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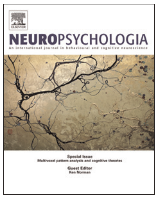

Memory integration in amnesia: Prior knowledge supports verbal short-term memory

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ABSTRACT

Short-term memory (STM) and long-term memory (LTM) have traditionally been considered cognitively distinct. However, it is known that STM can improve when to-be-remembered information appears in contexts that make contact with prior knowledge, suggesting a more interactive relationship between STM and LTM. The current study investigated whether the ability to leverage LTM in support of STM critically depends on the integrity of the hippocampus. Specifically, we investigated whether the hippocampus differentially supports between-domain versus within-domain STM–LTM integration given prior evidence that the representational domain of the elements being integrated in memory is a critical determinant of whether memory performance depends on the hippocampus. In Experiment 1, we investigated hippocampal contributions to within-domain STM–LTM integration by testing whether immediate verbal recall of words improves in MTL amnesic patients when words are presented in familiar verbal contexts (meaningful sentences) compared to unfamiliar verbal contexts (random word lists). Patients demonstrated a robust sentence superiority effect, whereby verbal STM performance improved in familiar compared to unfamiliar verbal contexts, and the magnitude of this effect did not differ from that in controls. In Experiment 2, we investigated hippocampal contributions to between-domain STM–LTM integration by testing whether immediate verbal recall of digits improves in MTL amnesic patients when digits are presented in a familiar visuospatial context (a typical keypad layout) compared to an unfamiliar visuospatial context (a random keypad layout). Immediate verbal recall improved in both patients and controls when digits were presented in the familiar compared to the unfamiliar keypad array, indicating a preserved ability to integrate activated verbal information with stored visuospatial knowledge. Together, these results demonstrate that immediate verbal recall in amnesia can benefit from two distinct types of semantic support, verbal and visuospatial, and that the hippocampus is not critical for leveraging stored semantic knowledge to improve memory performance.

1. Introduction

In everyday life, we frequently have to maintain information in mind over brief delays. Common examples include remembering a friend's telephone number between the time of hearing it and dialing it, or keeping a colleague's message in mind so that it can be conveyed to another colleague. It is well established that the ability to temporarily maintain information in mind is greatly improved when that information makes contact with pre-existing semantic knowledge. For example, a friend's telephone number is much easier to remember if it contains an ordered sequence of numbers (543–6789) compared to a random sequence of numbers (473–9586). Indeed, experimental studies have demonstrated that stored semantic knowledge can strongly impact immediate memory performance. Short-term serial recall of digits improves when digits appear in structured versus unstructured sequences (Bor et al., 2004) and short-term serial recall of words improves when words are presented within familiar verbal contexts (sentences) compared to unfamiliar verbal contexts (lists), a phenomenon that has been labeled the ‘sentence superiority effect’ (Baddeley et al., 2009; Brener, 1940; Miller and Selfridge, 1950).

Recently, a series of studies has demonstrated that immediate verbal recall also improves when to-be-remembered items are presented within familiar visuospatial contexts, even when those visuospatial contexts are incidental to the memory task at hand. Specifically, when subjects are presented with sequences of digits in a spatial array, immediate verbal recall of these digits (akin to a digit span test) improves when digits are presented in a familiar visuospatial context (a typical keypad display) compared to an unfamiliar visuospatial context (an atypical keypad display; Allen

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et al., In press; Darling et al., 2012, 2014; Darling and Havelka, 2010). This 'visuospatial bootstrapping effect' is thought to reflect facilitated recall when verbal digit information can be linked to pre-existing visuospatial representations. Together, these examples demonstrate the importance of interactions between short-term memory (STM) and long-term memory (LTM), and reveal how both verbal and visuospatial knowledge can be leveraged to support immediate verbal recall.

Although traditional models of human memory make clear distinctions between STM and LTM (Atkinson and Shiffrin, 1968; Baddeley and Hitch, 1974; James, 1890), more recent models of STM emphasize the importance of interactions between these two forms of memory (Baddeley, 2000; Cowan, 1988; Ranganath and Blumenfeld, 2005; Zhou et al., 2007). Baddeley (2000) has proposed that an episodic buffer serves as an interface between STM and LTM in which activated information held in STM can be integrated with stored long-term knowledge (Baddeley, 2000). An alternative, but complementary view, is that stored long-term knowledge influences immediate memory as a byproduct of an overlapping representational system in which STM reflects an activated subset of LTM representations (Cowan, 1999; Ericsson and Kintsch, 1995; Postle, 2006; Ranganath and Blumenfeld, 2005; Zhou et al., 2007). While the influence of pre-existing knowledge on STM is now widely recognized both theoretically and behaviorally, an important outstanding question is how interactions between STM and LTM are supported in the brain.

The current study investigates whether the contribution of pre-existing semantic representations to STM critically depends on associative processes supported by the medial temporal lobe (MTL), and the hippocampus in particular. The hippocampus is widely recognized as a key neural region that links individual elements within LTM, and recent evidence suggests that the hippocampus may play a similar role when linking elements within STM (Cashdollar et al., 2009; Finke et al., 2008; Hannula et al., 2006; Jonides et al., 2008; Olsen et al., 2012; Olson et al., 2006a, 2006b; Rose et al., 2012). However, it is currently unknown whether the hippocampus also supports interactions *across* STM and LTM. Consistent with this possibility, several recent neuroimaging studies have reported increased hippocampal activity associated with facilitated immediate verbal recall in familiar versus unfamiliar encoding contexts (Bonhage et al., 2014; Bor et al., 2004; Bor and Owen, 2007). Bor et al. (2004) found greater hippocampal activity when participants memorized mathematically structured digit sequences (2, 4, 6, 8, 9, 7, 5, 3) compared to unstructured digit sequences (9, 2, 7, 1, 4, 6, 5, 8) and Bonhage et al. (2014) found greater hippocampal activity when participants memorized lists of words appearing in the context of sentences versus lists. Interestingly, Bonhage et al. found that increased hippocampal activity during sentence encoding was accompanied by decreased frontal activity in classic language-related areas during sentence maintenance. They proposed that hippocampal activity during encoding may reflect relational binding processes that combine individual items (words) into larger units (chunks) based on syntactic or semantic information stored in LTM, and that this hippocampally-mediated chunking at encoding may unburden the neural systems supporting maintenance and rehearsal.

