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Repetition priming in amnesia: Distinguishing associative learning at different levels of abstraction

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ABSTRACT

Learned associations between stimuli and responses make important contributions to priming. The current study aimed to determine whether medial temporal lobe (MTL) binding mechanisms mediate this learning. Prior studies implicating the MTL in stimulus-response (S-R) learning have not isolated associative learning at the response level from associative learning at other levels of representation (e.g., task sets or decisions). The current study investigated whether the MTL is specifically involved in associative learning at the response level by testing a group of amnesic patients with MTL damage on a priming paradigm that isolates associative learning at the response level. Patients demonstrated intact priming when associative learning was isolated to the stimulus-response level. In contrast, their priming was reduced when associations between stimuli and more abstract representations (e.g., stimulus-task or stimulus-decision associations) could contribute to performance. These results provide novel neuropsychological evidence that S-R contributions to priming can be supported by regions outside the MTL, and suggest that the MTL may play a critical role in linking stimuli to more abstract tasks or decisions during priming.

1. Introduction

Incidental learning plays a foundational role in cognition. Repetition priming is one robust example of such learning in which repeated exposure to a stimulus leads to behavioral facilitation, evident in faster and/or more accurate responding to repeated versus novel stimuli and neural activity reductions (repetition suppression) in the same brain regions engaged during initial stimulus processing. Traditionally, these priming effects have been thought to reflect stimulus-level learning that is independent of task or response features and the 'tuning' of stimulus-specific perceptual or conceptual cortical representations (Desimone, 1996; Grill-Spector et al., 2006; Henson, 2003; Wiggs and Martin, 1998). However, accumulating evidence indicates that stimulus-level learning cannot account for all behavioral and neural priming effects, and that new associations formed between stimuli and co-occurring contextual features (i.e., 'instances') can also make important, and often dominant, contributions to priming (Dobbins et al., 2004; Henson et al., 2014; Hommel, 1998, 2007; Schacter et al., 2004; Schnyer et al., 2006; Waszak et al., 2003). For example, when stimuli are repeatedly classified, associations can form between stimuli and the responses made in the presence of those stimuli, often described as "stimulus-response (S-R) bindings" (Henson et al., 2014) or "event files" (Hommel, 1998). Subsequent encounter with a stimulus triggers the retrieval of the associated response, which can facilitate the translation of stimulus information into action. This facilitation is evident in enhanced behavioral priming when responses remain constant across stimulus repetitions compared to when they change, and is thought to reflect reduced demands on cognitive control functions such as response selection (Dennis and Perfect, 2013; Dobbins et al., 2004; Horner and Henson, 2009, 2011; Race et al., 2009; Schnyer et al., 2007; Waszak and Hommel, 2007). Although the impact of S-R learning on priming is now widely recognized, the neural mechanisms supporting this important form of learning remain an open question.

Associative processes supported by the medial temporal lobe (MTL) represent a candidate mechanism that may support S-R learning during priming. It is well established that the MTL, and the hippocampus in particular, plays a critical role in linking elements of experience in support of both declarative and non-declarative expressions of memory (Cohen et al., 1997; Eichenbaum and Cohen, 2001; Hannula and Greene, 2012; Henke, 2010; Konkel and Cohen, 2009). Consistent with this notion, MTL damage has been shown to disrupt priming that depends on learned associations between individual items (item-item associations) or contextual cueing (Chun and Phelps, 1999; Degonda et al., 2005; Gomes et al., 2016; Paller and Mayes, 1994; Verfaellie

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et al., 2006; but see Kan et al., 2007; Manns and Squire, 2001). In the context of S-R learning, the MTL has been proposed to link stimuli with co-occurring contextual features such as responses, providing a more direct mapping to response output when stimuli are repeated (Schacter et al., 2004). This proposal gained initial support from a neuropsychological study by Schnyer and colleagues (2006) in which participants repeatedly classified stimuli according to a decision rule ("Bigger than a shoebox?") with a button press indicating their response (e.g., "yes"). At test, participants again classified novel and repeated stimuli, but the classification task and response either stayed the same ("Bigger than a shoebox"/"yes") or were inverted ("Smaller than a shoebox"/"no"). Whereas healthy controls demonstrated greater priming when cues and responses repeated compared to when they changed across stimulus repetitions, a hallmark of S-R learning, this enhancement was absent in amnesic patients with MTL damage.

