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The Hippocampus is Particularly Important for Building Associations Across Stimulus Domains

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Abstract

The medial temporal lobe (MTL) is critical for binding together different attributes that together form memory for prior episodes, but whether it is preferentially involved in supporting specific types of associations is a topic of much debate. Some have argued that the MTL, specifically the hippocampus, may be specialized for binding information from different stimulus domains (e.g., linking visual and auditory stimuli). In the current study, we examined the role of the MTL in memory for associations within- vs. across-domains. Patients with either selective hippocampal lesions or more extensive MTL lesions studied pairs of items within the same stimulus domain (i.e., image-image or sound-sound pairs) or across different domains (i.e., image-sound pairs). Associative memory was subsequently tested by having participants discriminate between previously studied and rearranged pairs. Compared to healthy controls, the patients were significantly more impaired in the across-domain condition than the within-domain conditions. Similar deficits were observed for patients with hippocampal lesions and those with more extensive MTL lesions, suggesting that the hippocampus itself is particularly important for binding associations across stimulus domains.

Keywords

Associative Memory; Hippocampus; Domain Dichotomy

1. Introduction

It is well established that the medial temporal lobe is critical for episodic memory — that is, memory for unique events (Aggleton & Brown, 1999; N. J. Cohen & Squire, 1980; Eichenbaum, Yonelinas, & Ranganath, 2007; Moscovitch, 1992; Scoville & Milner, 1957).

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However, the manner in which the hippocampus and the surrounding structures of the medial temporal lobe (MTL) support different aspects of episodic memory continues to be intensely debated.

In general, the hippocampus is thought to play a critical role in associative memory, which entails binding together the different attributes of an episode (Giovanello, Verfaellie, & Keane, 2003; Konkel & Cohen, 2009; Mayes et al., 2004; Turriziani, Fadda, Caltagirone, & Carlesimo, 2004; but see Stark, Bayley, and Squire, 2002). However, the hippocampus may be more critical for supporting some types of associations than others. The domain-dichotomy theory proposes that the hippocampus may be preferentially involved in associative memory when the items to be bound and remembered are from different stimulus domains and processed in distinct cortical regions (Mayes, Montaldi, & Migo, 2007). For example, the hippocampus may be more important for linking auditory and visual stimuli vs. linking two visual stimuli. This distinction does not just hold for stimulus modalities, but extends to any content processed in different cortical regions: for example, the hippocampus may be recruited more for linking a word and a face vs. linking two words. Cortical regions outside the hippocampus may be sufficient to support the formation of associations within a single processing domain (e.g., from the visual system), because such within-domain signals converge in the ventral visual processing stream prior to reaching the hippocampus (Bussey & Saksida, 2007; Cowell, Bussey, & Saksida, 2006). There is evidence for a similar hierarchy of complexity in the auditory processing stream (Wessinger et al., 2001). Conversely, it is thought that across-domain signals are only adequately bound in memory at the level of the hippocampus. Studies examining this claim, however, have led to mixed results.

Thus far, only a handful of neuropsychological studies have directly contrasted within-and across-domain associative memory. Mayes et al. (2004) tested a patient with selective hippocampal damage on a battery of 18 associative recognition tasks and found that the patient was more impaired on the across-domain tasks (e.g., word-location, object-temporal order, face-voice, and scene-sound pairs) than the within-domain tasks (e.g., word-word and face-face pairs). Vargha-Khadem et al. (1997) found a similar pattern in three developmental hippocampal amnesics when comparing performance on across-domain tasks (object-place and voice-face pairs) to that of within-domain tasks (word-word and face-face pairs.) However, another study comparing associative memory impairments in selective hippocampal lesion patients found no difference between tasks with face-face pairs and face-word pairs (Turriziani et al., 2004).

Additionally, some neuroimaging studies have found evidence that the hippocampus is preferentially involved in tasks that require associations between different types of stimuli compared to associations between stimuli of the same type; this includes nonsense images and sounds (Butler & James, 2011), pictures paired with visual or verbal names (Gottlieb, Uncapher, & Rugg, 2010), and objects paired with scenes (Staresina, Cooper, & Henson, 2013). Other studies, however, have found no difference in hippocampal involvement for within- vs. across-domain associative tasks, including memory for face-face pairs compared to face-laugh pairs (Holdstock, Crane, Bachorowski, & Milner, 2010), and object-object and word-word pairs compared to object-word pairs (Park & Rugg, 2011).

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One possible reason for some inconsistencies seen in the existing literature is the use of different types of materials. Though this does not resolve the differing results in the three neuropsychological studies, which all used novel face stimuli in across- and within-domain pairs, it could provide an explanation for the many previous studies that have used verbal or easily verbalizable materials such as object-word pairs. If participants name the objects, then the task no longer requires learning of an across-domain association — instead, it may rely on a lexical or semantic association that would effectively be within-domain. Thus, in the present study, we used abstract stimuli in the visual and auditory domains designed to be difficult to verbalize in order to reduce the likelihood that verbal codes would be used and consequently mask any true across-domain effects.