Although recent neuroimaging evidence is consistent with the notion that the hippocampus links activated verbal representations in STM to stored knowledge in LTM (see also Rudner et al., 2007; Rudner and Ronnberg, 2008), it is currently unclear whether hippocampal activity observed in these neuroimaging studies is directly related to memory integration. Arguments against this notion come from a recent neuropsychological report that the sentence superiority effect is intact in a patient with developmental amnesia, who has extensive hippocampal damage acquired in childhood (Baddeley et al., 2010). This finding suggests that the ability to leverage stored linguistic knowledge in support of immediate verbal recall may not critically depend on the hippocampus. However, it is also important to note that the case of developmental amnesia may not be typical of adult-onset hippocampal damage, and that intact performance in this patient may reflect compensatory recruitment of brain regions outside the hippocampus (Baddeley et al., 2010).

Another intriguing possibility is that hippocampal involvement in the semantic facilitation of STM depends on the nature of the features being integrated in memory. Specifically, the hippocampus may not be necessary for linking activated representations with semantic knowledge from the same representational domain (e.g., integrating verbal representations held in STM with pre-existing verbal knowledge), but may instead be critical for integrating activated representations with semantic knowledge from a different domain (e.g., integrating verbal representations held in STM with pre-existing visuospatial knowledge). This hypothesis is informed by prior evidence from both the STM and LTM literature suggesting that the representational domain of the elements being integrated in memory is a critical determinant of whether memory performance depends on the hippocampus, with the hippocampus primarily involved in memory for cross-domain associations (Mayes et al., 2007; Mayes et al., 2004; Piekema et al., 2006, 2009; Race et al., 2013; Vargha-Khadem et al., 1997). However, there is also evidence that the hippocampus supports memory for all types of associations, both within-domain and cross-domain (Holdstock et al., 2010; Park and Rugg, 2011; Stark and Squire, 2003; Turriziani et al., 2004). Thus, important questions remain about hippocampal contributions to facilitated STM when to-be-remembered information is congruent with stored knowledge from (a) the same domain and (b) a different domain.

The current study uses a lesion-deficit approach to investigate the nature and necessity of hippocampal contributions to STM–LTM integration. Specifically, we investigate whether the hippocampus differentially supports cross-domain versus within-domain STM–LTM integration. Immediate verbal recall was measured in amnesic patients with adult-onset MTL damage in (1) verbal contexts (Experiment 1) and (2) visuospatial contexts (Experiment 2). If the hippocampus is only critical for integrating activated verbal material with semantic knowledge from a different domain, then amnesic patients should demonstrate a preserved immediate memory benefit when verbal items are encoded within familiar verbal contexts (Experiment 1) but should not demonstrate an immediate memory benefit when verbal items are presented in familiar visuospatial contexts (Experiment 2). In contrast, if the hippocampus plays a critical role in all types of STM–LTM integration, regardless of the representational domain of the features being integrated, amnesic patients should demonstrate a reduced immediate recall benefit in both familiar verbal and familiar visuospatial contexts. Finally, a third possibility is that the hippocampus does not play a critical role in *any* type of STM–LTM integration. If this is the case, then amnesic patients, like controls, should demonstrate immediate recall benefits in *both* familiar verbal and familiar visuospatial contexts.

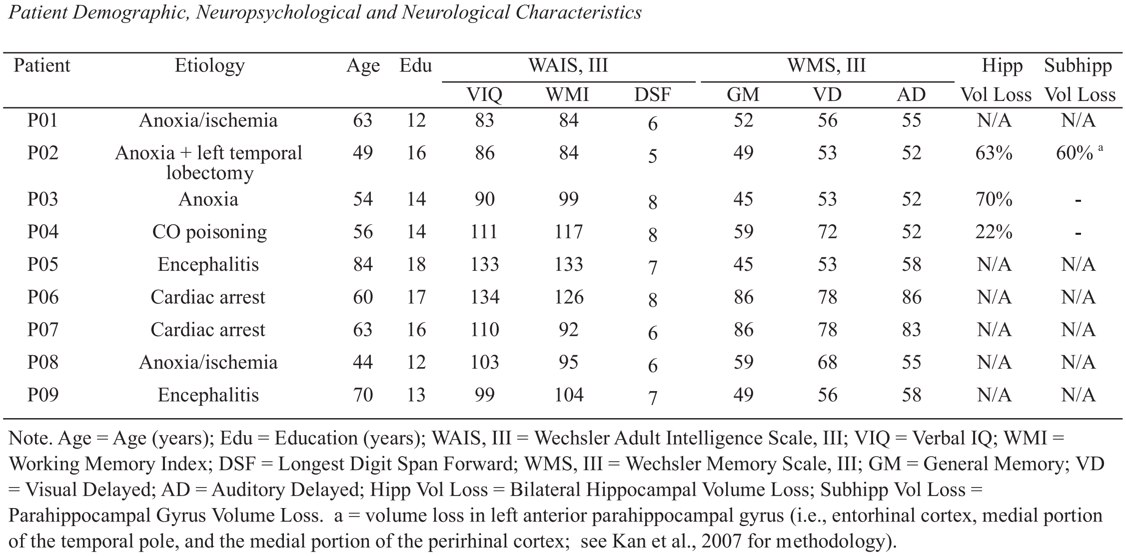
2. Experiment 1: sentence superiority effect

2.1. Materials and methods

2.1.1. Participants

Participants included eight amnesic patients with MTL lesions (P01–P08; Table 1). Patients' neuropsychological profiles indicate impairments isolated to the domain of memory with profound impairments in new learning. Three patients (P03, P04, and P08) had lesions restricted to the hippocampus (confirmed with

Table 1
Patient demographic, neuropsychological and neurological characteristics.