Additional evidence that the MTL mediates S-R contributions to priming comes from a neuroimaging study by Salimpoor et al. (2010). In this study, repetition suppression in cortical regions outside the MTL was accompanied by repetition enhancement (greater activity for repeated vs. novel stimuli) in the hippocampus (Salimpoor et al., 2010). Repetition-related recruitment of the hippocampus was also linked to behavioral performance on the task, with greater hippocampal repetition enhancement associated with greater behavioral priming. In addition, a functional connectivity analysis was performed to investigate whether interactions between the hippocampus and extra-MTL regions might contribute to behavioral priming. Functional connectivity between the hippocampus and neural regions involved in the representation and execution of responses (e.g., SMA and dorsal midcingulate cortex) significantly correlated with the magnitude of behavioral priming. These results provide complementary neuroimaging evidence suggesting that associative mechanisms supported by the hippocampus may mediate S-R contributions to priming.

Although the results of these prior studies are consistent with the notion that the MTL mediates S-R learning during priming, strong associative learning signals have also been reported throughout motor-related areas in the frontal lobes and striatum (e.g., Packard and Knowlton, 2002; Boettiger and D'Esposito, 2005). In addition, it is unclear whether priming effects previously attributed to S-R learning (Salimpoor et al., 2010; Schnyer et al., 2006) reflect MTL contributions to associative learning specifically at the response level. Many types of contextual features can become associated with a stimulus across repetitions, including the task rules or attentional state under which a stimulus is processed, decisions pertaining to a stimulus with respect to the rule, and responses made to a stimulus (Jiang et al., 2015). For example, in classification priming tasks in which a stimulus (e.g., "Car") is repeatedly categorized according to the same semantic task (e.g., "Bigger than a shoebox?") with a yes/no button press, associations can form between stimuli and task set representations (e.g., Car—Bigger than a shoebox?; S-T associations), stimuli and decision representations (e.g., Car—bigger; S-D associations), and stimuli and response representations (e.g., Car—yes; S-R associations). Retrieved associations between stimuli and representations at each of these levels (task, decision, or response) have been shown to contribute to neural and behavioral priming (Crump and Logan, 2010; Hommel, 2007; Horner and Henson, 2009; Hsu and Waszak, 2012; Race et al., 2009; Schnyer et al., 2007; Waszak et al., 2003, 2004; Wylie and Allport, 2000; Tobin and Race, 2017) and are thought to facilitate performance by reducing cognitive control demands at distinct levels of representation. For example, the recovery of learned stimulus-response associations has been associated with reduced demands on response selection, whereas the recovery of learned stimulus-task or stimulus-decision associations is thought to reduce demands on task or decision selection (e.g., selecting between competing task-sets or semantic representations) (Race et al., 2009). Retrieved associations may also reduce demands on the reprocessing of stimulus-level features, although the degree to which different types of associations bypass or re-engage stimulus-level processing remains an open question (Horner and Henson, 2011; Henson et al., 2017). Whereas the contribution of different types of retrieved associations is difficult to disentangle in a single behavioral measure of priming, particularly when multiple mappings remain fixed, prior neuroimaging studies have demonstrated that learning at multiple levels of representation occurs in tandem during priming even when retrieved responses alone could guide performance (Dobbins et al., 2004; Horner and Henson, 2009, 2011; Race et al., 2009). Importantly, prior studies implicating the MTL in S-R learning did not distinguish between retrieved associations at different representational levels (Salimpoor et al., 2010; Schnyer et al., 2006). A similar concern pertains to a recent report of intact priming in amnesic patients when responses repeated across stimulus repetitions (Henson et al., 2017). In that study, the relative contribution of associative learning at the response level (S-R learning) to priming could not be isolated, leaving unresolved the question of whether associative learning specifically at the response level critically depends on the MTL.