Another possible cause for the discrepant results is the inclusion of only one within-domain test condition. For example, Gottlieb and colleagues (2010) found that the hippocampus was more active for successful memory of auditory contexts paired with pictures than for visual contexts paired with pictures. This finding is consistent with the notion that the hippocampus is more involved in across- than within-domain associations. However, as those authors pointed out, an alternative possibility is that the observed difference may reflect a simple modality effect such that memory for auditory information places more demands on the hippocampus than visual information, possibly due to the more temporally extended nature of auditory materials. Though there was no behavioral difference in the subsequent memory of auditory and visual trials, there is evidence that auditory memory is inferior to visual memory (M. A. Cohen, Horowitz, & Wolfe, 2009), possibly further engaging the hippocampus in tasks with an auditory component. We therefore compared across-domain associative memory (visual-auditory) to two within-domain conditions (visual-visual and auditory-auditory) in order to separate any potential modality effects from the effects of crossing domain.

We tested healthy controls and patients with either selective hippocampal or more extensive MTL lesions on associative memory for within- and across-domain information, using abstract fractal-like images and sounds with no obvious verbal labels. Participants studied pairs of these items (image-image, sound-sound, or image-sound) and later made recognition judgments about intact and rearranged pairs. Patient deficits (i.e., performance relative to controls) were then compared across the three conditions. Because we were especially interested in the necessity of the hippocampus for these different types of associative memory, we also compared the performance of patients with selective hippocampal lesions to those with more extensive MTL lesions.

2. Methods

2.1 Participants

Patients with MTL lesions (n =11) and healthy age- and education-matched controls (n = 15) participated in exchange for monetary compensation. Five of the patients had selective hippocampal damage and six had extensive MTL damage that included the hippocampus and extended into surrounding MTL cortex. Each patient was administered a battery of neuropsychological tests including the WMS-R (Wechsler, 1987), the Doors and Peoples test (Baddeley, Emslie, & Nimmo-Smith, 1994), and the Shipley Institute of Living Scale (SILS)

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(Shipley, 1940). The SILS was used to estimate WAIS-R IQ (Zachary, Crumpton, & Spiegel, 1985). All controls scored within the normal range on all tests. Patient descriptions and neuropsychological test scores are shown in Table 1, and the etiology and lesion descriptions are listed in detail below.

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 (see Figure 1). The cavities had a rounded shape and resembled pathologic cavities described in specimens of hypoxia-related CA1 necrosis (Nakada, Kwee, Fujii, & Knight, 2005). The extent of damage was determined from the patient's MRI scan, and there was no apparent damage in the surrounding MTL structures, including the parahippocampal gyrus.

Patient 1003 had limbic encephalitis that resulted in bilateral hippocampal damage with no apparent damage to the surrounding MTL cortex (see Figure 1). Grey matter volume estimates indicated that the left and right hippocampi were reduced in volume, but no other MTL structures showed significant volume reduction. See Aly, Ranganath, and Yonelinas (2013) for estimates of grey matter volume for this patient (referenced as Patient 2 in that study).

Patient 1005 had a traumatic brain injury due to a car accident and suffered bilateral damage to the MTL, including hippocampus. The extent of damage was assessed from the patient's high-resolution MRI scan (see Figure 1). For specific estimates of grey matter loss in the hippocampus and surrounding parahippocampal gyrus, see Kolarik et al. (2016).

Patient 1006 suffered a traumatic brain injury due to a car accident, resulting in a hypoxic event and selective hippocampal damage. Clinical scans appeared normal with the exception of volume reductions in the hippocampi. Grey matter volume estimates indicated that both the left and right hippocampi were reduced in volume, but no other MTL structures showed significant volume reduction. See Aly et al. (2013) for estimates of grey matter volume for this patient (referenced as Patient 1 in that study).

Patient 1007 had viral encephalitis, resulting in encephalomalacia and extensive volume loss in the right temporal lobe, including the hippocampus and surrounding parahippocampal gyrus (see Figure 1). There also appeared to be some evidence of atrophy in the right orbitofrontal cortex.

Patient 1008 suffered a prenatal right posterior cerebral artery infarct resulting in damage to the right occipital-temporal cortex. An MRI taken as an adult revealed significant damage to the posterior hippocampus and parahippocampal gyrus, as well as the fusiform and lingual gyri. The patient also has left hemianopsia.

Patients 1009 and 1012 had left temporal lobectomies to treat intractable epilepsy. The surgeries were standard temporal lobe resections, in which approximately 4 cm of the anterior temporal lobe, including the anterior half of the hippocampus, the amygdala, and the anterior third of the parahippocampal gyrus, were removed. Patient 1009 underwent a high-resolution MRI scan and the rest of the brain appeared to be normal post-surgery.