Patient Demographic, Neuropsychological and Neurological Characteristics

Patient	Etiology	Age	Edu	WAIS, III			WMS, III			Hipp	Subhipp
				VIQ	WMI	DSF	GM	VD	AD	Vol Loss	Vol Loss
P01	Anoxia/ischemia	63	12	83	84	6	52	56	55	N/A	N/A
P02	Anoxia + left temporal lobectomy	49	16	86	84	5	49	53	52	63%	60% [a]
P03	Anoxia	54	14	90	99	8	45	53	52	70%	-
P04	CO poisoning	56	14	111	117	8	59	72	52	22%	-
P05	Encephalitis	84	18	133	133	7	45	53	58	N/A	N/A
P06	Cardiac arrest	60	17	134	126	8	86	78	86	N/A	N/A
P07	Cardiac arrest	63	16	110	92	6	86	78	83	N/A	N/A
P08	Anoxia/ischemia	44	12	103	95	6	59	68	55	N/A	N/A
P09	Encephalitis	70	13	99	104	7	49	56	58	N/A	N/A

Note. Age = Age (years); Edu = Education (years); WAIS, III = Wechsler Adult Intelligence Scale, III; VIQ = Verbal IQ; WMI = Working Memory Index; DSF = Longest Digit Span Forward; WMS, III = Wechsler Memory Scale, III; GM = General Memory; VD = Visual Delayed; AD = Auditory Delayed; Hipp Vol Loss = Bilateral Hippocampal Volume Loss; Subhipp Vol Loss = Parahippocampal Gyrus Volume Loss. a = volume loss in left anterior parahippocampal gyrus (i.e., entorhinal cortex, medial portion of the temporal pole, and the medial portion of the perirhinal cortex; see Kan et al., 2007 for methodology).

volumetrics in two patients; see Table 1), one patient (P01) had a lesion that included the hippocampus and MTL cortices, and two patients (P02 and P05) had damage to the hippocampus and MTL cortices as well as damage extending into the anterolateral temporal cortex. For the encephalitic patient P09, MRI was acquired in the acute phase of the illness, and no visible lesions were observed on T1-weighted images. However, T2-flair images showed bilateral hyperintensities in the hippocampus, MTL cortices, and anterior insula. Structural CT and MRI scans depicting patients' lesions are presented in Fig. 1. Two of the cardiac arrest patients (P06 and P07) could not be scanned due to medical contraindications but MTL pathology can be inferred on the basis of etiology and neuropsychological profile. Volumetric data for the hippocampus and MTL cortices was available for three patients (P02, P03, P04) using methodology reported elsewhere (Kan et al., 2007).

Sixteen healthy controls also participated and were matched to the patient group in terms of mean age (60 ± 12.3), education (14 ± 2.2), verbal IQ (106 ± 19.8), and forward digit span (7 ± 1.4). All participants were paid for their participation and provided informed consent in accordance with the procedures of the