The current study aimed to address this question by testing amnesic patients with MTL damage on a priming paradigm that isolates response learning from associative learning at other levels of representation. Participants performed a semantic classification task in which they repeatedly classified stimuli according to one of two semantic rules. Like the paradigm used by Schnyer et al. (2006), the current paradigm included a condition in which stimuli were then re-processed at test under the same classification task, and associative learning could occur at the task, decision, and response levels. This gave us the opportunity to replicate their prior finding of impaired within-task priming in amnesia. Of critical interest, we also included a condition in which stimuli were re-processed at test according to a different classification task. In this condition, both the tasks and decisions previously associated with a stimulus were rendered invalid such that retrieved associations at the task and decision level could not drive facilitated performance. Importantly, however, within a subset of these trials learned response associations remained valid and could contribute to performance. In this way, priming effects due to associative learning at the response level could be isolated from effects due to associative learning at higher (task/decision) levels of representation. We predicted that if associative learning at the response level critically depends on the MTL, then patients should demonstrate reduced priming in this latter condition compared to controls. Alternatively, if response learning can be mediated by regions outside the MTL, then patients should perform as well as controls in this condition. A secondary goal was to investigate whether S-R learning during priming differentially depends on binding functions supported by MTL cortex versus the hippocampus, given that the prior report of impaired S-R learning in amnesia by Schnyer and colleagues did not consider the impact of extent of MTL damage. To investigate this question, we compared the performance of amnesic patients whose MTL damage was restricted to the hippocampus (H group) to that of patients whose MTL damage included the hippocampus and MTL cortex (H+ group).

2. Materials and methods

2.1. Participants

Twelve amnesic patients with MTL lesions (9 male, 3 female) participated in the study. Data from one patient was excluded due to excessive drowsiness during the experiment (which resulted in mean RTs greater than four standard deviations from the patient mean). Neuropsychological profiles for the remaining eleven amnesic patients are described in Table 1 and indicate severe impairments isolated to the domain of memory with profound deficits in new learning. Volumetric data for the hippocampus and MTL cortices were available for six patients. Of those, four had lesions restricted to the hippocampus (P04, P07, P09, P11; H group) and two (P01, P02) had lesions that included the hippocampus and MTL cortices. For the amnesic patients P03 and

Table 1
Patient demographic, neuropsychological and neurological characteristics.

Patient	Etiology	Age	Edu	WAIS, III		WMS,III			Hipp	Parahipp	Group
				VIQ	WMI	GM	VD	AD	Vol	Vol	
P01	Encephalitis	55	14	93	90	45	56	55	73%	78%*	H+
P02	Encephalitis	67	12	106	121	69	68	77	66%	72%+	H+
P03	Hypoxic/ischemic	60	12	88	75	52	56	55	N/A	N/A	H+
P04	Hypoxic/ischemic	54	14	106	115	59	72	52	22%	–	H+
P05	Encephalitis	82	18	133	133	45	53	58	N/A	N/A	H+
P06	Hypoxic/ischemic	58	17	131	126	86	78	86	N/A	N/A	–
P07	Stroke	62	18	117	88	67	75	55	62%	–	H+
P08	Hypoxic/ischemic	60	16	100	92	86	78	83	N/A	N/A	–
P09	Hypoxic/ischemic	47	12	103	95	59	68	55	46%	–	H+
P10	Encephalitis	73	13	99	104	49	56	58	N/A	N/A	H+
P11	Stroke	50	20	111	99	60	65	58	43%	–	H+

Note. Age = Age (years); Edu = Education (years); WAIS, III = Wechsler Adult Intelligence Scale, III; VIQ = Verbal IQ; WMI = Working Memory Index; WMS, III = Wechsler Memory Scale, III; GM = General Memory; VD = Visual Delay; AD = Auditory Delay; Hipp Vol = Bilateral Hippocampal Volume Loss; Parahipp Vol = Parahippocampal Gyrus Volume Loss. * = volume loss in bilateral anterior parahippocampal gyrus and left posterior parahippocampal gyrus. + = volume loss in bilateral anterior parahippocampal gyrus and right posterior parahippocampal gyrus. (for methodology see Kan et al., 2007; Race et al., 2015). H = patients with radiologically-confirmed damage restricted to the hippocampus; H+ = patients with radiologically-confirmed damage to the hippocampus and MTL cortex.

P05, computerized tomography (CT) scans were available and visual inspection indicated hippocampal and parahippocampal gyrus damage. For the encephalitic patient P10, 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. Patients with radiologically-confirmed damage to both the hippocampus and MTL cortex (P01, P02, P03, P05, P10) comprised the H+ group. Two of the cardiac arrest patients (P06 and P08) could not be scanned due to medical contraindications but MTL pathology can be inferred on the basis of etiology and neuropsychological profile. These patients are not included in the amnesia subgroup analyses given that we could not radiologically determine whether or not they had extra-hippocampal damage.

Eighteen healthy controls also participated (12 male, 6 female) and were matched to the patient group in terms of mean age (60.2 years, range 41–75), education (14.7 years, range 12–18), and verbal IQ (109, range 88–133). 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.

