-resolution bindings but when the memory load (i.e., complexity) was increased to a set size of 5 items. It is well known that the MTL, and particularly the hippocampus, is critical for binding event elements, especially as the complexity of relational binding increases (Cohen and Eichenbaum, 1993; Diana et al., 2007; Konkel et al., 2008). Extending upon this, the high-resolution binding model proposes that hippocampal dependence on a task is also determined by the quality or resolution with which relational bindings must be maintained (Yonelinas, 2013). Thus, the current results are novel in showing for the first time that the role of the hippocampus in performance is determined by both the complexity and the resolution of the required bindings.

The finding that MTL damage selectively reduced the accuracy of low-confidence responses and estimates of sensing, while not influencing high-confidence responses and estimates of perceiving, parallels recent findings in studies of scene perception. Specifically, 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). Converging results across a series of behavioral studies conducted by Aly and Yonelinas (2012) further supports a phenomenological distinction between perceiving-based and sensing-based performance. They showed that discrimination judgments are supported by the joint contribution of two functionally independent processes: perceiving and sensing. Specifically, perceiving refers to a discrete state in which individuals are consciously aware of local, distinct details that differ between two images, and these responses are typically associated with very high confidence. Sensing refers to a graded signal that indicates the strength of global, relational match/mismatch between two images, and these responses are typically associated with lower confidence. In conjunction with the current results, these findings indicate a critical role of the MTL, especially the hippocampus, in a sensing process that underlies both perception and 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. However, the two patients in the current study with what appeared to be 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.

The finding that hippocampal damage leads to a reduction in the accuracy of low-confidence working memory judgments in the current study, as well as low-confidence perceptual judgments in scene discrimination (Aly et al., 2013), is striking given that it is well established that hippocampal damage impairs the highest confidence recognition responses and those associated with vivid recollection (Eichenbaum et al., 2007; Fortin et al., 2004; Koen and Yonelinas, 2014; Quamme et al., 2004; Yonelinas et al., 2002; Yonelinas et al., 2005). Why would the hippocampus contribute to long-term recognition 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 and 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 nonstudied 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 recollection signal in recognition memory and a low-confidence sensing signal in perception and working memory. Taken with the current findings, this suggests that the hippocampus supports complex high-resolution bindings in service of perception, working memory, and long-term recollection.

An examination of an alternative two-parameter ROC model supported our conclusion that MTL damage leads to a selective VWM deficit for low-confidence strength-based judgments. Although our main analyses were conducted by fitting the ROCs to the DPSD model (Yonelinas, 1994), we also analyzed working memory performance by fitting the ROCs to the UVSD model which is the most common alternative ROC model (Swets, 1973; Yonelinas and Parks, 2007). We showed that, regardless of which two-parameter model was used to fit the ROCs, MTL patients were selectively impaired in the strength parameter (i.e., sensing for the DPSD model and d' for the UVSD model) and not in the other parameter (i.e., perceiving for the DPSD model and variance ratio for the UVSD model). That is, damage to the MTL produced a reduction only in the VWM process or component associated with a graded strength signal, irrespective of ROC model assumptions. Again, this is the opposite of what is seen in recognition memory, in which hippocampal damage leads to reductions only in the non-strength parameter – recollection for the DPSD model and variance ratio for the UVSD model (Yonelinas and Parks, 2007). Thus, interpreted in the context of either model, these findings support the supposition that the MTL, and hippocampus especially, is critically involved in both the process that influences variance ratio/recollection in recognition memory and the process that influences strength/sensing in working memory and perception (see supplemental analyses of Aly et al., 2013 for similar conclusions from a perception task).

Given that MTL damage produced selective deficits in sensing (or strength), while leaving perceiving (or variance ratio) intact, the results indicate that only some VWM processes or components are dependent on the MTL. Thus, the selective sensing-based VWM deficit observed in the patients demonstrates the utility of taking a process dissociation approach. Typically, studies examining VWM in MTL patients have collected binary responses (e.g., yes/no or same/different) which only allows for the derivation of a single-point measure of performance, such as proportion correct or d' (e.g., Jeneson et al., 2012; Olson et al., 2006a; but see Warren et al., 2014; Zhang et al., 2012). The current ROC results highlight the limitations of binary response tasks and offer insight into why the existing literature has been mixed with respect to whether or not the hippocampus, and surrounding MTL structures, are critical for working memory. That is, an examination of performance across levels of response criteria showed that the patients only exhibited a VWM impairment at a moderate response criterion (i.e., the midpoint of the ROC), which is influenced by the responses for which participants were least confident. In contrast, performance was comparable between the patients and controls at more strict or more lax levels of response criteria (i.e., the extreme ends of the ROC), which are influenced by the responses for which participants were most confident. This demonstrates that whether an experiment will show MTL involvement in a binary response task or not can depend on the specific response criterion that participants adopt in that particular experiment. Considering the crucial influence that response criterion can have, it is not surprising that the existing literature has been equivocal regarding the role of the MTL, and specifically the hippocampus, in working memory.

Finally, in the current study we used an ROC approach to assess MTL-related impairments in sensing- and perceiving-based VWM. However, other studies have employed the color wheel task, which also allows for process dissociation, to examine two very different measures of performance: the quality (precision) and quantity (capacity) of VWM representations (Warren et al., 2014; Wilken and Ma, 2004; Zhang et al., 2012; Zhang and Luck, 2008). Thus far, the two studies that have used the color wheel task to examine VWM in MTL patients have found conflicting results. Warren et al. (2014) found that MTL damage produced selective impairments in the quantity of VWM representations, whereas Zhang et al. (2012) found instead that the quality of VWM representations was reduced. Therefore, it is difficult to know how, or even if, the color wheel task parameters of quantity and quality are related to our parameters of sensing and perceiving. Future studies exploring the relationship between quantity/quality and sensing/perceiving would benefit from a within-subjects examination of the relationships between these parameters across tasks.

In summary, the current neuropsychological findings indicate that the MTL, especially the hippocampus, is critically involved in working memory discriminations based on low-confidence sensing judgments of change. Working memory discriminations based on high-confidence perceiving judgments of change do not appear to be dependent on the MTL. Moreover, selective sensing-based deficits were observed when the task required either high-resolution bindings or high-complexity bindings, suggesting both of these factors play a critical role in MTL-dependent working memory. Together, these results provide evidence that only some working memory processes are dependent on the MTL, and are consistent with the proposal that the MTL plays a critical role in forming complex, high-resolution bindings.

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