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Reconstructing Relational Information

Kevin M Horecka¹, Michael Dulas¹, Hillary Schwarb¹, Heather Lucas², Melissa Duff³, and Neal J Cohen¹

¹Beckman Institute for Advanced Science and Technology, University of Illinois at Urbana-Champaign; Urbana, IL

²Department of Psychology, Louisiana State University; Baton Rouge, LA

³Hearing and Speech Sciences, Vanderbilt University Medical Center; Nashville, TN

Abstract

Hippocampal involvement in learning and remembering relational information has an extensive history, often focusing specifically on spatial information. In humans, spatial reconstruction (SR) paradigms are a powerful tool for evaluating an individuals' spatial-relational memory. In SR tasks, participants study locations of items in space and subsequently reconstruct the studied display after a short delay. Previous work has revealed that patients with hippocampal damage are impaired both in overall placement accuracy as well as on a specific measure of relational memory efficacy, “swaps” (i.e. when the relative location of two items is reversed). However, the necessity of the hippocampus for other *types* of spatial-relational information involved in reconstruction behaviors (e.g. where in the environment and relative to which other items an item was located) have not yet been investigated systematically. In this work, three patients with hippocampal damage and nine healthy matched comparison participants performed an SR task. An analysis framework was developed to independently assess three first-order *types* of relations: 1) memory for the binding of specific item identities to locations, 2) memory for arrangement of items in relation to each other or the environment bounds, regardless of memory for the item identity, and 3) higher-order, compound relational errors (i.e. errors involving multiple pieces of relational information). Reconstruction errors were evaluated to determine the degree to which patients and comparisons differed (or not) on each *type* of spatial-relational information. Data revealed that the primary group difference in performance was for identity-location information. However, when the locations of items were evaluated without regarding the identities, no group difference was found in the number of item placements to studied locations. The present work provides a principled approach to analysis of SR data and clarifies our understanding of the *types* of spatial relations impaired in hippocampal damaged.

Keywords

Binding; declarative memory; spatial reconstruction; relational memory; online processing

Introduction

Relational memory is critically supported by the hippocampus (Cohen & Eichenbaum, 1993; Eichenbaum & Cohen, 2001; Konkel & Cohen, 2009; Konkel, Warren, Duff, Tranel, & Cohen, 2008). For example, memory for relationships of items to spatial locations is highly sensitive to hippocampal damage in humans (Hartley et al., 2007; R. J. Allen, Vargha-Khadem, & Baddeley, 2014; Smith & Milner, 1981a; Watson, Voss, Warren, Tranel, & Cohen, 2013). Moreover, it has been shown previously that the hippocampus is necessary for all “manner” of relational memory (Konkel et al., 2008); that is, it is critical for binding information regardless of the informational domain, be it spatial, temporal, sequential, associative, etc. However, while the hippocampus can be involved regardless of the domain of information, there are many possible relations between the constituent elements within a given domain, such as item identities (i.e. labels that distinguish items from one another, such as names), locations (i.e. positions in the domain in which an item was present during study), and environmental elements (i.e. the boundary of the environment or landmarks). It is possible that not all of the relational information among these elements critically relies on the hippocampus, and that some *types* of relational information may not be impaired by hippocampal damage.

Importantly, we distinguish between a *manner* of relation and *type* of relation. Hippocampal involvement in all *manner* of relation means, more generally, that the hippocampus can be involved regardless of the informational domains (i.e. spatial, temporal, social, associative, etc.). However, within a given domain, particular *types* of relational information exist (and are enumerated here) which may not all be equivalent in terms of hippocampal involvement. It is possible that when comparing *types* of relations in two different domains, seemingly similar relations may have distinct representations with different amounts of reliance on specific memory systems. For instance, item-item relations within a spatial domain containing several items can be used to derive information about item locations even with an imperfect representation of each individual relation (this point will be elaborated upon later), while item-item relations in an arbitrary word pair cannot be easily used to derive additional information about other arbitrary word pairs. Similarly, item-environment relations in some spatial tasks may or may not be informationally equivalent to item-environment relations in other tasks (such as studying the location of a single item in a scene vs. the locations of many items within an empty environment). A primary reason for this difficulty is in the diversity of uses of terms like ‘item’ and ‘environment’ across different tasks.