2.2. Stimuli

The stimulus set consisted of 320 concrete nouns that referred to objects that were either smaller or larger than a shoebox and either natural or man-made. Stimuli were divided into lists of 16 words, matched for mean word length and frequency and containing four words from each of the smaller/larger x natural/man-made crossings. Participants were run on four independent study-test blocks, comprised of 80 words each (five lists). Across participants, lists were counterbalanced across conditions. Each study-test block also included eight words that served as buffer trials (four words at the beginning of study and four words at the beginning of test) and were excluded from analysis.

2.3. Procedure and analysis

Instructions and practice were given prior to the start of the experiment. The same trial structure was maintained across each of the four study-test blocks. At the start of each trial, a task cue ("SMALLER?" or "NATURAL?") was presented above a central fixation cross for 500 ms, indicating the categorization decision to be made for that trial, followed by presentation of a target word below the fixation cross. The task cue "SMALLER?" prompted participants to decide whether a target word referred to an object smaller than a shoebox, whereas the task cue "NATURAL?" prompted participants to decide whether a target word referred to an object that naturally occurred in the environment. Participants indicated their responses with "yes" or "no" button presses on a keyboard, using their right middle and index finger. Once a response was made, a fixation cross was presented for 500 ms before the start of the next trial. Throughout the experiment, participants were encouraged to respond as quickly and as accurately as possible.

In each of the four study phases, participants classified 32 stimuli three times (primed stimuli) intermixed with 32 stimuli presented one time (which served as fillers). Half of the stimuli were classified according to the smaller task and half were classified according to the natural task. During each test phase, participants viewed the 32 primed stimuli from the study phase again intermixed with 16 new stimuli (Novel trials). Sixteen of the primed stimuli were paired with the same task across study and test and therefore also required the same decision and response across repetitions (Task-Repeat Response-Repeat), whereas the other 16 primed stimuli were paired with a different task across study and test (Task-Different) and therefore required a different decision. Of these trials, half also required a different response at test (Task-Different Response-Different) whereas half required the same response at test (Task-Different Response-Repeat). As a result of this manipulation, the level of associative learning that could contribute to priming at test varied across conditions (Fig. 1): (a) Task-Repeat Response-Repeat (TR-RR) priming could reflect associative learning at the stimulus-task, stimulus-decision, or stimulus-response levels; (b) Task-Different Response-Repeat (TD-RR) priming could reflect associative learning only at the stimulus-response level; (c) Task-Different Response-Different (TD-RD) priming could not reflect associative learning at any level. Novel trials at test served as baseline items from which to calculate repetition priming.

Data from the critical test phase restricted to correct trials (items correctly classified at study and test) was analyzed using Analysis of Variance (ANOVA). Trials that were two or more standard deviations from a participant's mean were excluded from RT analysis. Analysis of RTs included proportional priming scores [(Novel-Repeated)/ Novel] to accommodate overall RT differences across groups. An alpha level of 0.05 was used for all frequentist statistical tests. Bayesian analyses were performed in order to indicate the relative support for the null hypothesis when priming effects did not significantly differ in patients and controls. Bayes factors were computed in the JASP software package (JASP team, 2018, v.0.9.0.1) using the standardized implementation of Bayesian independent samples *t*-tests (Cauchy (0, 0.707)).