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Patients 1011 and 1015 suffered a mild hypoxic episode as a result of a cardiac arrest and have presumed selective hippocampal damage (Gadian et al., 2000; Hopkins, Kesner, & Goldstein, 1995; Kono, Kono, & Shida, 1983; Rempel-Clower, Zola, Squire, & Amaral, 1996; Smith, Auer, & Siesjo, 1984). These patients have a defibrillator and are thus unable to undergo structural MRI scanning to confirm the extent and selectivity of the damage.

Patient 1016 has a large left temporal hematoma due to a motorcycle accident, which unilaterally affected the hippocampus as well as the medial, inferior and lateral temporal lobe. Clinical MRI scans showed no areas of restricted diffusion outside the area of the left temporal hemorrhage.

Six patients (1002, 1008, 1011, 1012, 1015, 1016) and five controls did not complete all testing sessions because they were unavailable for personal or unrelated health reasons during the study and could not be scheduled for further sessions. We used all available data, regardless of whether all test sessions had been completed or not.

2.2 Stimuli, design, and procedure

To discourage verbalization strategies, we used abstract visual and auditory stimuli (see Figure 2). Visual stimuli were drawn from a pool of 600 fractal images created using Tiera-Zon Fractal Generator and resized to 320 × 240 pixels. Auditory stimuli were drawn from a pool of 310 non-verbal, non-representational sound clips found online and edited in Audacity sound editor to be nonverbalizable (for details see Parks & Yonelinas, 2015). Sound clips were edited to a duration of 2 s.

Each of the three associative memory tasks consisted of several study-test blocks. During each study phase, a series of stimulus pairs were presented at a rate of 4 s per pair. Participants were instructed to remember the pairings by linking the items together in some way. After each stimulus pair presentation, they rated their ability to make a link on a 1 *(no link)* to 4 *(strong link)* scale. During each test phase, item pairs were presented with the same timing as in the study phase and only included items encountered in the immediately preceding study phase. Half of the test pairs were intact (i.e., two items that had been studied together) and half were rearranged (i.e., two items that had been studied in separate pairs). Intact and rearranged trials were presented in random order. Participants reported whether pairs were intact or rearranged using a 6-point confidence scale: 1 = *sure rearranged,* 2 = *maybe rearranged,* 3 = *guess rearranged,* 4 = *guess intact,* 5 = *maybe intact,* 6 = *sure intact.* Responses were self-paced and the confidence scale remained on the screen until a response was made. Short breaks between study and test phases were also self-paced, but participants were instructed to take extended breaks only after finishing a test phase.

Tasks were administered to the participants in a counterbalanced order, with a span of at least three months between sessions to minimize interference. Participants were given full instructions and completed four practice trials at the beginning of each session. Prior to testing patients and matched controls, pilot studies were conducted with young, healthy participants to ensure that overall performance was roughly equated across the different conditions by adjusting the length of study and test blocks. An additional pilot study was done in young adults using sound-sound pairs to ensure participants could distinguish each

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sound within the pair. Pairs which were rated as a single sound were not used in the current study. Each task is described below.

In the Within Visual (Vis-Vis) condition, two fractal images were presented side-by-side on the screen for 2 s, then repeated for another 2 s after a 100ms blank screen. Each fractal was presented on the same side of the screen at study and test. The task was administered across five study-test blocks, with 24 pairs in each study list followed by a mixture of 12 intact and 12 rearranged pairs in each test list.

In the Within Auditory (Aud-Aud) task, two sounds were presented simultaneously for 2 s, then repeated for another 2 s after 100 ms of silence. The sounds were presented as distinct items by playing each through the right or left channel of headphones. Each sound was presented through the same lateralized headphone channel at study and test. The task was administered across 10 study-test blocks, with 12 pairs in each study list followed by a mixture of six intact and six rearranged pairs in each test list.

In the Across Visual-Auditory (Vis-Aud) task, a fractal image and an abstract sound were presented simultaneously for 2 s, then repeated for another 2 s after a 100 ms blank screen. Each fractal was presented in the center of the screen and each sound was played though both headphone channels. The task was administered across three study-test blocks, with 40 pairs in each study list followed by a mixture of 20 intact and 20 rearranged pairs in each test list.

In a separate session, participants were also tested in a condition that examined associative memory for sequentially presented fractal-sound pairs, but those results are outside the scope of the current study and will not be discussed here.

2. Results

Receiver operating characteristics (ROCs) were used to assess performance for each participant by plotting the hit rate against the false alarm rate at each level of response confidence (Green & Swets, 1966; Macmillan & Creelman, 2005). The aggregate ROCs for patients and controls are plotted for each condition in Figure 3. Performance is indicated by the distance between the ROC curve and the chance diagonal, with worse performance falling closer to the diagonal. Visual examination of the aggregate ROCs suggests that the patients were generally impaired, but the difference between patient and control ROCs was greater in the across- than the within-domain conditions, indicative of a larger deficit in across-domain associative recognition.