It is the aim of this work to precisely define *types* of relations within the spatial domain in such a way as to determine if memory for specific *types* of spatial relations are impaired (or not) by damage to the hippocampus. To this end, we propose a framework for systematically classifying *types* of relations in a spatial memory task. This framework allows us to: 1) distinguish multiple types of first-order (i.e. pairwise or one-to-one) and higher-order (i.e. group-wise or many-to-many) spatial relations, and 2) determine if these various types of spatial relations are differentially impaired by hippocampal damage by inferring the presence or absence of relational information via observations of different types of errors in a reconstruction.

Here we take advantage of the rich data generated by spatial reconstruction (SR) paradigms, in which multiple items are studied in various spatial locations before participants are asked to reconstruct (i.e. freely place) each item in its remembered location. There is a long tradition of using SR paradigms to study spatial memory (Huttenlocher & Presson, 1979) and its susceptibility to hippocampal damage (Jeneson, Mauldin, & Squire, 2010; Smith & Milner, 1981; Watson et al., 2013). These experiments have historically used a general quantification of “misplacement error” in space by calculating the sum of the Euclidean distance between each placed item and its studied location. The typical finding of these experiments is that individuals with hippocampal damage show increased overall misplacement relative to comparison participants.

One critique of the use of misplacement as the sole metric of performance on SR tasks has been that it provides relatively little information about the nature of spatial memory deficits following hippocampal damage (Watson et al, 2013). Explanations have been more specific with other paradigms (e.g., virtual Morris Water Maze; vMWM) and these explanations could be extended to SR tasks. Previous data in rodents in a variation of the Morris Water Maze has shown that the ability to remember precise spatial locations amongst a group of possible locations was impaired when the rats were given hippocampal lesions (Gilbert, Kesner, & DeCoteau, 1998). In humans, the Precision and Binding Model (PBM; Yonelinas, 2013) states that the hippocampus is critical for high-resolution binding of information as shown by poorer precision of spatial navigation in hippocampal damaged patients in a vMWM (Kolarik et al., 2016; Kolarik, Baer, Shahlaie, Yonelinas, & Ekstrom, 2017). In this framework, high levels of misplacement could theoretically reflect an inability to remember coordinates on a “grid-like” mental representation of the display, with patients showing a deficit in the resolution of the grid. Alternatively, high misplacement could reflect a deficit in representing inter-object configural or relational information (among other possibilities, discussed below; Corsi, 1972; Kessels, van Zandvoort, Postma, Kappelle, & de Haan, 2000; Uttal & Chiong, 2004). Because the role of resolution in misplacement is unclear, there have been recent attempts to develop additional metrics of spatial reconstruction performance that help to disentangle these possibilities (Jeneson et al., 2010; Watson et al., 2013). In particular, Watson et al. (2013) focused on a very specific type of spatial relational error termed a “swap” error. “Swap” errors are errors in which the relative position on each x and y axis for a pair of items is flipped. Such errors are strongly associated with hippocampal damage. In fact, patients with hippocampal lesions even make “swap” errors in set sizes as small as two items and at surprisingly short time scales (Watson et al., 2013). Moreover, “swap” errors have been used in evaluation of memory healthy individuals in a variety of other experimental paradigms (Clark et al., 2017; Lucas et al., 2016; Schwarb et al., 2017a; Schwarb, Johnson, McGarry, & Cohen, 2016).

These data suggest that when the hippocampus is impaired, relational binding errors occur regardless of the number of items to be remembered (e.g., in a set size invariant manner). Moreover, swap errors in Watson et al. (2013) were found to be a significant contributor to the overall differences in misplacement rates between patients and healthy comparison participants. However, there are many additional potential relation-based explanations for increased misplacement in hippocampal patients. Patients could be making global errors of some sort (i.e. moving all items down, squishing items together, or rotating all the items),

local or “noisy” errors (i.e. placing items pseudo-randomly based on a heuristic or limited memory for locations), or relational errors (i.e. placing items in the wrong location given their identity, but that location would have been valid for a different item). Thus, in the present study, rather than focus on one type of spatial relational error (e.g. swaps), we sought to identify the multiple types of relations in space, to organize them in a systematic framework, and to determine if all, or only some, types of relations are impacted by hippocampal damage.