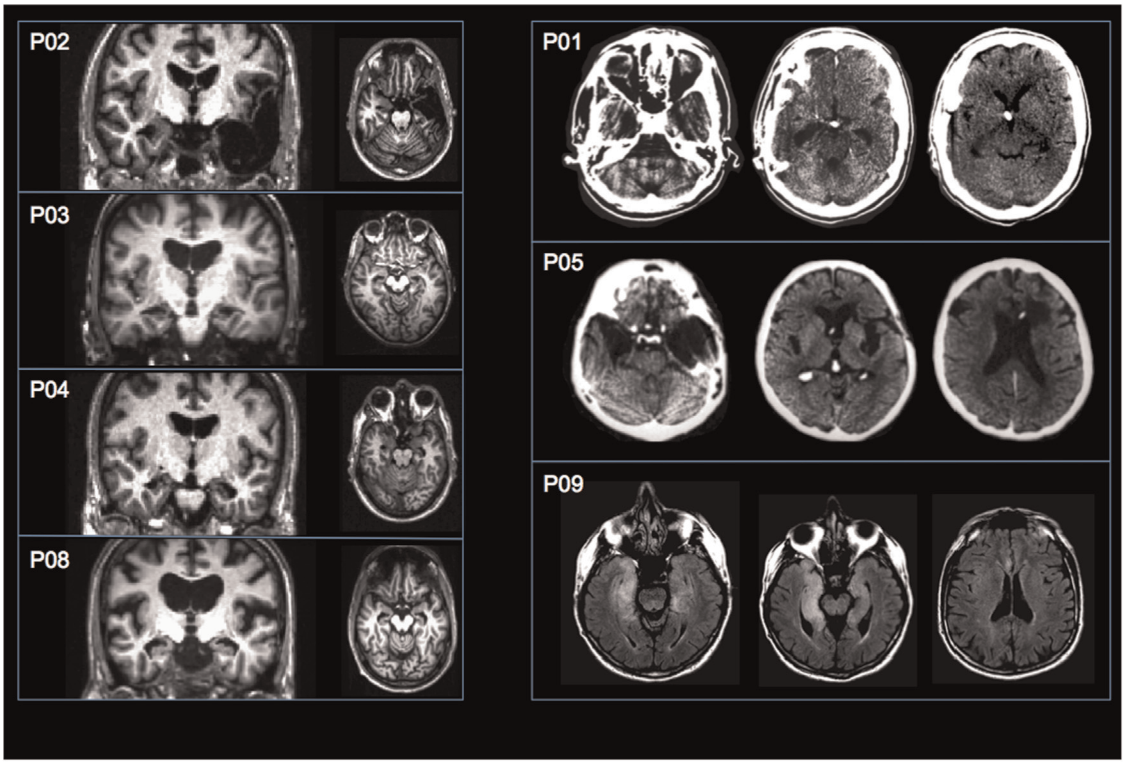


Fig. 1. Structural CT and MRI scans depicting medial temporal lobe (MTL) lesions for seven of the nine amnesic patients (see Section 2.1). The left side of the brain is displayed on the right side of the image. T1-weighted MRI images show lesion locations for P02, P03, P04, and P08 in the coronal and axial plane, CT scans show lesion locations for P01 and P05 in the axial plane, and T2-flair images show lesion location for P09 in the axial plane.

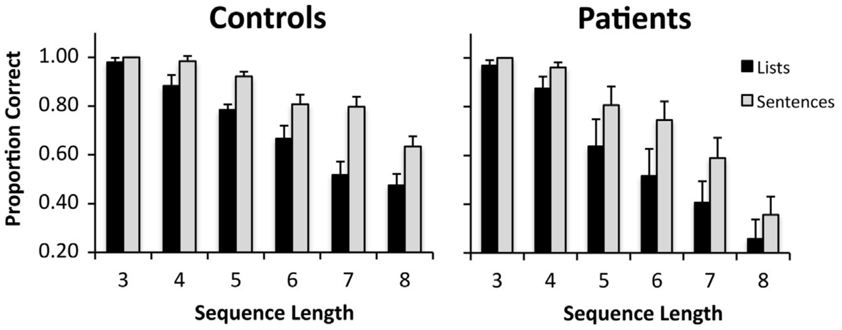


Fig. 2. Sentence superiority effect. Proportion of words correctly remembered at each sequence length when words were presented as sentences (gray bars) or random word lists (black bars).

Institutional Review Boards at Boston University and the VA Boston Healthcare System.

2.1.2. *Stimuli*

To test the sentence superiority effect, sequences of words were combined into (a) random lists and (b) constrained sentences following the methods of Baddeley et al. (2009, 2010). To avoid ceiling and floor effects, a limited set of words was repeatedly used and permuted across conditions. The set of words included four adjectives (tall, sad, old, fat), four nouns (teacher, soldier, waiter, bishop), four verbs (meets, insults, follows, helps) and three function words (not, and, or). In the sentence condition, word sequences were always syntactically and semantically correct (e.g., “fat waiter meets and helps teacher”). In the list condition, the word sequences did not abide by semantic or syntactic rules (e.g., “helps not soldier old bishop insults”). The sentence and list conditions each contained 24 sequences of words ranging from three to eight words in length (four sequences at each length). Word length and word frequency were matched between random lists and constrained sentences at each list length. Because a limited pool of words was used across trials, all words were highly familiar and accurate memory performance depended on remembering the most recent combination of words. It has previously been demonstrated that immediate memory for such constrained sentences is reliably greater than that for random lists of the same words in healthy adults (Baddeley et al., 2009, 2010).

2.1.3. *Procedure*

Words were visually presented on a computer screen in a sequential manner at a rate of one word per second. Participants were instructed to remember the words in the order in which they were presented. At the end of the sequence a command prompted participants to verbally recall the sequence in the correct order. Following the procedure of Baddeley et al. (2010), the session started with four sentence trials that were each three words long, followed by four list trials that were each three words long. Sequence length was gradually increased by one word until a sequence length of eight, with alternating sets of four sentences and four lists at each length.

2.2. *Results*

Memory recall performance is presented in Fig. 2. Performance was scored as the mean proportion of words correctly recalled in each sequence. Following the procedure of Baddeley et al. (2010), a recalled word was classified as correct if it was produced in the correct position relative to an adjacent word and/or correctly located in the first or last serial positions.[1] The overall pattern of performance in amnesic patients mirrored that of controls, with better word recall in the sentence than in the list condition. To verify the reliability of this effect, mean accuracy was entered into a 2 × 2 × 6 mixed model ANOVA with factors of group (patient, control), context (list, sentence), and sequence length (3, 4, 5, 6, 7, or 8 words long). A reliable sentence superiority effect was observed, with higher word recall in the sentence condition than in the list condition (main effect of context, $F(1, 22)=87.26$, $p<.001$). Although overall recall performance was higher in controls (main effect of group, $F(1, 22)=4.43$, $p<.05$), the magnitude of the sentence superiority effect did not differ across groups (context × group, $F(1, 22)<1$, $p=.75$) and follow-up context × sequence length ANOVAs within each group confirmed that the sentence superiority effect was significant in both controls ($F(1, 15)=96.73$, $p<.001$) and patients ($F(1, 7)=19.17$, $p<.005$). Furthermore, while the magnitude of the sentence superiority effect differed across sequence lengths (context × sequence length, $F(5, 110)=5.93$, $p<.001$), reflecting a reduced effect when performance was close to ceiling, the magnitude of the sentence superiority did not differ between patients and controls across sequence lengths (context × sequence length × group; $F(5, 110)=1.57$, $p=.18$). Follow-up pairwise comparisons confirmed that the magnitude of the sentence superiority effect did not differ between groups at any of the sequence lengths ($ts(22)<1.66$, $ps>.11$).