Performance was first quantified by collapsing across recognition confidence and calculating d' — a parametric index of discriminability based on signal detection theory[1]. Confidence responses 1–3 were collapsed into a single “rearranged” response, and confidence responses 4–6 were collapsed into a single “intact” response. Individual patient scores are presented in Table 2; mean hit rate, false alarm rate, and d' scores for each condition are shown in Table

[1]We also repeated all analyses with another common measure of performance (i.e., A', which is a nonparametric version of d' Grier, 1971), but observed the same pattern of results.

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3. We then calculated a deficit score for each patient by subtracting the patient's d' from the mean control performance in each task and dividing by the standard deviation of the control group. This deficit score is especially informative because, although we attempted to equate task difficulty with list length, there were numerical differences in the mean accuracy scores of controls.

Not all participants were able to complete all three tasks and therefore a linear mixed model approach was taken to preserve the within-subject variance. Linear mixed models were analyzed in R 3.2.3, using the lmerTest package to fit the models and the lsmeans package to estimate post hoc comparisons. The assumption of variance homogeneity was violated due to unequal sample sizes and unbalanced participation across conditions, thus degrees of freedom were estimated using Satterthwaite approximation which results in non-integer numbers. The effect sizes corresponding to Cohen's d were calculated using least squared means and standard errors.

A 2 (group) × 3 (condition) linear mixed model ANOVA of the d' scores (Figure 4a) predictably revealed a significant main effect of group, $F(1, 23.54) = 8.79$, $p = .007$, $d = .27$, indicating that the patients were impaired relative to controls. There was also a significant main effect of condition, $F(2, 31.49) = 9.14$, $p < .001$, $d = .22$, and a significant interaction, $F(2, 31.49) = 5.43$, $p = .009$, $d = .15$, suggesting the conditions were differentially difficult for patients and controls. Planned comparisons between patient and control scores for each condition showed that patients were significantly impaired in the Aud-Vis condition, $t(32.52) = 3.67$, $p < .001$, and the Aud-Aud condition, $t(36.09) = 2.40$, $p = .022$, but only marginally so in the Vis-Vis condition, $t(31.34) = 1.79$, $p = .080$.

In accordance with the ROCs, examination of the deficit scores (Figure 4b) suggests that the patients were more impaired in the across-domain condition (Vis-Aud) than in the within-domain conditions (Vis-Vis and Aud-Aud). Moreover, visual examination of the individual patient scores shows that both the selective hippocampal patients (circles) and the MTL patients (triangles) showed larger impairments in the across domain-condition than the within-domain conditions, suggesting that hippocampal damage alone is sufficient to produce more pronounced across-domain associative deficits. These observations were supported by a 2 (etiology) × 3 (condition) linear mixed model ANOVA using the deficit scores. We found a significant main effect of condition on patient deficit, $F(2, 12.03) = 9.39$, $p = .003$, $d = .44$. Post hoc tests using Tukey's HSD correction confirmed that the across-domain deficit (Vis-Aud: $M = -1.25$, $SD = 0.39$) was significantly greater than both of the within-domain deficits (Vis-Vis: $M = -0.62$, $SD = 0.38$, $t(21.48) = 3.33$, $p = .008$; Aud-Aud: $M = -0.63$, $SD = 0.09$, $t(21.84) = 2.72$, $p = .032$), while deficits in the two within-domain conditions did not differ from one another, $t(20.16) = 0.24$, $p = .969$. Subsequently, we examined whether there were any differences between the deficits of patients with selective hippocampal damage and those with more extensive MTL damage, and found the same pattern of results in both patient groups, with neither a significant main effect of patient etiology, $F(1, 8.54) = 0.11$, $p = .744$, nor a significant interaction, $F(2, 12.03) = 0.19$, $p = .828$.

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For completeness, the ROCs were fit to the dual-process signal detection model (Yonelinas, 1994) to derive parameter estimates of recollection (R) and familiarity (F). Both R and F estimates were numerically lower in patients than in controls. Due to low patient performance, the R estimates in the patient group were near zero; floor performance thus negates a meaningful comparison across conditions. Given our prediction that across-domain tasks rely on the hippocampus more than within-domain tasks, we would anticipate that the healthy controls show higher estimates of recollection in across- compared to within-domain conditions. Therefore, we conducted a 2 (parameter) × 3 (condition) linear mixed model ANOVA considering only the estimates from controls to see if there was a difference across tasks. We found a main effect of parameter, $F(1, 46.43) = 50.81$, $p < .001$, $d = .52$, but no main effect of condition, $F(2, 49.54) = 0.77$, $p = .468$, nor a condition by parameter interaction, $F(1, 46.43) = 0.45$, $p = .639$. Note that the main effect of parameter is not meaningful, because recollection and familiarity are measured on different scales (probability and d′, respectively).