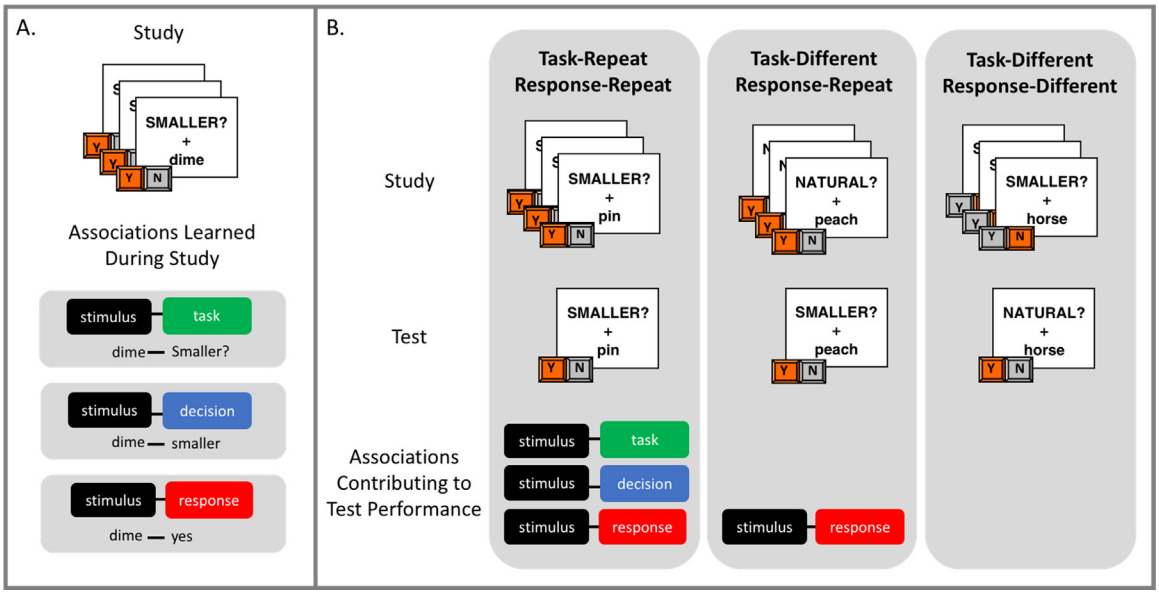

Fig. 1. Schematic of priming task and types of contextual associations learned during priming. (A) Panel A depicts an example stimulus displayed during the study phase and the associations learned during study. During the study phase, critical stimuli were presented three times with the same task cue (e.g., "Smaller?") and participants made the same decision (e.g., smaller/larger) and pressed one of two buttons to indicate a "yes" (Y) or "no" (N) response. Associations formed between stimuli and tasks (e.g., dime-Smaller?), stimuli and decisions (e.g., dime-smaller) and stimuli and responses (e.g., dime-yes). (B) Panel B depicts three different examples of stimuli presented at study (top) and then again at test (bottom) and the associations potentially contributing to performance at test. At test, items presented at study were presented again either with the same task cue (Task-Repeat) or a different task cue (Task-Different). For Task-Repeat trials, the tasks, decisions, and responses associated with a stimulus always repeated from study to test, and associative learning at each of these levels could potentially contribute to performance. For Task-Different trials, the tasks and decisions associated with a stimulus did not repeat from study to test, such that associative learning at these levels could not contribute to performance. However, half of these trials required the same response as at study (Task-Different Response-Repeat). For these trials, associative learning at the response level could contribute to performance and could be isolated from associative learning at the task/decision levels.

3. Results

Mean reaction time (RT) and accuracy were determined for each condition at test (Table 2) and submitted to a 2 × 3 ANOVA with factors of Group (patient, control) and Condition (N, TR-RR, TD-RR, TD-RD). For reaction times, there was no main effect of Group ($F(1,27) = 3.01$, $p = .09$, $\eta_p^2 = 0.10$), but there was a significant main effect of Condition ($F(3,81) = 20.81$, $p < .001$, $\eta_p^2 = 0.43$), which was modified by a Group × Condition interaction ($F(3,81) = 4.04$, $p = .02$, $\eta_p^2 = 0.13$). Controls demonstrated significant RT facilitation compared to Novel trials (positive priming) for both TR-RR ($F(1,17) = 37.75$, $p < 0.001$, $\eta_p^2 = 0.69$) and TD-RR trials ($F(1,17) = 40.45$, $p < .001$, $\eta_p^2 = 0.70$) and significant RT slowing compared to Novel trials (negative priming) for TD-RD trials ($F(1,17) = 9.51$, $p = .007$, $\eta_p^2 = 0.36$). In contrast, patients demonstrated significant positive priming only for TD-RR trials ($F(1,10) = 7.38$, $p = .02$, $\eta_p^2 = 0.43$); priming for TR-RR and TD-RD trials in patients was not significant ($Fs(1,10) < 2.80$, $ps > .12$, $\eta_p^2 < 0.21$). Accuracy did not differ between the patient and control groups ($F(1,27) = 0.46$, $p = .50$, $\eta_p^2 = 0.02$). Although there was a main effect of Condition ($F(3,81) = 69.59$, $p < .001$, $\eta_p^2 = 0.72$), there was not a significant Group × Condition interaction for accuracy ($F(3,81) = 0.36$, $p = .67$, $\eta_p^2 = 0.01$).

