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Teasing apart tangrams: Testing hippocampal pattern separation with a collaborative referencing paradigm

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Abstract

The hippocampus and the medial temporal lobe cortex (MTLC) both contribute to long-term memory. While their contributions are thought to be dissociable, the nature of the representations that each region supports remains unclear. The Complementary Learning Systems (CLS) modeling approach suggests that hippocampus represents overlapping information in a sparser and therefore more separated fashion than MTLC. We tested this prediction using a collaborative referencing paradigm whereby hippocampal amnesic patients and a partner work together to develop and use unique labels for a set of abstract visual stimuli (tangrams) across extended interactions. Previously, we reported that amnesic patients demonstrate intact learning when the tangrams are conceptually dissimilar. Here, we manipulated the degree of visual similarity; half of the stimuli were dissimilar to one another (e.g., camel, giraffe), and half were similar (e.g., birds). We hypothesized that while patients would have little difficulty with the dissimilar tangrams (quickly arriving at unique and concise labels) they would be unable to rapidly form distinct representations of highly similar visual patterns. Consistent with this prediction, patients and both healthy and brain-damaged comparison participants showed similar rates of learning for dissimilar tangrams, but the similar tangrams proved more difficult for hippocampal patients as reflected in the greater number of words they used to describe each similar card. This result supports the CLS model's central claim of hippocampal specialization for pattern separation, and suggests that our collaborative referencing paradigm may be a useful tool for observing extended encoding of complex representations.

The medial temporal lobes (MTL) are widely acknowledged to play a necessary role in memory (Scoville & Milner, 1957), and there is strong evidence that different MTL components make dissociable contributions to memory performance (Aggleton & Brown, 1999; Cohen & Eichenbaum, 1993; Eichenbaum & Cohen, 2001). Theories of MTL function typically divide the region into at least two distinct components: the hippocampus; and the adjacent neocortex, including perirhinal, entorhinal, and parahippocampal cortices (i.e., medial temporal lobe cortex or MTLC). Different theorists have assigned different functions to these components, but a broadly-shared assumption is that the hippocampus is a higher-order mnemonic processor than the MTLC and therefore necessary for relational memory (Eichenbaum & Cohen, 2001), recollection (Aggleton & Brown, 1999), or complex

(visuo)spatial representations (Cowell, Bussey, & Saksida, 2010). Although these characterizations vary, the nature of the system's underlying representations must be shaped and limited by the neural connectivity of hippocampus and MTLC. Following from that premise, one particularly promising theoretical approach has been to model the unique neural connectivity of MTLC and hippocampus and to make inferences based on model performance under different conditions (McClelland, McNaughton, & O'Reilly, 1995; Norman & O'Reilly, 2003; Norman, 2010). A straightforward prediction of such models is that focal hippocampal damage should make pattern separation (and completion) more difficult. We sought to evaluate this claim by testing the ability of patients with bilateral hippocampal lesions to learn about a set of items in which the degree of visual similarity was manipulated.

Mnemonic contributions of the hippocampus have been described by a variety of mechanistic models, including the Complementary Learning Systems (CLS) framework (McClelland et al., 1995; Norman & O'Reilly, 2003). According to the CLS model, patterns of connectivity within the hippocampus make it uniquely well-suited both to rapidly separate novel inputs into distinct neural representations and to complete degraded, previously-experienced inputs into previously-learned patterns. Meanwhile, the generic neocortical connections within MTLC slowly sharpen many overlapping representations simultaneously; the highly separated representations of hippocampus are much less likely to overlap and can therefore be distinguished quickly. Hippocampal damage should therefore impair the ability to distinguish old from new items when test items are presented one at a time and lures resemble the target (e.g., in a Yes/No recognition task). Absent hippocampus, the overlapping features of a lure resembling the target will activate many features of the target in an MTLC representation and could result in a false alarm. Meanwhile, MTLC alone is thought to be sufficient to discriminate lures from targets so long as both are presented simultaneously, as in a forced-choice test format. In this case, the similarity of target's stored representation all test items can be compared simultaneously and directly, and should be diagnostic. Notably, MTLC does not possess patterns of intraregional connectivity that differ from most neocortex, and presumably any cortical region with appropriate inputs could support similar representations. Hence, MTLC will be used here as shorthand for non-hippocampal neocortical regions, and our methods attempted to dissociate hippocampal representation from other cortical representations.