3. Discussion

The aim of the current study was to test whether the medial temporal lobe (MTL), particularly the hippocampus, is preferentially involved in forming associations that bridge stimulus domains. To this end, we tested patients with selective hippocampal lesions and more extensive MTL lesions on tasks that varied whether the associations to be remembered came from the same domain (i.e., visual-visual or auditory-auditory) or different domains (i.e., visual-auditory). The patients showed a significantly more pronounced impairment for across-domain associations compared to within-domain associations. Importantly, the patients showed comparable deficits in the within-domain conditions, suggesting that the across-domain deficits were not simply due to poor memory for auditory materials. The more pronounced deficits for across- vs. within-domain associations were as apparent in patients with selective hippocampal damage as those with extensive MTL damage, suggesting that these domain effects reflect the contribution of the hippocampus. This pattern of results supports the notion that the hippocampus is preferentially involved in forming associations between items that come from different domains, providing direct support for the domain-dichotomy theory (Mayes et al., 2007).

The current results are also consistent with previous studies that have shown more hippocampal involvement and larger patient deficits for across- than within-domain associations (Butler & James, 2011; Gottlieb et al., 2010; Mayes et al., 2004; Vargha-Khadem et al., 1997). Why some previous studies have failed to find significantly greater hippocampal involvement in across- vs. within-domain conditions is not clear, but one important factor may have been the use of verbal or easily verbalizable materials. For example, in an imaging study of associative recognition, Park and Rugg (2011) found comparable levels of hippocampal activity during object-object, word-word, and object-word pairs. The use of verbalizable materials, especially those that were images of the stimuli in the word list (i.e., the word “chair” and a picture of a chair), may have led participants to process and encode all of the stimuli using verbal codes, thus effectively making it a within-domain task. The fractal images and abstract sounds used in the current study were chosen to be difficult to verbalize and difficult to link to existing semantic

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knowledge. Importantly, our results demonstrate that when the stimuli are difficult to verbalize, a larger difference in patient deficits for across- vs. within-domain associations is observed, in line with the predictions of the domain-dichotomy theory.

One concern regarding the abstract auditory stimuli is that, because the sounds were presented simultaneously, participants could perceive them as a single item, making the Aud-Aud associative task effectively a single-item recognition task. However, we do not believe this is the case for two reasons. First, a pilot study was conducted to verify that participants perceived the sounds as two separate sounds, and any sound pairs that were perceived as a single sound were not used in the main experiment. Second, if sound pairs were perceived as a single item, and single item recognition is usually relatively spared in amnesics relative to associative memory, one would predict less impairment for the Aud-Aud condition than the Vis-Vis condition in the patients. However, we found no evidence for such differential sparing.

Another concern regarding the task design was the difference in list length between conditions given that longer list lengths typically worsen recognition impairments in amnesics. We decided to balance performance across tasks in healthy controls rather than balance list length across tasks, which would then lead to performance differences. However, it should be noted that in the Aud-Aud task, which has the shortest list length (12 pairs per block), patients do not show higher performance than the Vis-Vis task, which has twice as many items per block.

Our results provide insight into the role of the hippocampus in binding stimuli across visual and auditory domains. However, future studies will be needed to investigate other across-domain conditions and modalities to determine exactly how broadly this function of the hippocampus extends. For example, hippocampal involvement has also been found in some across-domain tasks that used different categories of visual stimuli, such as objects and scenes (Staresina et al., 2013). Hippocampal involvement may be important here because objects and scenes are known to be processed in partly distinct cortical regions, and thus may require upstream processing to be associated in long-term memory. Further investigation is necessary to fully delineate the specific materials and conditions which engage the hippocampus (and the MTL more broadly) in associative binding. It should be noted that all but one of the MTL-lesioned patients had unilateral damage, thus MTL structures in one hemisphere were intact. The functioning parahippocampal gyrus structures in the spared hemisphere could potentially support within-domain associations. If the MTL-lesioned patients had bilateral damage, we would expect within-domain associations to be more impaired in MTL patients than hippocampal patients, and both patient groups to be equivalently impaired in across-domain associations.

The finding that the hippocampus was particularly important for across-domain associations should not be interpreted as indicating that the hippocampus is not involved in within-modality associations: the current patients were significantly impaired in the Aud-Aud condition and were marginally impaired in the Vis-Vis condition. Moreover, many previous studies have reported significant within-domain associative memory deficits in patients with hippocampal damage (Giovanello et al., 2003; Troyer, D'Souza, Vandermorris, & Murphy,

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2011; Turriziani et al., 2004). The critical point is that hippocampal processing seems to be relatively more important for forming mnemonic associations that incorporate different stimulus domains.