2.2.1. *Amnesic patient subgroup analysis*

In order to investigate whether the magnitude of the sentence superiority effect differed in patients with MTL damage limited to the hippocampus versus patients whose MTL damage extended beyond the hippocampus, recall performance was separately analyzed for the patients with volumetrically or visually confirmed damage limited to the hippocampus (P03, P04 and P08; H-only group) and for the patients with volumetrically or visually confirmed MTL damage that included the hippocampus and MTL cortex (P01, P02, P05; H+ group). Memory recall performance was greater in the sentence than the list conditions in both the H-only group (mean sentence recall=.77 ± .29, mean list recall=.62 ± .36) and the H+ group (mean sentence recall=.74 ± .30, mean list recall=.66 ± .37). Mean accuracy at each list length was entered into a 2 × 2 × 6 mixed model ANOVA with factors of group (H-only patients, H+ patients), context (list, sentence), and sequence length (3, 4, 5, 6, 7, or 8 words long). Overall recall performance did not differ between the two patient groups (main effect of group, $F(1, 4)<1$, $p=.72$). Importantly, the magnitude of the sentence superiority effect did not differ between groups (context × group, $F(1, 4)=.21$, $p=.67$) and did not differ between groups across the sequence lengths (context × sequence length × group, $F(5, 20)=1.49$, $p=.24$).

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[1] Results did not differ when accuracy was calculated using strict serial position scoring.

2.3. Discussion: Experiment 1

A reliable sentence superiority effect was observed in amnesic patients with adult-onset hippocampal damage. Specifically, immediate serial recall of words improved in amnesia when words were presented in sentences compared to random word lists. These results support a prior observation of preserved sentence superiority in developmental amnesia (Baddeley et al., 2010) and extend these results to adult-onset amnesia. Although hippocampal activity has previously been observed in association with the sentence superiority effect in healthy adults (Bonhage et al., 2014), the current results indicate that an intact hippocampus is not *necessary* in order for immediate memory to benefit from pre-existing linguistic information stored in LTM.

3. Experiment 2: visuospatial bootstrapping effect

The finding of an intact sentence superiority effect in adult-onset amnesia suggests that within-domain STM–LTM integration does not depend on the hippocampus. However, it has been suggested that the hippocampus may only be critical for associating cross-domain information represented in non-adjacent and weakly connected neocortical regions (Mayes et al., 2001, 2007; Vargha-Khadem et al., 1997). Thus, in Experiment 2 we investigated whether the hippocampus plays a critical role when integrating active verbal representations held in STM with pre-existing *visuospatial* knowledge. To test this hypothesis, we examined whether the visuospatial bootstrapping effect is present in adult-onset amnesic patients with hippocampal damage. If the hippocampus plays a critical role in cross-domain STM–LTM integration, amnesic patients' immediate digit recall should not benefit from the presentation of digits in familiar visuospatial contexts (no typical keypad advantage should be observed). In contrast, if the hippocampus does not play a critical role in cross-domain STM–LTM integration, amnesic patients should demonstrate an intact ability to leverage stored visuospatial knowledge in support of immediate verbal recall (intact typical keypad advantage). Before testing whether patients' recall performance can improve in the typical keypad encoding context (Experiment 2b), we first wanted to establish that semantic long-term representations of a typical keypad are intact and available in amnesia and that patients can access this representation as well as controls (Experiment 2a), a precondition for investigating the visuospatial bootstrapping effect.

3.1. Experiment 2a

3.1.1. Materials and methods

3.1.1.1. Participants. The amnesic patient group included the eight amnesic patients with MTL lesions who participated in Experiment 1 and one additional MTL amnesic patient (P01–P09; Table 1). A different group of sixteen healthy controls also participated and were matched to the patient group in terms of mean age (65 ± 9.5), education (16 ± 2.1), and verbal IQ (107 ± 10.7). All participants were paid for their participation and provided informed consent in accordance with the procedures of the Institutional Review Boards at Boston University and the VA Boston Healthcare System.

3.1.1.2. Procedure. To test whether long-term visuospatial knowledge about a typical keypad is intact in amnesia, sets of three non-repeating digits were concurrently presented on a computer screen and participants had to enter the digits as quickly as possible into a keypad that had either (i) a typical keypad layout or (ii) an atypical keypad layout (in which digits were arranged in a pseudorandom pattern so that the digit-location mapping was unfamiliar). Importantly, the spatial position and distance between digits was matched across the typical and atypical keypad number sets so that motor movements were equivalent across conditions. Participants performed 42 trials of the typical keypad condition and 42 trials of the atypical keypad condition, with the order of conditions counterbalanced across participants, and reaction times and accuracy were collected. In the atypical keypad condition, the layout of the atypical keypad changed every 14 trials to reduce potential effects of digit-location learning across trials in controls. If the long-term representation of a typical keypad is intact in amnesia, and patients can access this representation as well as controls, patients and controls should demonstrate similar reaction time facilitation when entering digits into a typical versus an atypical keypad.

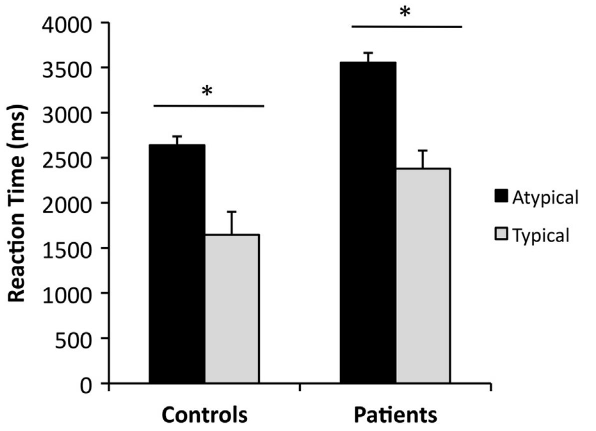

Fig. 3. Long-term knowledge of a typical keypad. Mean reaction time to type digits into a typical keypad (gray bars) and an atypical keypad (black bars). Patients and controls demonstrated an equivalent typical keypad advantage.