At the core of our proposed framework is the classification of three primary types of first-order spatial relations: item-environment relations (e.g., one item is in the upper left corner of the display), item-item relations (e.g., one item is below and to the left of another item), and identity-location relations (e.g., item A belongs in location A). Note that terminologically, the use of the word “item” here is specific to location information (with identity information being separated out as identity-location information). An analogy to help clarify the meaning of these different relations can be found in navigating a shopping mall. Pretend that you need to return a pair of shoes to Nordstrom, one of several department stores at your local shopping mall. There are many ways that you might remember the location of Nordstrom. You might remember that it is on the third floor at the south end of the mall (i.e., item-environment relation). You might remember that it is one floor below the Macy's (i.e., item-item relation). Or you may remember that there are department stores at every corner of the mall, and a specific one at the south-east corner is Nordstrom (i.e., identity-location relation). Each relationship provides you with information about the possible location of Nordstrom, but some are more precise than others. The hippocampus has been implicated for decades in item-environment relations. Indeed, animal models demonstrate hippocampal place cell firing tied to the distance and direction of item cues in an environment (Gothard, Skaggs, & McNaughton, 1996; Gothard, Skaggs, Moore, & McNaughton, 1996; O'Keefe & Burgess, 1996). While humans with hippocampal damage are able to retain some item-location information via maintenance in working memory, this maintenance is transient (R. J. Allen et al., 2014; Libby, Hannula, & Ranganath, 2014). In both humans and animals, arbitrary item-item association has been extensively studied. Memory for item-item relations is impaired following selective damage to the medial temporal lobe in rodents (Bunsey & Eichenbaum, 1993), monkeys (Murray, Gaffan, & Mishkin, 1993), and humans (Giovanello, Verfaellie, & Keane, 2003; Konkel et al., 2008). Furthermore, humans with hippocampal damage show item-item impairments for all manner of relations (e.g. spatial, temporal, associative, etc.; Konkel et al., 2008).

In addition to these first order relations, we examine higher-order, compound relations (e.g., item A, B, and C form a group), which can contribute to compound spatial relational memory errors (e.g. the group is translated to the left, all of the items are squished towards the group's center, or two items swap locations). Compound relational errors can be seen in two forms in our analysis. Firstly, swaps of items (i.e. when two items are placed in each other's location) and cycles of items (i.e. when more than two items are placed in each other's locations) are forms of compound error primarily involving multiple identity-location errors. Secondly, various transformation errors (translation, scaling, and rotation) are forms of compound errors involving multiple item-item and/or item-environment errors.

In addition to first-order (i.e. pairwise) and higher-order (i.e. compound) relations, we can begin to consider the question of how general, Gestalten shape information, i.e. configural features which constitute parts of a unified whole, may be used independently of the hippocampus to maintain more global spatial information. While the current data cannot provide a definitive response to this proposal, the relevant data are suggestive and considered.

Finally, given the evidence that hippocampal damage impairs reconstruction performance even at very small set sizes (Watson et al., 2013), the implication of varying set size on memory for these different types of spatial relational information was considered. To this end, we take advantage of an existing dataset (Watson et al., 2013) that recorded SR task performance from hippocampal patients across set sizes (i.e., from 2 items to 5 items) and reanalyze those data using the current analysis framework. We first evaluate the extent to which hippocampal patients and comparison participants committed relational memory errors of particular types even at small set sizes (e.g., 2 items). Second, we determine whether those error types change or remain consistent as set size increased.

In summary, in the work presented here, we investigate the types of relations that are sensitive to hippocampal damage from a first principles approach by breaking down reconstruction errors in an SR task into multiple error types, which can then be evaluated simultaneously. We consider three types of first-order relations (i.e., item-environment, item-item, and identity-location relations) as well as two types of higher-order compound relations (i.e., swaps and cycles). We evaluate the degree to which the overall difference in misplacement between hippocampal patients and matched comparisons can be explained by these distinct error types. Finally, we discuss the implications of these findings for theories of hippocampal function.

Materials and Methods

Participants

Behavioral data were collected from 3 patients with hippocampal damaged and profound declarative memory impairment or amnesia (see Table 1 for details) and 9 healthy comparison participants. Three of the healthy comparison participants were matched to each hippocampal patient for sex, age ($\pm$ 5 years), and education ($\pm$ 2 years).

Two patients experienced anoxic/hypoxic episodes (1846, 2563) resulting in bilateral hippocampal damage and the third patient contracted herpes simplex encephalitis (1951) leading to more extensive bilateral MTL damage affecting the hippocampus, amygdala, and surrounding cortices (Figure 1). Structural MRI examinations completed on 2 of the 3 patients confirmed bilateral hippocampal damage and volumetric analyses revealed significantly reduced hippocampal volumes. Participant 2563 wears a pacemaker and was unable to undergo MRI examination and thus their damage was confirmed by computerized tomography; damage was confined to the hippocampus.