Our results do not indicate that the cortex can never support across-domain associations — only that cortical regions may not be as proficient at supporting such associative learning as the hippocampus. For example, across-domain associative memory was not reduced to chance in the patients: there was some preserved across-domain learning, presumably supported by spared cortical regions. Recent work has indicated that familiarity, which often relies on the MTL cortex, can also support associative memory. For example, hippocampal patients exhibit reduced associative memory impairments if the materials are unitized (i.e., treated as a single unit) during encoding (e.g., treating 'cloud-lawn' as a compound word rather than as an association between two separate words, Quamme, Yonelinas, & Norman, 2007). Unitization increases familiarity-based associative recognition, which relies on the perirhinal cortex (PRc) rather than the hippocampus (Eichenbaum et al., 2007; Haskins, Yonelinas, Quamme, & Ranganath, 2008). Thus, when paired with faces, words describing an occupation (Turriziani et al., 2004) and laughs (Holdstock et al., 2010) could become attributes of the depicted face and thus unitized or processed together as a single item, which could, in turn, reduce reliance on the hippocampus in these across-domain conditions. In the face-laugh study by Holdstock and colleagues (2010), participants were instructed to judge how well the laugh and face went together to aid in encoding; a method used to encourage unitization. Even with fractal-sound pairs, participants may be able to unitize the stimuli if instructed to treat the sound as though it was produced by the image. Indeed, recent behavioral studies have shown that unitization can be a particularly useful strategy for increasing the utility of familiarity in supporting across-domain associative memory specifically, including fractal-sound pairs and face-word pairs (Parks & Yonelinas, 2015). In the current study, the instructions to simply link the fractal and sound in this study did not seem to confer unitization benefits in terms of sparing associative memory for patients.

Moreover, other work has shown that the PRc can, at least in some situations, support across-modality processing (Holdstock, Hocking, Notley, Devlin, & Price, 2009; Taylor, Moss, Stamatakis, & Tyler, 2006). Holdstock et al. (2009) found that the PRc was more active during an across-domain visual-tactile perceptual matching task compared to analogous within-domain tasks, but that this effect was only present when the stimuli were congruent. That is, when the visual and tactile information could integrate to represent the same shape. Taylor et al. (2006) used auditory and visual stimuli in a perceptual matching task and also found greater activity in the PRc for across- vs within-domain trials. Furthermore, though they did not find a significant effect of congruency in the imaging study, MTL-lesioned patients showed a greater impairment for across-domain tasks with incongruent pairs. This suggests that when the stimuli are perceptually or semantically congruent, treating the stimuli pairs as a single object with multimodal features could promote unitization and be supported by the PRc. Though these studies used a perceptual task and did not measure memory for the associations, they give valuable insight into the function of the PRc in integrative processing which may support memory, especially in situations when unitization can be utilized. Further exploration of the similarities and differences between episodic, semantic, and perceptual associations will be fruitful.

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In sum, the current results highlight the importance of the hippocampus for forming associative memories that bridge stimulus domains, and suggest that within-domain associations can be represented to some extent by cortical areas outside of the hippocampus and medial temporal lobe. These results reveal intricacies in how the brain supports associative memory and suggest that not all associations are equivalently dependent on the hippocampus.

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Highlights

- Patients with damage to the MTL were tested on associative memory for within-domain and across-domain pairs
- Patient memory impairments were significantly greater for across-domain associations than within-domain associations.
- Patients with restricted hippocampal damage and those with extensive MTL damage showed the same pattern.
- This finding supports the Domain Dichotomy Theory.

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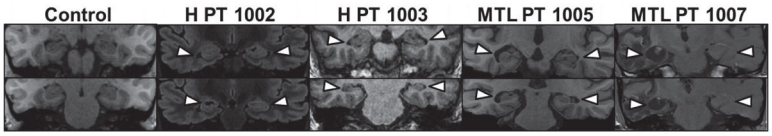

Figure 1.

Sample MRI images for a healthy control, two patients with selective hippocampal damage (1002, 1003), and two patients with extensive MTL damage (1005, 1007).

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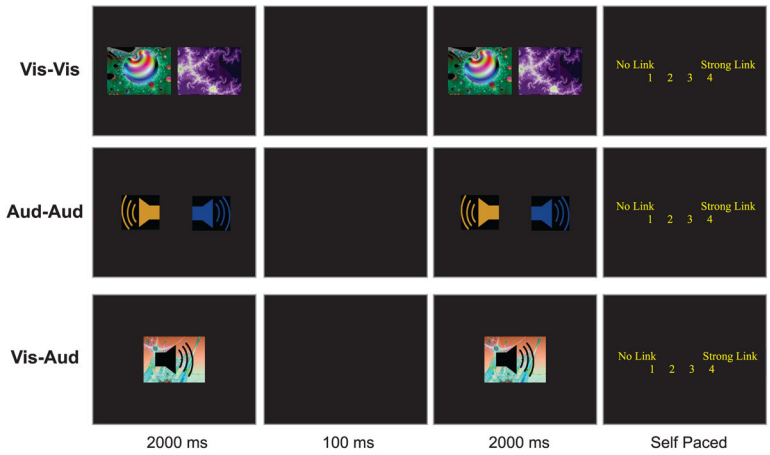

Figure 2.