Research directly testing CLS predictions in humans with hippocampal damage has been rare and equivocal. While two patients with focal hippocampal damage (Holdstock et al., 2002; Holdstock, Mayes, Gong, Roberts, & Kapur, 2005; Mayes, Holdstock, Isaac, Hunkin, & Roberts, 2002) and others with MCI (Westerberg et al., 2006) behaved as predicted by the CLS by exhibiting better forced-choice than Yes/No performance, other hippocampal lesion patients have not (Bayley, Wixted, Hopkins, & Squire, 2008). While the predictions of CLS in forced choice and Yes/No paradigms are clear, recognition has long been a disputatious arena for memory researchers in part because the data are relatively sparse. Mnemonic representations are evaluated often only once in a test phase using either binary or confidence-graded measures of recognition, leaving the underlying qualities of the representations and the encoding-time representations largely unexplored. At the same time, thorough study of amnesic patients' representations and encoding is challenging given their memory impairment. The manipulation of tasks that can produce apparently normal representations despite hippocampal damage may provide an avenue of investigation.

Patients with hippocampal damage can exhibit normal learning in some circumstances. In our previous work using a collaborative referencing task, we examined the ability of patients with hippocampal amnesia to acquire referential labels for a set of cards displaying Chinese tangrams across a series of communicative interactions with familiar partners (Duff, Hengst,

Tranel, & Cohen, 2006). To complete the task, participant pairs (patient and familiar partner) sat at a table facing each other with identical boards with 12 numbered spaces and a set of 12 identical cards on the table in front of each participant. A low barrier was placed between the partners, obscuring each person's view of the other's stimulus cards. Amnesic patients (directors) communicated to their partner (matchers) how to fill the numbered spaces so that at the end of the trial the two boards looked alike. The task was completed across 24 trials (6 trials per session, 2 sessions on 2 consecutive days). We found that despite profound declarative memory impairments the patients developed and used unique references for each card (e.g., *siesta man*), which across trials they produced in an increasingly concise and simplified form, requiring fewer words and less time to complete the task. In fact, the patients demonstrated a rate of learning comparable to that of healthy comparison participants. Given that the observed learning occurred gradually, and at a normal rate, we have argued that the learning was achieved through the tuning of cortical processors associated with non-relational memory (e.g., MTLC).

In the current experiment, we acquired similarly rich data about learned (or tuned) representations by modifying the collaborative referencing task to use stimuli that would differentially benefit from normal pattern separation. Instead of heterogeneous stimuli, items in the current set belonged to two conditions: half were visually *similar* (see bottom row of Figure 1) to one another; while the other half were *dissimilar* (see top row of Figure 1) to one another and to the items in the *similar* setⁱ. Although tangrams are abstract and interpreted idiosyncratically, items in our *similar* set resembled stylized birds as reflected in the labels assigned to them (see Results). Put another way, the overlapping visual features of the *similar* set were intended to yield conceptual overlap which would in turn require greater attention to distinguishing features of individual items. We hypothesized that MTLC representations would be poorly suited to this because of substantial visual similarity (i.e., overlap) in the initial representations. Meanwhile, hippocampal representations are well separated immediately, potentially allowing rapid unique identification. Healthy participants with highly separated hippocampal representations were therefore expected to show no difference in learning rates between *similar* and *dissimilar* items, while amnesic patients relying on MTLC representations alone were expected to represent *similar* items less efficiently than *dissimilar* items, with differences evident in longer descriptions of *similar* items and slower learning for those items.

Participants included two amnesic pairs (amnesic patients and their familiar partners (e.g., spouse, sibling) and six comparison pairs (healthy participants and their familiar partners) (see Table 1)ⁱⁱ. Healthy comparison participants included 5 men and 1 woman and were on average 62.6±8.5 years old with 16.4±2.6 years of education.