Experimental Paradigm

Participants completed a computerized spatial reconstruction task (Monti et al., 2015; see top of Fig. 2). Participants studied 6 items (gray scale, nameable objects; Brodeur, Guérard, & Bouras, 2014) per trial, arranged pseudo-randomly in an 950×600 pixel area within a 1280×1024 pixel computer screen across 32 total trials. During the study phase, participants viewed the 6 items for 16 seconds, followed by a 5 second delay (blank screen). At test, which began immediately after the delay, items were randomly placed in a line at the top of the screen, and participants used a mouse to drag each item to its remembered location on the screen. Participants had unlimited time to reconstruct the studied display. When they were finished, participants pressed space bar to start the next study trial. Participants' eye movements were recorded throughout the experiment. Eye tracking data are not reported here and will be reported elsewhere (Lucas, Duff, & Cohen, in preparation).

To determine if item-environment, item-item, identity-location, and compound relations showed selective differences in performance between patients and comparison participants, a new set of tools for analyzing spatial reconstruction data were created. These methodologies were designed with the intention of making as few assumptions as possible about the nature of the reconstruction to separate the types of errors via more mathematically rigorous and interpretable metrics. This approach applies Point Set Registration methods (see Besi & Mckay, 1992 for an introduction to the topic), in which a set of points (often derived from key points in an image) are assigned to an independent set of points (often from a reference image) based on an inferred relationship between the two sets. The SR paradigm is analogous to the Point Set Registration process of understanding the relationship between reconstructed points and their target (i.e., studied) counterparts, with two primary differences. Firstly, in the case of Point Set Registration, it is often not guaranteed that every point in the data set will correspond one-to-one with a point in the target. In the case of the SR task, we have a much stronger reason to assume that such a one-to-one correspondence should exist (though it may be interesting to consider the sorts of memory errors that might cause this assumption to be violated). Secondly, in Point Set Registration, it is often the case that there are many more points from which to define a model than exist in the SR task. For this second reason, especially, it is important that we proceed with caution in what models we apply to our data to avoid overfitting to a small set of points.

The model for the comparison of the reconstructed and target (i.e., studied) points can be thought of as having four primary components: identity remapping (wherein the identity of each item is removed and the set of placed item locations is mapped onto the target locations in a way which minimizes error), global error correction (wherein global translation, scaling, and rotation errors are subtracted from the placed item locations), location placement evaluation (wherein a binary determination of accuracy is made for each location), and compound error evaluation (wherein “swaps,” in which two items are misassigned to each other's locations, and “cycles,” in which more than two items are misassigned to each other's locations, are identified).

Identity Remapping

For this first step, identity remapping, a one-to-one mapping between the reconstructed points and targets must be created. This mapping can be determined by a variety of methods, each with their own advantages and disadvantages (Burkard, Dell'Amico, & Martello, 2012); however, for the sake of simplicity and interpretability, it is often preferable to find the mapping which globally minimizes the overall error in the reconstruction (effectively eliminating any effects of item identity-location misassociation in the reconstruction). This can be solved using the following Assignment Problem (H. W. Kuhn, 1956; Harold W. Kuhn, 2010; Munkres, 1957) equation:

$$\min \sum_i \sum_j C_{ij} X_{ij}$$

where C_{ij} is the cost matrix associating each vertex in a graph and X_{ij} is the binary assignment of an undirected edge to the graph. Using the above equation, we find the set of X_{ij} associations (which we will call “the map”) which results in the smallest numerical value, forming a minimal one-to-one mapping of the placed item location to a target (studied) location.

Global Error Transformations

Once a one-to-one mapping has been found, the next primary component to be determined is the global error transformation which finds shared error across all the items. This transform could be any function, and with enough parameters, the items could be mapped perfectly onto their assigned target locations. However, because our intention is to differentiate between global relational errors and item-level errors, a simplified transformation is used such that only translation, scaling, and rotational errors are included in the model. Together, these transformation components describe a 4 parameter system (x translation, y translation, scale, and rotation), which can be used to model global error across all items in a trial (cf. Similarity Transform; Cederberg, 2001). One could speculate as to what might cause these different types of errors (i.e. translation being a misrepresentation of the entire stimulus space in the environment with an offset, scaling being a squishing or stretching of the stimulus space, and rotation being a misrepresentation of the directions in the environment). Regardless, by identifying this global error, we can subtract out its effects from each item's location so as to get a more precise measure of individual item accuracy independent of shared, systematic, spatial errors. The similarity transform can be more precisely stated as a solution to the equation:

$$f(x) = rAx + t$$

where r is the ratio of similarity (or scaling factor), A is an $n \times n$ orthogonal matrix and t is a translation vector. A can be decomposed into a single θ value which represents the magnitude of rotation around the point set center. This transformation can be computed using Umeyama's algorithm (Umeyama, 1991) which uses Singular Value Decomposition