Although there was no main effect of Group in the RT analysis above, RTs in patients were numerically slower than RTs in controls, motivating an analysis of proportional priming scores. Proportional priming scores (Novel-Repeat/Novel) were entered into a 2 × 3 ANOVA with factors of Group (patient, control) and Condition (TR-RR, TD-RR, TD-RD) (Fig. 2A). There was no main effect of Group ($F(1,27) = 0.001$, $p = .98$, $\eta_p^2 < 0.001$) but there was a significant main effect of Condition ($F(2,54) = 26.17$, $p < .001$, $\eta_p^2 = 0.49$). Importantly, the main effect of Condition was modified by a significant Group x Condition interaction ($F(2,54) = 6.92$, $p = .002$, $\eta_p^2 = .20$). Follow-up analyses revealed that the magnitude of proportional priming in patients and controls did not differ for TD-RR trials, when associations only at the response level could contribute to performance ($t(27) = 0.29$, $p = 0.78$). In contrast, proportional priming was reduced in amnesic patients compared to controls for TR-RR trials ($t(27) = 2.22$, $p < .05$), when associations at the task, decision, or response level could contribute to performance (replicating the results of Schnyer et al., 2006). Proportional priming also differed between groups for TD-RD trials ($t(27) = 2.15$, $p < .05$), reflecting the presence of negative priming in controls but not in patients.

Performance was next analyzed separately for the patients with volumetrically confirmed damage limited to the hippocampus (H group) and for the patients with volumetrically or visually confirmed MTL damage that included the hippocampus and surrounding MTL cortex (H+ group) (Fig. 2B). A 2 × 3 ANOVA with factors of Group (H group, H+ group) and Condition (TR-RR, TD-RR, TD-RD) was performed on proportional priming scores. There was no main effect of Group ($F(1,7) = 0.02$, $p = .91$, $\eta_p^2 = 0.002$) nor Group × Condition interaction ($F(2,14) = 2.98$, $p = .08$, $\eta_p^2 = 0.30$). We next compared the magnitude of TD-RR priming in the H+ group and controls in order to more directly evaluate whether priming was intact in patients whose lesion extended into MTL cortex when associations only at the response level could contribute to performance. TD-RR priming did not differ

Table 2
RTs (ms) and response accuracy across conditions in controls and amnesic patients (SD in parentheses). TR-RR = Task-Repeat Response-Repeat; TD-RR = Task-Different Response-Repeat; TD-RD = Task-Different Response-Different.

	Control		Patient	
	RT	Accuracy	RT	Accuracy
TR-RR	1612 (311)	0.86 (0.10)	1943 (483)	0.83 (0.11)
TD-RR	1614 (295)	0.85 (0.08)	1874 (430)	0.85 (0.12)
TD-RD	1799 (403)	0.65 (0.17)	1981 (494)	0.61 (0.20)
Novel	1731 (347)	0.91 (0.06)	2003 (520)	0.89 (07)

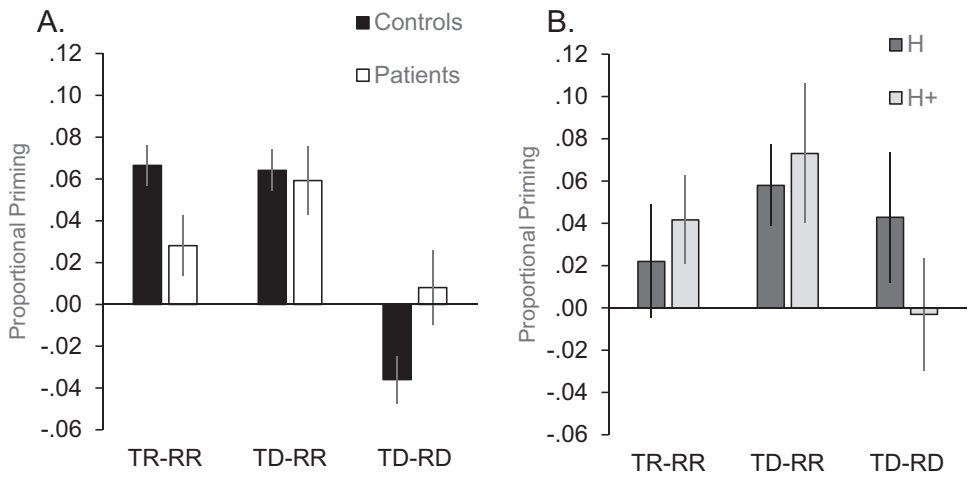

Fig. 2. Proportional priming effects. (A) Proportional priming in controls (black) and amnesic patients (white) for Task-Repeat Response-Repeat trials (TR-RR) in which stimulus-task, stimulus-decision, and stimulus-response associations repeat from study to test, Task-Different Response-Repeat trials (TD-RR) in which associations only at the stimulus-response level repeat from study to test, and Task-Different Response-Different trials (TD-RD) in which no associations repeat from study to test. (B) Proportional priming plotted separately for patients with lesions restricted to the hippocampus (H) and patients with lesions to the hippocampus and MTL cortex (H+). Error bars indicate SEM.