Although placement accuracy was high, both amnesic and comparison pairs found the similar tangrams (birds) more challenging; 77% (34/44) of placement errors were made on the similar tangrams. On average, the two amnesic pairs made more errors at placing the cards than comparison pairs (average=11.0 errors across the 24 trials (96.1 % accuracy), while on average only 3.6 errors were made by the comparison pairs across the 24 trials (98.7% accuracy).

The main dependent variable of interest was the *initial description word count*: the first attempt by the director (amnesic patient) at describing each of the 12 cards during each trial,

ⁱIn pilot work, 7 healthy individuals rated the distinctiveness of each tangram in comparison to the others. Each distinct tangram (those on the top row of Figure 1) was rated as being distinct from the other 11. The similar tangrams (those on the bottom row) were each rated as being distinct from each of the top 6, but were rated as highly similar to the other tangrams on the bottom row.

ⁱⁱThe two amnesic pairs participated in the Duff et al. (2006) study while the healthy pairs were recruited for this study.

before the matcher provided substantive input (see Duff et al., 2006 Supplementary Methods). We analyzed the number of words in the initial description of the similar and dissimilar tangrams separately across trials to assess learning across card types.

Across the entire task, we found that amnesic (AM) and healthy comparison (NC) directors demonstrated a comparable reduction in the number of words used to describe the dissimilar cards (average NC Trial 1=43.2 words; Trial 24=18.2 words; *70.8% reduction*; AM Trial 1=74.5 words; Trial 24=27.5 words; *57.8% reduction*; *Mann-Whitney U test: Z=0; p=1.0*). The critical comparison here was how healthy and amnesic directors described the highly similar tangrams (birds). All directors required more words to describe the similar cards than they did for the dissimilar cards, particularly on the initial trials (e.g., on Trial 2, NCs used on average 94.0 words for the similar cards and only 34.0 words for the dissimilar cards, while AMs averaged 80.0 and 55.5 words, respectively), again suggesting that generating unique representations and references for these cards was challenging. However, the comparison directors' displayed significantly larger reduction in the average number of words required to describe the similar cards across trials (average NC Trial 1=114.2 words; Trial 24=14.8 words; *87.0% reduction*) than the amnesic directors, who were particularly challenged on the similar cards and required more than twice as many words to reference those cards on the final trial as healthy comparison participants (AM Trial 1= 83.5 words; Trial 24=38.5 words; *53.9% reduction*; *Mann-Whitney U test: Z=-2.0; p=0.04*; see Figure 2).

Finally, by the end of the task, comparison directors were consistently using concise, unique, and even somewhat arbitrary, labels for the similar tangrams (e.g., *hummingbird, eagle, goose, phoenix*). Strikingly, amnesic directors' were less concise and more generic (e.g., "*bird with uneven wings and the triangle head*," "*bird in flight with the triangle head*," "*bird flying, looking straight left*"). One amnesic director expressed awareness of the difficulty in generating unique labels for the similar tangrams (e.g., "*I just can't get names for the birds*").

In order to tie our result more closely to hippocampal damage and not to the presence of brain damage more generally, we collected data using an identical protocol from one braindamaged comparison participant (BDC participant) and his healthy partner. The BDC participant was a 56-year-old male with low-average intelligence (WAIS-III FSIQ of 85) and no declarative memory impairment (WMS-III GMI=95). Structural MRI data revealed a lesion in the dorsal aspects of the left parietal cortex, but there was no damage to hippocampus or any MTL structure. Like healthy comparison directors, and in striking contrast to amnesic patients, the BDC director showed comparable rates of reduction in the words used to describe both the dissimilar (Trial 1=34 words; Trial 24=12 words; *64.7% reduction*) and similar tangrams (Trial 1=63 words; Trial 24=23 words; *63.5% reduction*). Likewise, by the end of the task the BDC pair was able to develop concise, unique labels for the similar tangrams, including *goose, buzzard, and two-tailed hawk*.