Schematic of study trials for each condition. The only difference between study and test trials was during the response period. On study trials, participants made 1–4 link judgments (shown below); on test trials, participants made 1–6 confidence judgments (intact or rearranged).

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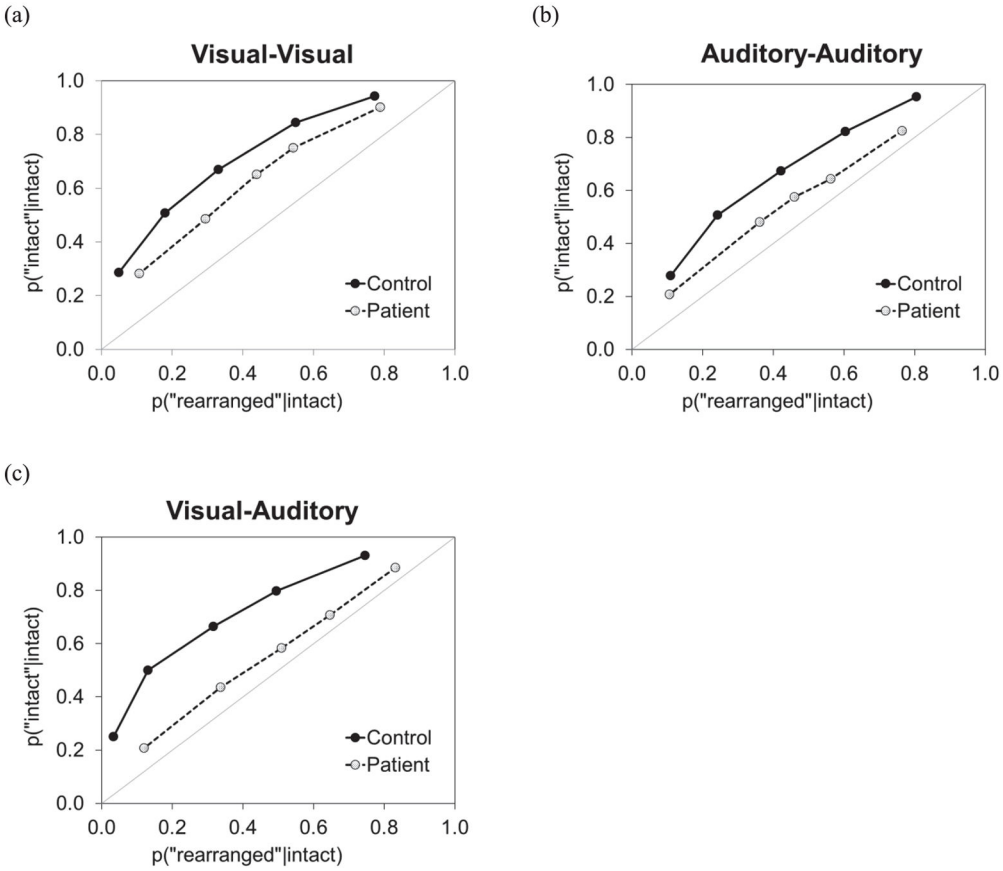

Figure 3.

Aggregate Patient and Control ROCs. (a) Visual-Visual within-domain condition. (b) Auditory-Auditory within-domain condition. (c) Visual-Auditory across-domain condition. In all conditions, patient ROCs are closer to the chance diagonal, indicating impaired performance on the task. The larger separation between patient and control ROCs in the across-domain condition suggests a greater patient deficit for this condition.

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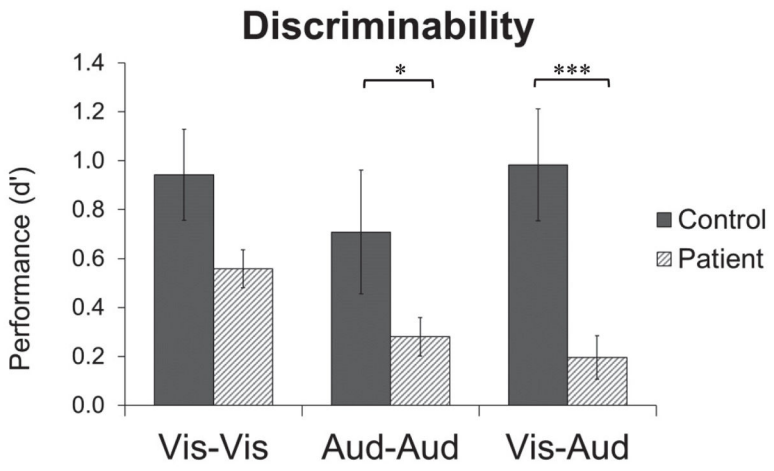
A.