(Cline & Dhillon, 2006; Golub & Kahan, 1965) to obtain a transformation matrix. It is useful to note that it is not always possible to find a transformation given a set of points if they do not actually share any global error of the types we've specified (i.e. translation, scaling, and rotation). In our model, we allow rotation to fail independently of translation and scaling, as it is more difficult to find rotational components in small data sets. If all attempts to find a transformation fail, no global adjustments are made and the transformation data from those trials are excluded from the analysis. Singular Value Decomposition computes the transformation matrix by solving the following equation:

$$M = U \Sigma V^*$$

where M is the dot product of the reconstructed and target point locations divided by the number of points, U and V^* are unitary matrices, and Σ is a diagonal matrix of non-negative, real numbers. Umeyama's algorithm allows the decomposition of the matrix M into the translation, scaling, and rotation components.

Location Placement Evaluation

Now that associative and global errors have been subtracted from the point locations, a measure of reconstructed-to-target location placement accuracy can be evaluated in a manner that is not influenced by incorrect item-identity choices or global rearrangement. Previous studies have attempted to include accurate placement as an aspect of the analysis using an arbitrarily chosen distance value (Jeneson et al., 2010). However, an inflexible threshold imposes a very strict, nonlinear boundary on our evaluation of accuracy, which is difficult to handle without training participants to operate within this constraint (potentially influencing behavior in unintentional ways). It would be preferable for such a boundary decision to be made flexibly, based on the variability in local misplacement (i.e. misplacement that is not shared amongst the items nor due to item identity errors). To accomplish this goal, we determine accuracy based on the data by creating a statistical distribution of the misplacement after correcting for item-identity and global error and use the confidence intervals for the distribution (in this case, 95% confidence intervals) as the accuracy threshold. This distribution could be formed on a trial-by-trial basis, but it is more stable to compute it across all trials for an individual as there are more sample points (192 points instead of 6). This trade-off means that the threshold will be slightly stricter than the data would suggest for earlier trials and slightly less strict for later trials:

$$d < \bar{x} + z^* \frac{\sigma}{\sqrt{n}}$$

This choice trades a rigid, predetermined threshold condition for a new assumption: that the participant placement of items will generally be in the studied locations (to a degree specified by the confidence interval width). This assumption may not be correct for patients with hippocampal damage as overall misplacement for patients is greater than for matched comparisons (Huttenlocher & Presson, 1979; Jeneson et al., 2010; Smith & Milner, 1981a).

Therefore, we opt to use the accuracy thresholds computed from the comparisons as the measure of accuracy for the patients. This choice allows our definition of placement accuracy to be unified between the groups, with the matched comparisons determining their associated patient's placement accuracy threshold. This adjustment is necessary in deciding a threshold for patients because we are forming a statistical distribution based on individual item misplacement which incorporates all the individual item variability. This item variability is not necessarily matched between patients and comparisons given that the comparisons generally perform better. Thus, we use the stricter criteria, the comparison thresholds, for placement accuracy in patients.

Compound Identity Error Evaluation

Finally, once all item-location assignment and global errors have been subtracted from the data and placement location accuracies have been determined, item-to-location mapping can be examined for both accurate locations and inaccurate locations. Using the mapping from the first step of the analysis and the accuracy from the previous step, we can also find if there are any accurate or partially accurate location-cycles of items where items were potentially assigned to the wrong location (i.e. within the threshold we have defined for our binary location accuracy judgement but with a center on a different item's studied location). The cycles are computed via a graph-theoretical connected-components analysis where closed loops in the graph of associations are treated as individual components (Hopcroft & Tarjan, 1973). If an item exists in a single-component system, it is assigned correctly with its target (studied) location. Otherwise, the items in the component system form a cycle, where the simplest cycle would be a 2-cycle, which can also be thought of as a swap, and higher order cycles can also be found (up to a 6-cycle, as 6 items are being tested). In the general case, an N-cycle is possible where N is the number of items under test. Note, this “swap” is computed differently than our previous version of “swaps” (Watson et al., 2013), as the metric described here includes location accuracy (with item identity ignored) as part of the requirement for being called a “swap”. We believe that this new metric is more consistent with the general item-location misbinding interpretation of a “swap” error. These error types are collectively called compound errors.