3.1.2. Results

Both groups were highly accurate when entering digits into the typical and atypical keypads (accuracy $>$ 98% across conditions in both groups) and were faster to enter digits into the typical keypad compared to the atypical keypad (control reaction time benefit in the typical vs. atypical keypad condition = 993 ms, patient reaction time benefit in the typical vs. atypical keypad condition = 1177 ms) (Fig. 3). Mean reaction times were entered into a 2 × 2 ANOVA with factors of group (patient, control) and keypad context (typical, atypical; analysis performed on log transformed data). Although overall reaction times were slower in patients (main effect of group; $F(1,23)=14.86$, $p<.001$), the reaction time advantage for the typical keypad was equivalent across groups (non-significant group × condition interaction; $F(1,23)=.66$, $p=.42$) and there was no difference in the percent improvement in reaction times for the typical vs. atypical keypad across groups ($t(23)=1.13$, $p=.27$). These results indicate that long-term visuospatial knowledge about a typical keypad is not degraded or less accessible in amnesia.

3.2. Experiment 2b

3.2.1. Materials and methods

3.2.1.1. Participants. Participants included the same nine amnesic patients with MTL lesions who participated in Experiment 2a (run in a separate session) and sixteen new healthy controls who were matched to the patient group in terms of mean age (62 ± 10.0), education (15 ± 2.5), verbal IQ (110 ± 12.7), and forward digit span (7 ± 1.3).

3.2.1.2. Stimuli. The experimental stimuli and procedure were modeled on the studies of (Allen et al., In press; Darling et al., 2012, 2014; Darling and Havelka, 2010). Sequences of six digits were created in which the digits 0–9 were randomly sampled without replacement. In the typical keypad condition, the digits were presented in the format of a traditional telephone keypad (Fig. 4A). In the atypical keypad condition, the digits appeared within the same grid as in the typical keypad condition, but the digits were arranged in a pseudorandom pattern so the digit-location mapping was unfamiliar (Fig. 4B). The layout of the atypical keypad changed every eight trials to reduce potential effects of digit-location learning across trials (Darling et al., 2012). The spatial position and distance between digits was matched across the typical and atypical digit sequences to ensure that eye movements would be equivalent across memory conditions.

3.2.1.3. Procedure. Participants performed two blocks of immediate serial digit recall, with 24 trials per block. In one block digits were presented in the context of a typical keypad array and in the other block digits were presented in the context of an atypical keypad array, with the order of blocks counterbalanced across participants. Sequences of digits were indicated by sequentially highlighting the background of individual digits in the keypad arrays in green. Each digit was highlighted for 1000 ms with a 250 ms delay between digits and participants were instructed to remember the digits in the order in which they were presented. At the end of the sequence a command prompted the participant to verbally recall the sequence in the correct order.

3.2.2. Results

Memory recall performance is presented in Fig. 5. Recall accuracy was calculated as the mean proportion of digits correctly recalled in each sequence. This analysis approach mirrors that used in Experiment 1 and follows the approach used by Allen et al. (In press).[2] One patient (P04) was excluded from analysis due to ceiling performance across conditions, leaving eight patients and sixteen controls for the final analysis.

The overall pattern of performance in amnesic patients mirrored that of controls, with better digit recall in the typical keypad context than in the atypical keypad context. To verify the reliability of this effect, mean accuracy was entered into a 2 × 2 ANOVA with factors of group (patient, control) and keypad context (typical, atypical). Overall memory recall performance did not significantly differ between groups (main effect of group, $F(1,22)=3.59$, $p=.07$). Importantly, a reliable typical keypad advantage was observed, with higher digit recall accuracy in the typical than the atypical keypad condition (main effect of context, $F(1,22)=17.02$, $p<.001$) and the magnitude of the typical keypad advantage did not differ between patients and controls (group × context, $F(1,22)<1.0$, $p>.97$). Follow-up pairwise comparisons confirmed that a reliable typical keypad advantage was present in both controls ($t(15)=3.53$, $p<.005$) and patients ($t(7)=2.58$, $p<.05$).

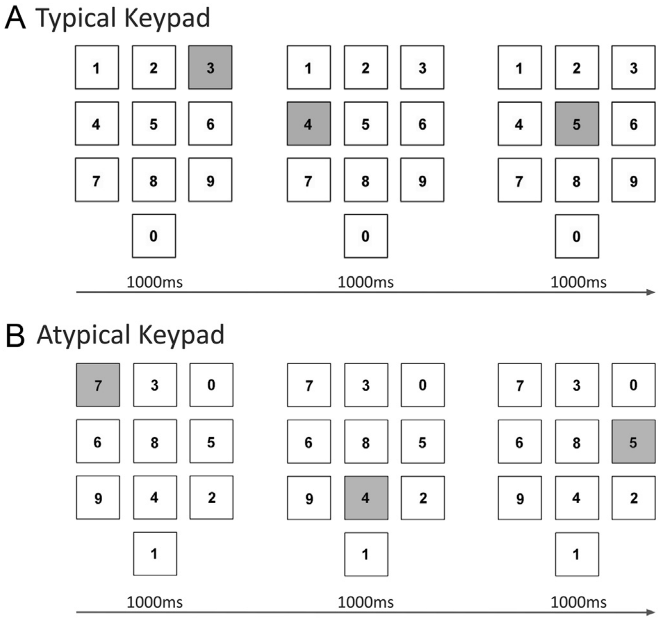

Fig. 4. Keypad displays used in Experiment 2b. A. Typical keypad display. B. Atypical keypad display. For each display type, to-be-remembered sequences of six digits were presented by sequentially highlighting relevant squares (e.g., 6…1…9… etc.). Squares are highlighted in gray for presentation purposes but were highlighted in green for the actual experiment.