between H+ patients and controls ($t(21) = 0.34$, $p = .73$). Although this analysis has lower power compared to the whole-group analysis and should therefore be interpreted with caution, it suggest that S-R learning does not depend on the MTL more broadly.

We performed additional analyses using Bayes factors to compare the fit of the data under the null hypothesis (no difference in TD-RR priming scores for patients and controls) and the alternative hypothesis (different TD-RR priming scores for patients and controls). Bayesian analysis provided additional evidence favoring the null over the alternative hypothesis, both when comparing control performance to the patient group as a whole ($BF_{01} = 2.72$) and when comparing control performance to the subgroup of H+ patients ($BF_{01} = 2.23$).

4. Discussion

Accumulating evidence suggests that learned associations between stimuli and responses make significant contributions to priming. The current study aimed to determine whether MTL binding mechanisms mediate this learning. To do so, we tested amnesic patients with MTL damage on a priming paradigm that isolated S-R learning from associative learning at more abstract (stimulus-task, stimulus-decision) levels of representation. Patients demonstrated intact priming in a condition that isolated associative learning at the stimulus-response level. This was the case even when patients' neural damage extended beyond the hippocampus and included the MTL cortex. In contrast, priming was reduced in amnesic patients when learned associations between stimuli and higher-order representations (e.g., stimulus-task or stimulus-decision bindings) could contribute to performance. These results provide novel neuropsychological evidence that S-R contributions to priming are independent of the MTL, resolving an outstanding debate in the literature (Henson et al., 2017; Schnyer et al., 2006). Furthermore, they suggest that the MTL plays a critical role in linking stimuli to more abstract tasks or decisions. These results highlight the multiple, distinct cognitive and neural mechanisms that support repetition priming and inform theories of MTL function more broadly.

Although the contribution of S-R learning to priming is now well established (for review see Henson et al., 2017), there have been few prior investigations aimed at determining the neural basis of this learning. Instance-based models of priming have proposed that the MTL mediates S-R learning (Schacter et al., 2004), aligning with theories of MTL function that emphasize MTL contributions to both declarative and non-declarative memory (Cohen et al., 1997). However, prior research testing this hypothesis has not isolated S-R learning from other forms of associative learning during priming (Henson et al., 2017; Salimpoor et al., 2010; Schnyer et al., 2006). By isolating learning effects at the response level, the current study fills a gap in the literature and more directly tests MTL contributions to S-R learning in particular. Importantly, the finding that S-R learning is intact in amnesia even when neural damage extends into MTL cortex indicates that neural mechanisms outside the MTL must support this form of stimulus-specific associative learning. One possibility is that S-R learning depends on regions such as the striatum or premotor cortex that are involved in motor learning or action mapping (Boettiger and D'Esposito, 2005; Packard and Knowlton, 2002; Peterson and Seger, 2013; Suzuki, 2008). S-R learning during priming could also be supported by functional links between these regions, as has been demonstrated in the case of learning visuomotor associations between sensory cues and behavioral responses (Nixon et al., 2004). Future studies should investigate this question in order to more precisely specify the neural mechanisms that enable this important form of incidental associative learning.

The finding of intact S-R learning in MTL amnesia also challenges the notion that the MTL is involved in all forms of relational memory. According to relational theories of MTL function, the MTL, and hippocampus in particular, plays an obligatory role in binding items to co-occurring contextual features in support of both declarative and non-declarative expressions of memory (Cohen et al., 1997; Hannula and Greene, 2012; Henke, 2010; Olsen et al., 2012; Ryan and Cohen, 2004). However, the majority of studies supporting this theory have investigated associations between individual stimuli (item-item associations) or associations between stimuli and other contextual features such as colors or spatial locations. The current results reveal that the at least one form of relational memory, memory for associations between stimuli and responses, does not depend on the hippocampus.