In summary, this process produces a set of nine output metrics. The 1&2) translation (x and y), 3) scaling, and 4) rotation magnitudes from the transformation step, 5) the number of items within the location accuracy threshold after removing both the item identities and the number of compound errors of various types. For consistency with our previous work, we will consider 6) 2-cycles, aka swaps, in isolation of 7) >2-cycles in statistical analysis. Further, any system with one or more inaccurate items is treated as a 8&9) “partial” cycle (or swap), versus those in which all locations contain an accurately placed item.

Gestalten Shape-Like Information

There are many ways to define “shape”, and this proposal evaluates only one such definition. Shape is defined here via the location vertices and their relative positions, such that the shape is altered with item placements in non-studied locations and unaltered with transformations such as translation and scaling. Under this definition of shape, shape can be thought of as the highest order of compound identity-location and item-item relational

information which includes all pairwise relations amongst items without regard for item-environment relations. One way to dissociate identity-location and item-item relations is to strip away the identity information and treat all items as if they were anonymous (i.e. unlabeled) in order to determine if the placement locations match up with any studied locations (see Identity Remapping above for details). The current study takes steps to evaluate and dissociate the degree to which shape-like information may be maintained by hippocampal patients by comparing the number of correct location placements (disregarding item identity) and the magnitude of different types of global errors (i.e. error which is shared between multiple items in the reconstruction), such as translation (i.e. a fixed offset in x and/or y of all items), scaling (i.e. all items being closer to or farther from a central point without a change in angle between any item pair), and rotation (i.e. all items rotated some distance around a central point) between the groups which might suggest differences in shape memory.

Statistical Analysis

Welch's *t*-test for unequal variance and unequal sample size (two-tailed) were conducted unless otherwise indicated. An alpha level of 0.05 was used to determine significance. Degrees of freedom for each *t*-test were adjusted using the Welch-Setterthwaite equation to correct for unequal sample size and variance. Repeated measures ANOVA were used when comparing metric performances and set size data. All ANOVA used Huynh-Feldt correction for non-sphericity.

Reanalysis of Watson et al. (2013) Set Size Data

Previous work from our group showed that hippocampal patients committed swap-like relational memory errors even at set sizes as small as 2 items, whereas such errors were virtually non-existent in comparison participants even at size sizes of 5. These data suggest that hippocampal damage leads to a pervasive inability to retain relational information even in the most restrictive circumstances. To investigate whether all types of relations are set size invariant, we conducted a reanalysis of a previously acquired data set (Watson et al., 2013) to determine if the patterns seen in the new data set hold in the previous one. The data contained four patients and four matched comparisons. Because that data set contained variations in set size, a repeated measures ANOVA was run to determine if the average error magnitudes across set sizes differed for each type of error. There was an overlap of one patient in both studies, 1846, though the data were collected approximately 4 years apart.

Results

Differences in Misplacement Accounted for by Global Errors

Consistent with previous work (Jeneson et al., 2010; Smith & Milner, 1981; Watson et al., 2013), the hippocampal patients show significantly more overall misplacement (difference between means is 109.2 pixels; $t(4.85) = 3.96, p = 0.02$) than the comparison participants (Fig. 4 “Original”). However, our new analysis framework allows us to determine the degree to which this misplacement difference can be accounted for by the different types of spatial relational errors.