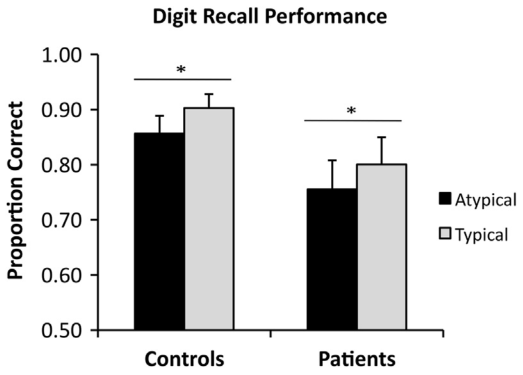

Fig. 5. Visuospatial bootstrapping effect. Proportion of digits correctly recalled when digits were presented in the context of a typical keypad (gray bars) or atypical keypad (black bars).

3.2.2.1. Amnesic patient subgroup analysis. In order to investigate whether the magnitude of the typical keypad benefit differed in patients with MTL damage limited to the hippocampus versus patients whose MTL damage extended beyond the hippocampus, recall performance was separately analyzed for patients with volumetrically or visually confirmed damage limited to the hippocampus (P03 and P08; H-only group) and patients with volumetrically or visually confirmed MTL damage that included the hippocampus and MTL cortex (P01, P02, P05; H+ group). Memory recall performance was greater in the typical keypad condition than the atypical keypad condition in both the H-only group (mean typical recall=.72 ± .12, mean atypical recall=.66 ± .12) and the H+ group (mean typical recall=.79 ± .20, mean atypical recall=.72 ± .17). Mean accuracy was entered into a 2 × 2 mixed model ANOVA with factors of group (H-only patients, H+ patients) and keypad context (typical, atypical). Overall recall performance did not differ between the two patient groups (main effect of group, $F(1, 3)<1$, $p=.69$) and the magnitude of the typical keypad benefit did not differ between groups (context × group, $F(1, 3)<1$, $p=.77$).

3.3. Discussion: Experiment 2

The results from Experiment 2a indicate that amnesic patients with hippocampal damage have intact pre-existing visuospatial knowledge of a typical keypad. The results from Experiment 2b reveal that amnesic patients are able to leverage this pre-existing

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[2] Previous investigations of the visuospatial bootstrapping effect have also analyzed mean proportion of trials on which all items were successfully recalled (e.g., Darling and Havelka, 2010; Darling et al., 2012). This latter analysis approach yielded a similar pattern of results.

visuospatial knowledge in support of immediate verbal recall to the same extent as controls. Together, the results from Experiment 1 and 2 reveal that regions outside the MTL can support the integration of activated verbal representations held in STM with stored knowledge from the same or a different domain.

4. General discussion

The present study investigated whether interactions between STM and LTM critically depend on the hippocampus. Specifically, we tested whether STM in MTL amnesics improves when to-be-remembered information is congruent with pre-existing knowledge from (a) the same domain and (b) a different domain. In Experiment 1, we tested within-domain STM–LTM integration by investigating the sentence superiority effect, whereby immediate word recall improves when words appear in the context of sentences versus random word lists. Both amnesic patients and healthy controls demonstrated similarly improved immediate verbal recall in the context of sentences. These results confirm the finding in developmental amnesia that integrating active verbal representations with pre-existing linguistic knowledge does not depend on the hippocampus (Baddeley et al., 2010) and extend this finding to hippocampal damage acquired in adulthood. In Experiment 2, we tested cross-domain STM–LTM integration by investigating the visuospatial bootstrapping effect, whereby immediate digit recall improves when digits appear in the context of a typical keypad array versus an atypical keypad array. In both amnesic patients and healthy controls, immediate digit recall improved in the context of a typical keypad, and the magnitude of this improvement did not differ across groups. These results provide the first evidence that integrating active verbal representations in STM with pre-existing visuospatial knowledge does not depend on the hippocampus. Together, the results from Experiments 1 and 2 demonstrate that both within-domain and cross-domain STM–LTM integration are intact in adult-onset amnesia and can be supported by extra-hippocampal brain regions. Furthermore, the finding in both Experiments 1 and 2 of intact STM–LTM integration in patients whose neural damage extended into MTL cortex reveals that STM–LTM integration is not only independent of the hippocampus, but is also independent of the MTL more broadly.

Interactions between STM and LTM in the verbal domain have been widely studied behaviorally (Thorn and Page, 2009). In the case of the sentence superiority effect, facilitated word recall in the context of sentences versus lists has been taken as a classic example of ‘chunking’, whereby stored linguistic knowledge serves to integrate individual verbal items into higher-order chunks that can be more easily recalled (Ericsson and Kintsch, 1995; Miller and Selfridge, 1950). Specifically, linguistic knowledge about the grammatical, syntactic and semantic structure of language is thought to combine activated verbal material into larger units, which reduces memory load and improves recall performance (Baddeley et al., 2009, 2010; Bonhage et al., 2014). Recently, it has been proposed that hippocampally-mediated relational binding supports this verbal chunking during STM, based on the observation that hippocampal activity increases when words are encoded in the context of sentences versus lists (Bonhage et al., 2014). However, the current finding that the sentence superiority effect is preserved in amnesia reveals that this is not the case (see also Baddeley et al., 2010) and suggests that hippocampal activity during sentence encoding may simply reflect feed-forward projections from extra-MTL cortices that are responsible for the short-term maintenance of stimulus representations or the encoding of these representations into episodic LTM.