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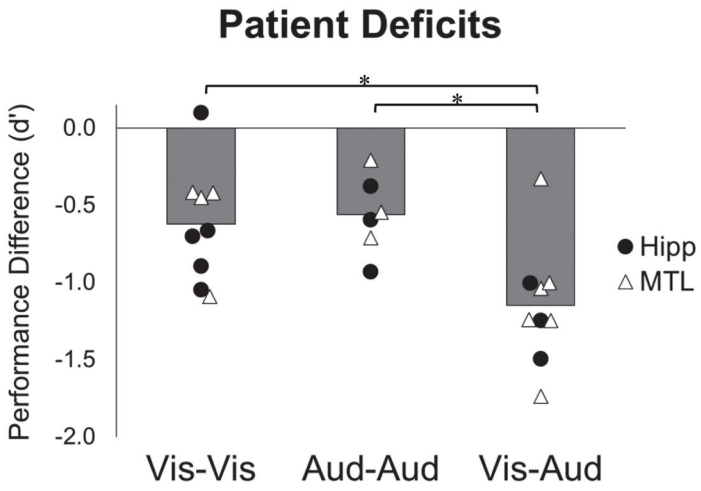

Figure 4.

Patient and control performance on each condition. Error bars represent ±1 SEM.

A. Overall discriminability (d') was impaired in patients.

*$p < .05$, ***$p < .001$

B. Deficit scores (patient d' minus mean control d') show that patients are impaired to a greater degree on across-domain tasks than within-domain tasks. There was no significant difference in impairment between patients with selective hippocampal damage (circles) and patients with more extensive MTL damage (triangles).

*$p < .05$

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Table 1

Patient Descriptions and Neuropsychological Battery Scores

		WAIS-R			WMS-R (*z*-score)					D&P (%tile)
Patient	**Damage**	**Age**	**Ed**	**EstIQ**	**Verbal**	**Visual**	**Gen**	**Attn**	**Delay**	
1002	Bilateral HC	31	18	110	−1.47	−1.07	−1.53	−0.87	−0.87	10%
1003	Bilateral HC Bilateral HC +	60	12	112	−1.80	−0.27	−1.53	0.07	−2.20	1%
1005	PHG	30	19	110	−0.07	1.07	0.33	0.27	−0.40	5%
1006	Bilateral HC	30	17	110	−1.33	0.33	−0.87	0.20	−2.13	1%
1007	R MTL + OFC	41	18	106	0.87	−0.87	0.13	1.20	−0.07	10%
1008	RMTL	71	12	83	0.07	−1.53	0.40	0.00	−0.27	5%
1009	LMTL	47	17	97	−1.60	0.40	−1.13	−0.67	−0.60	50%
1011	Bilateral HC *	52	16	96	−2.53	2.00	−1.40	−0.20	−1.13	1%
1012	LMTL	56	21	112	−1.40	0.93	−0.80	1.67	−0.40	n/a
1015	Bilateral HC *	52	13	94	−0.40	−1.53	−0.87	−0.27	−1.33	25%
1016	LMTL	63	12	75	−2.93	−1.07	−3.20	−0.87	−1.73	5%

Note: The Shipley Institute of Living Scale (Shipley, 1940) was used to estimate WAIS-R IQ (Zachary et al., 1985). The Doors and People test is based on recognition and recall (Baddeley et al., 1994); the generalized memory percentile is reported.

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

* These patients suffered a mild hypoxic episode as a result of a cardiac arrest and have presumed selective hippocampal damage. They are unable to undergo structural MRI scanning to confirm the extent and selectivity of the damage due to implanted defibrillators.

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Table 2

Individual Patient Scores (d') for Each Condition

Condition	1002	1003	1005	1006	1007	1008	1009	1011	1012	1015	1016
Vis-Vis	1.00	0.39	0.68	0.53	0.66	0.27	0.68	0.51	-	0.29	-
Aud-Aud	0.25	0.00	0.29	0.42	0.17	-	0.55	-	-	-	-
Vis-Aud	-	0.29	0.13	0.13	0.30	0.13	0.76	−0.04	0.27	-	−0.21

Note: Six patients (1002, 1008, 1011, 1012, 1015, 1016) and five controls did not complete all testing sessions because they were unavailable for personal or unrelated health reasons during the study and could not be scheduled for further sessions.

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Table 3

Mean Measures of Performance and Patient Deficits

	Controls				Patients				
Condition	***n***	***d´*(SD)**	**Hits (SD)**	**FAs (SD)**	***n***	***d´*(SD)**	**Hits (SD)**	**FAs (SD)**	**Deficit (SD)**
Vis-Vis	11	0.94 (.62)	0.67 (.13)	0.33 (.14)	9	0.56 (.23)	0.65 (.09)	0.44 (.13)	−0.62 (.37)
Aud-Aud	8	0.71 (.76)	0.67 (.10)	0.42 (.19)	6	0.28 (.19)	0.56 (.06)	0.44 (.04)	−0.56 (.25)
Vis-Aud	11	0.98 (.69)	0.66 (.15)	0.32 (.13)	9	0.20 (.27)	0.58 (.17)	0.51 (.22)	−1.15 (.39)

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