A repeated measures ANOVA was performed with group by misplacement at each analysis step (original, post-remapped, and post-transformed). A main effect of both group ($F(1, 10) = 8.097, p=0.02$) and misplacement ($F(1.34, 13.41)=45.392, p<0.001$) was found, as well as an interaction between group and misplacement ($F(1.34, 13.41) = 7.536, p = 0.01$). Follow-up t-tests help clarify these results, and can be understood by examining each step in isolation. The first step in our analysis process was to remap the item-location relations to quantify the misplacement accounted for by identity-location errors. This quantity is the sum of all of the misplacement accounted for by each identity-location error (Fig. 4 “Post-Remapped”) and, indeed, performing this procedure removes the majority of the difference in misplacement between the two groups (difference between means is 26.6 pixels; $t(9.33) = 2.59, p = 0.03$). This procedure also shows a significant difference in the magnitude of the reduction of overall misplacement between patients and comparison participants ($t(5.67) = 2.81, p = 0.04$) as would be expected given the relative magnitudes of the original misplacement. Note that the reduction in misplacement from remapping accounts for over 75% of the difference between the groups. In other words, the majority of the difference in performance between patients and comparison is due to identity-location errors. Regarding the transformation misplacement (Fig. 4 “Post-Transformed”), follow up t-tests confirmed both patients and comparison participants show a significant reduction in their misplacement via the transformation procedure ($t(3.82) = 4.18, p = 0.03$ and $t(13.41) = 2.36, p = 0.03$ respectively). However, the patients and comparison participants show no difference in the amount of misplacement accounted for by the global error amongst their items ($t(9.89) = 0.51, p = 0.62$). When the different transformation components (translation, scaling, and rotation; Fig 5c) are observed independently, we see that only rotation has a significantly different magnitude, with patients having larger magnitude rotation errors than comparisons ($t(9.18) = 2.72, p = 0.02$).

Once all global transformation procedures are performed, patients and comparisons still show differences in the remaining misplacement (difference between means is 33.0 pixels; $t(9.54) = 4.57, p = 0.001$). This misplacement is “local” misplacement, which is not shared by all items nor accounted for by identity-location errors. Note that because there is no significant difference between patients and comparisons in the amount of global misplacement error, the final difference between the groups is still significant.

First-Order and Higher-Order Relational Errors

When we evaluated the location placement accuracy of identities to their assigned locations, there were three primary first-order comparisons of interest. The first two comparisons addressed the question of whether patients could remember identity-location information as often as comparisons, evaluated by: 1) the number of correct placements and 2) the number of items placed in another item's location. The third comparison of interest addressed the question of whether the patients could remember just the location information as often as comparisons regardless of identity, which was evaluated by examining the number of items placed in any valid location (note that this is just the sum of 1 and 2). To examine group differences in these quantities (particularly 2 and 3), we performed a between groups repeated measure ANOVA on the identity-location errors (i.e. 2, above) and the total number of items placed in any valid location (i.e. 3, above, the sum of the identity-location errors

and the correctly placed items). We found a significant interaction of group and these two quantities ($F(1, 10) = 17.127, p=0.002$). Follow up Welch's t-tests showed that hippocampal patients made fewer accurate placements of the correct identity to the correct studied location (e.g., successful identity-location binding) than comparison participants ($t(5.21)=5.45, p=0.003$; Fig 6). Importantly, however, patients had more placements of items in another item's studied location (i.e. correct item-location relations with incorrect identity-location relation) than comparison participants ($t(5.06)=2.83, p=0.04$; Fig 6.), even after subtracting the global errors. When we looked at memory for locations (regardless of identity; i.e. items placed in any valid location), we found no significant difference between patients and comparisons ($t(4.71)=0.71, p=0.51$).

In regard to compound errors (i.e. swaps or cycles), we saw no difference between patients and comparison participants ($t(9.96)=0.39, p=0.71$ for swaps and $t(7.11)=1.75, p=0.12$ for cycles, respectively) despite large differences in individual identity-location assignment.

The fact that patients and healthy comparison participants had similar memory for locations (ignoring identity assignment) serves as the first piece of evidence suggesting the possibility that some shape-like information (albeit only in the form of a set of vertices) may be used by patients to reconstruct spatial location. In any case, it is clear that some aspects of relational information in the reconstruction (i.e. some combination of item-environment or item-item relations) was not impaired in hippocampal damaged patients.

Differences in Accuracy of Item-Location Associations across Set Sizes

As our previous work showed that patients committed relational memory errors even at very low item set sizes, it is useful to ask if, given our new framework for analyzing various types of relational information, we see the same pattern of impairment across all set sizes. We took advantage of our previous data set from Watson et al 2013 to determine if the number of studied items impacts the different types of spatial-relational errors discussed here. In a 2×4 ANOVA with factors group (patients and comparisons) and set size (2, 3, 4, 5), hippocampal patients showed no main effect of set size ($F(3,9) = 0.746, p = 0.552$) on accuracy of placing items in their target locations, placing roughly only a single item in its correct location (identity-location relation) regardless of set size (2 to 5). However, the main effect of set size was significant for comparisons ($F(2.64, 7.93) = 4.51, p = 0.04$). Importantly, as reported previously (Watson et al., 2013), only patients committed identity-location errors at small set sizes; comparisons did not. Furthermore, when considering performance at set size 5, in which both groups made identity-location errors, there were no significant group differences for other types of compound relational errors, namely swaps and cycles; swaps ($t(5.0) = 0.2597, p = 0.8055$) and cycles ($t(5) = 0.1800, p = 0.8642$). Taken together, these data show that across set sizes, patients show specific impairment to identity-location information without showing any significant compound relational error differences once the set size is sufficiently high for comparisons to begin making identity-location errors.