Our results show a clear influence of hippocampal pattern separation as indexed by rates of learning and by the nature and length of references. As expected based on previous work, all participants showed a similar rate of learning for the *dissimilar* items especially during the first 6 trials (Trial 1–6 mean (SD) slope of regression lines for NC=-3.76 (4.02), i.e., 3.76 fewer words used per trial, range -7.40 to 3.40; AM mean=-6.50, range -10.43 to -2.57, i.e., within or less than the normal range), but amnesic patients were selectively impaired when confronted with *similar* items (Trial 1–6 mean (SD) slope of regression line NC=-14.37 (8.57), range -28.66 to -6.25 ; AM mean =-1.56, range -4.25 to 1.09, i.e., outside and greater than the normal range). We tested the reliability of these differences using a modified statistical technique appropriate for small sample sizes that has been reported

elsewhere (Konkel et al., 2008; Berryhill et al., 2007; Olson et al., 2006)ⁱⁱⁱ, and while the groups were indistinguishable for *dissimilar items* (observed $T(1.28) = -0.74$ was < 2.87 , the 95% level of the permuted set), amnesic patients showed reliably slower reductions in word counts for *similar items* (observed $T(5.69) = 2.11$ was > 1.83 , the 95% level of the permuted set). Importantly, the dissociation was evident both within the amnesic patient group itself and between comparison groups and the amnesic patients. Over the course of 24 trials, the patients consistently used more words to describe *similar items* despite their normal learning patterns for the *dissimilar items*. This gross deficit appeared to be specific to hippocampal damage, as the BDC pair mirrored healthy performance with *similar* and *dissimilar items* while the amnesic pairs did not.

Impairments in pattern separation after hippocampal damage provide a compelling explanation for these results. Described using the terminology of CLS (Norman & O'Reilly, 2003; Norman, 2010), without the highly separated representations unique to the hippocampus, the amnesic patients would be forced to rely on slower sharpening within MTL to support distinct representations of the knowledge being developed about each item. While this tuning would be sufficient to equal normal learning when the set of learned items was heterogeneous, increased homogeneity within the set would cause learning to be generalized to the features common to items in the *similar* set. This kind of destructive retuning of connections between previously-encountered features could be construed as a form of catastrophic interference (McCloskey & Cohen, 1989) that the hippocampus normally prevents. Overlapping, interfering representations would not preserve useful knowledge that could improve performance on later trials.

Although explicit tests of CLS in human amnesic patients have been rare, other researchers have examined the effects of item similarity on learning after MTL lesions. Conditional discrimination learning tasks requiring participants to learn which of two items is correct have suggested that greater similarity may impair performance in MTL-lesion patients (Barens et al., 2005; Graham et al., 2006; Lee et al., 2005; Lee, Barens, & Graham, 2005), but with the caveat that hippocampal damage affected only scene representations, while leaving object representations undisturbed. Our results clearly suggest that sufficiently similar object representations may indeed benefit from hippocampal processing, and the rapid but measurable learning evident in NCs indicates that hippocampal influence is more likely mnemonic than perceptual in nature. This aligns with recent neuroimaging work that has identified regionally specific hippocampal contributions to object-based pattern separation and pattern completion (Bakker, Kirwan, Miller, & Stark, 2008; Carr, Rissman, & Wagner, 2010; Kirwan, Jones, Miller, & Stark, 2007; Stark, Yassa, & Stark, 2010; Yassa et al., 2010).

Focal hippocampal lesions impaired the ability of patients to learn about *similar*, but not *dissimilar*, items, and this finding is congruent with existing theories positing a unique hippocampal contribution to pattern separation. Use of our version of a collaborative referencing task (see Duff et al., 2008) provided new insight into the formation of and changes in mnemonic representations over time, and may be a useful tool for subsequent investigations.

ⁱⁱⁱGroup-level differences in learning rates, characterized as regression slopes fitted to initial word counts for each pair across Trials 1–6, were analyzed using permutation tests. First, we calculated T values for observed group differences in learning rates (T tests did not assume equal variance between groups, and therefore used the Welch modification to degrees of freedom). Then, the eight (two amnesic and six normal comparison) learning rate values were randomized, and the T value reflecting the difference between the first two randomized observations and the remaining six was recorded. This procedure was repeated 1000 times, yielding a sample of all possible T values that could have arisen from the observed learning rates. The sample was then sorted, and the T value at the 95th percentile of the sorted sample was used as our lower bound for reliability. We conducted a similar permutation analysis using the nonparametric two-sample Wilcoxon test, and the same pattern of results was obtained.