Notably, a similar conclusion was reached by Henson et al. (2017) based on their finding that patients with hippocampal lesions demonstrated equivalent priming compared to controls when responses repeated across stimulus repetitions. However, response repetition in that study was always accompanied by decision repetition, making the relative contribution of S-R and S-D learning to priming difficult to distinguish (Henson et al., 2017). By isolating priming effects due to S-R learning from priming effects due to associative learning at other (task/decision) levels, the current study is able to more precisely specify that associative learning at the response level does not depend on the hippocampus. In addition, the present finding that S-R learning was intact in amnesic patients whose damage extends into MTL cortex provides novel evidence that S-R learning depends on regions outside the MTL.

Although S-R learning was intact in amnesic patients in the current study, their priming was reduced when associations at higher levels of representation (stimulus-task or stimulus-decision) could contribute to performance. This result suggests that the MTL may play a critical role in some forms of associative learning during priming, and aligns with the prior finding of impaired within-task priming in amnesia by Schnyer et al. (2006). An outstanding question is whether these priming impairments in amnesia reflect associative learning deficits at the

stimulus-task level, stimulus-decision level, or both. Relevant to this question is the fact that Henson et al. (2017) observed intact priming in amnesia in a task in which stimulus-decision bindings, but not stimulus-task bindings, could contribute to performance (tasks never repeated from study to test). Therefore, we suggest that observations of impaired within-task priming in amnesia in a previous study (Schnyer et al., 2006) and in the current task likely reflect binding deficits at the task level. Indeed, it is well established that associations can form between stimuli and the task sets under which they are processed (e.g., "task files"), and that stimulus-task bindings make important contributions to priming and action selection (Cookson et al., 2016; Crump and Logan, 2010; Waszak et al., 2003, 2004; Wylie and Allport, 2000). Notably, a recent neuroimaging study found evidence for hippocampal involvement in the binding of stimuli to more abstract task representations and attentional control states during sequential (short-lag) priming (Jiang et al., 2015). Given preliminary evidence that associative learning effects in tasks that assess short-lag vs. long-lag priming can be dissociated (Moeller and Frings, 2014), future studies that isolate task-level learning are needed to explore whether the hippocampus similarly mediates stimulus-task binding during long-lag priming. More broadly, in light of recent proposals that MTL-mediated binding supports memory over multiple timescales (Kumaran, 2008; Ranganath and Blumenfeld, 2005), it will be important for future studies to compare different types of associative learning, and their dependence on the hippocampus, during short-lag and long-lag priming.

An unexpected finding in our study was the presence of negative priming in controls, but not patients, when tasks and responses differed across stimulus repetitions (TD-RD trials). Negative priming in controls has been observed in prior priming studies when learned associations at the task, decision, or response levels conflict with current goals (Horner and Henson, 2012; Race, Badre and Wagner, 2010; Tobin and Race, 2017) and is thought to reflect increased demands on frontal cognitive control processes required to resolve this interference. While it is an open question whether the retrieval of learned associations occurs obligatorily or only when retrieval of learned associations leads to accurate responding on a majority of trials, the absence of negative priming in patients in the current study suggests that such interference due to associative learning may be diminished following MTL damage. Indeed, this would be the case if, as a result of MTL damage, fewer associations (such as stimulus-task associations) are present to conflict with current goals when tasks differ across repetitions. More broadly, the finding that amnesic patients demonstrate reductions in both positive priming (for TR-RR trials) and negative priming (for TD-RD trials) suggests that MTL-mediated learning during priming can both increase or decrease control demands. Although future research will need to more directly test this interaction between MTL-mediated learning and demands on cognitive control during priming, such an interaction would align with recent theories emphasizing MTL contributions to adaptive information processing and automaticity (Jiang et al., 2015).

5. Conclusion

Despite long-standing evidence that repetition priming can be intact in MTL amnesia, recent evidence suggests that MTL binding processes contribute to performance on some priming tasks, particularly when performance is supported by learned associations. Specifying the nature of these MTL contributions to priming has important implications for our understanding of the processes and representations that underlie different forms of memory, as well as the functional role of the MTL in long-term memory. By distinguishing the contribution of different forms of associative learning during priming, the current study reveals that MTL-mediated binding may play a critical role in guiding adaptive behavior via stimulus-based associative learning at higher (task/decision) but not at lower (response) levels of the perception-action hierarchy (Fuster, 2006).

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