Taken in isolation, the finding that the sentence superiority effect is preserved in amnesia could be interpreted in the context of domain-specific theories of hippocampal function that propose that the hippocampus does not play a critical role in associating within-domain representations in adjacent or overlapping neocortical regions (Mayes et al., 2001, 2007; Vargha-Khadem et al., 1997). According to this view, hippocampal binding is only necessary for linking cross-domain representations in non-adjacent and weakly connected neocortical regions. Evidence supporting this theory comes from prior observations that memory for within-domain associations, such as face–face or word–word associations, is intact in amnesia whereas memory for cross-domain associations, such as item-location or face–voice associations, is impaired (e.g., Mayes et al., 2001, 2004, 2007; Vargha-Khadem et al., 1997; Cashdollar et al., 2009; Finke et al., 2008; Hannula et al., 2006; Olson et al., 2006a, 2006b; Piekema et al., 2009). The results from Experiment 1 might be seen as extending this domain-specific theory of hippocampal function to the binding of information *across* STM and LTM. However, this would lead to the prediction that cross-domain STM–LTM integration should be impaired in amnesia, and we know from Experiment 2 that amnesic patients were able to leverage stored *visuospatial* knowledge in support of immediate verbal recall as well as controls. The finding that both within-domain and cross-domain STM–LTM integration are intact in amnesia instead suggests that hippocampally-mediated binding that links features within STM and LTM fundamentally differs from the binding functions that support STM–LTM integration. An important difference is that hippocampally-mediated binding entails the establishment of a link between two arbitrary features, whereas binding during STM–LTM integration occurs between two features (e.g. a digit and its location) that have a pre-existing relationship based on stored knowledge. As such, pre-existing semantic knowledge may provide a scaffold that facilitates the encoding and/or retrieval of to-be-remembered information during STM. Such semantic scaffolding might obviate the need for hippocampal involvement.

A similar proposal has been put forth in the context of semantic facilitation of LTM. The ability to leverage pre-existing semantic knowledge in support of episodic LTM is well established and manifests as improved LTM when to-be-remembered information is embedded in congruent versus incongruent semantic contexts (Anderson et al., 1978; Craik and Tulving, 1975). It has been proposed that semantic knowledge serves to enhance episodic LTM by anchoring to-be-remembered information so that it is processed more deeply (a levels-of-processing view; Craik and Lockhart, 1972) or is more efficiently organized (a schematic scaffolding view; Bartlett, 1932). Critically, this integration with prior semantic knowledge appears to bypass the need for hippocampally-mediated encoding and retrieval, as demonstrated by preserved semantic facilitation of LTM in amnesia and reduced MTL activity during the encoding of semantically congruent information into LTM (Kan et al., 2009; van Kesteren et al., 2012, 2013; but see Staresina et al., 2009). The current results suggest that semantic knowledge could similarly enhance STM performance by providing a mental scaffold to anchor and organize activated representations in STM. Consistent with this view, it has been shown that STM in amnesia can improve when to-be-remembered information is familiar and makes contact with pre-existing semantic knowledge (e.g., famous versus novel faces) (Rose et al., 2012). Additionally, it is known that procedural knowledge about motor programs can contribute to STM (Mecklinger et al., 2002, 2004). An important outstanding question is whether such procedural scaffolding of STM is also MTL-independent, relying on extra-MTL regions such as the striatum or premotor cortex. In principle, STM could also benefit from newly acquired episodic information. While the neural basis of such episodic scaffolding of STM has not been studied, it is likely that the hippocampus is necessary to leverage newly acquired episodic information in support of immediate verbal recall.

How does the finding that extra-MTL regions support within-domain and cross-domain STM–LTM integration fit with recent models of STM that highlight interactions between STM and LTM? In Baddeley's revised working memory model (2000), separate STM and LTM representations interact through an episodic buffer that links different representational formats. Although it has been proposed that the integrative functions of the episodic buffer may be supported by MTL regions such as the hippocampus (Berlingeri et al., 2008; Luck et al., 2010), Baddeley cautions against linking the buffer to a single brain region and instead argues that memory integration likely results from interactions between distributed neural regions (Baddeley, 2000; Baddeley et al., 2010, 2011). In state-based models of STM, interactions between STM and LTM occur naturally through a shared representational system in which the contents of STM represent a temporarily activated subset of LTM (Cowan, 1999; Postle, 2006; Ranganath and Blumenfeld, 2005; Zhou et al., 2007). By this view, new associations can be formed between elements that fall within the current focus of attention. Importantly, this attentional focus has been proposed to reflect processes supported by extra-hippocampal regions such as prefrontal and parietal lobes (Cowan and Chen, 2009). Thus, in both models, interactions between brain regions outside the hippocampus make important contributions to STM–LTM integration. Understanding the nature and necessity of different extra-MTL regions for STM–LTM integration represents an important area for future research. Of particular interest is the potential contribution of medial and lateral PFC regions that have recently been implicated in the semantic facilitation of episodic memory (Bonhage et al., 2014; Bor et al., 2004; Bor and Owen, 2007; Schlichting and Preston, 2015; van Kesteren et al., 2012, 2013). Recent neuroimaging evidence suggests that the medial PFC guides the integration of new information into pre-existing memory models during encoding (van Kesteren et al., 2013; Schlichting and Preston, 2015). In addition, lateral PFC is thought to support strategic cognitive control processes that enable the recoding and organization of STM contents into familiar or regular structures that can be better recalled (Bor et al., 2004). Future investigations should investigate how these frontal systems may independently or interactively support different forms of memory integration.

5. Conclusion

The results of the current study demonstrate that the hippocampus is not necessary to leverage stored verbal and visuospatial knowledge in support of immediate verbal recall. This raises the question of whether intact semantic knowledge can be used as a scaffold to support the performance of other STM tasks that are often impaired following hippocampal damage, such as short-term associative memory. Recent evidence suggests that stored schematic knowledge may differentially affect LTM for items and associations, with schema effects having a more immediate impact on associative than on item memory (van Kesteren et al., 2013). Future studies should explore whether intact prior knowledge can protect against different forms of short-term forgetting in amnesia.

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