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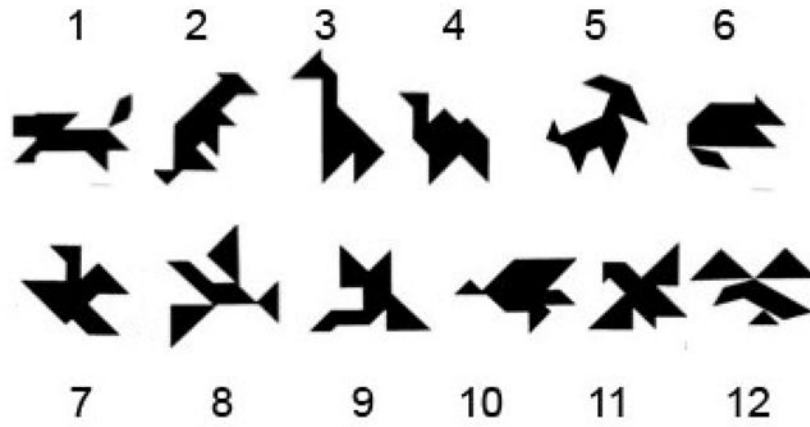


Figure 1.
The set of tangrams for which participants and their partners collaboratively generated labels. (Top row: dissimilar cards; Bottom row: similar cards).

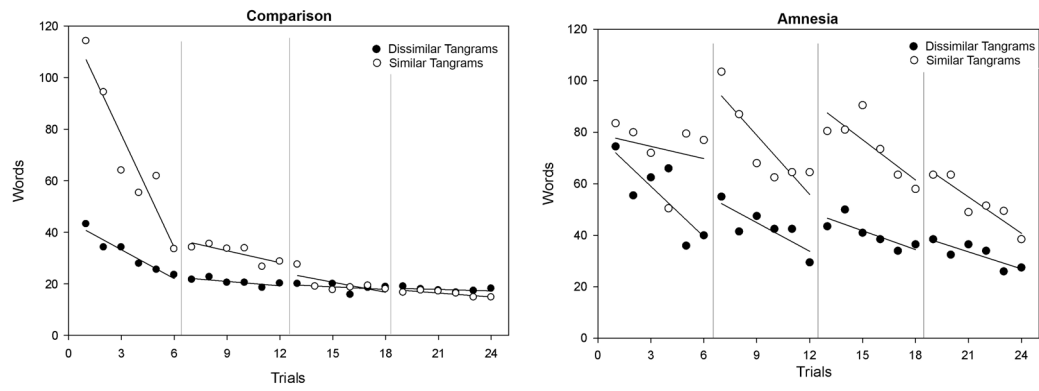


Figure 2. Mean word counts (words required for referencing the cards) for healthy comparison (left panel) and amnesic patients (right panel) to reference all 12 tangrams on each of the trials; shown with session-by-session linear trends. Note that while the comparison participants rapidly reduce their word counts for both similar and dissimilar items, the amnesic participants show much slower reductions in word counts for the similar tangrams.

Table 1

Participants' Demographic, Neuropsychological, and Anatomical Characteristics

Patient	Sex	Ed	Year of Birth	WAIS-III FSIQ	WMS-III GMI	Etiology; Damage	HC Volume
2363	Male	16	1956	98	73	Anoxia; Bilateral HC damage	-2.64
2563	Male	16	1955	102	75	Anoxia; Bilateral HC damage	N/A

Note. Ed = Education; WAIS-III = Wechsler Adult Intelligence Scale; FSIQ = Full Scale Intelligence Quotient, WMS-III GMI = Wechsler Memory Scale-III; GMI = General Memory Index; HC = hippocampus. Hippocampal z-score represent the combined (left and right hemisphere) studentised residuals of hippocampal volume relative to a group of comparison subjects (Allen et al., 2006). Patient 2563 wears a pacemaker and was unable to undergo the MRI examination. Only damage to the HC was visible on computerised tomography (see Duff et al., 2006, 2009; Hannula et al., 2007 for more extensive description of patients).