Discussion

The present study investigated the impact of hippocampal damage on various types of relations in a spatial memory task. While the role of hippocampus in spatial memory has an

extensive history (Hayes, Ryan, Schnyer, & Nadel, 2004; O'Keefe & Nadel, 1978; L. Ryan, Lin, Ketcham, & Nadel, 2009), the present data demonstrated that patients with hippocampal damage are not impaired relative to healthy comparison participants on *all types* of spatial errors; rather they demonstrate particular deficits in identity-location relational memory.

There are many reasons why identity-location relationships, specifically, might be impaired with hippocampal damage. Consider a case where a single item is presented in a bounded spatial environment. Only one type of relational information, namely the item-environment relations, is necessary to remember where that item belongs. Remembering the identity of that item is not necessary to complete the task. However, if a second item is added to the display, each item has an item-environment relationship, but also item-item relations and identity-location relations. It is, of course, not necessary to encode all three relation types to represent the display because some relations provide redundant information (i.e. the item-item relations contain information which is redundant with the item-environment relations). However, for an accurate representation, the identity-location relationship is not redundant with other types of relations and must always be considered. Identity-location relations are entirely arbitrary (in the SR task) and the critical component for successful memory performance; in line with previous theories of relational memory performance, arbitrary identity-location relationships are the type of relations that are most hippocampally dependent in this spatial memory task. As mentioned previously, it is important to note that item-item and item-environment information in this task and framework are not necessarily equivalent to seemingly similar relations in other domains (i.e. item-item where both are words or item-environment where it is the mapping of an object *including its identity* to a spatial location); this is due primarily to the specificity with which we have defined these terms (i.e. 'items,' in this case, have had their identity information removed and specifically reference spatial-only information).

The assertion that the *arbitrary* type of relational information in this task is the type showing impairment is consistent with previous findings showing that hippocampal function is related to memory for *arbitrary* relations between words (Giovanello et al., 2003), spatial locations in a scene (D. E. Hannula et al., 2006), temporal relations (Davachi & DuBrow, 2015), and even relations in abstract social space (Eichenbaum, 2015; Tavares et al., 2015). The data bear out this conclusion by showing that if we remove the identity information from the patient data, we see the difference between the groups in overall misplacement reduced by over 75%. Furthermore, when stripped of identity information, patients and healthy comparison participants do not differ on the number of correctly chosen locations. This shows that although patients show impaired memory for arbitrary relations in all stimulus domains, including spatial relations, they are not impaired on all *types* of spatial relations (i.e. they are able to reconstruct some item-environment and item-item relations). Patients with hippocampal damage show a deficit in reconstructing the *specific* item identity to its *specific* studied location.

The present data also demonstrated that hippocampal patients and comparison participants do not differ in compound spatial relational memory errors (e.g., translation, scaling, swapping, and cycles). And while rotation errors showed a statistical difference in magnitude between patients and comparison participants, the magnitude was quite small

(0.86 degrees), accounting for very little overall misplacement difference between the groups. Moreover, because the very first step in the analysis is to remove identity information, the total amount of possible rotation is artificially restricted to no more than the half of the maximum angle between two items from the rotation center, making it more complicated to interpret global error type than scaling and translation that have no such restrictions. It is, of course, possible that the significant difference in rotation errors is due to additional memory deficits. Unlike scaling and translation, in which pairwise spatial relations are invariant (i.e. if item A is above and to the right of item B and a translation or scaling transform is performed, item A will always still be above and to the right of item B), pairwise spatial relations are not invariant under rotation. This could point to further, more subtle deficits in particular types of relations, but further investigation into this error type is needed.

It is interesting to note that some misplacement remains as local, “noisy” misplacement after the removal of identity and global errors, and this local misplacement was significantly greater in patients than comparison participants. This is consistent with previous data in rodents with hippocampal lesions showing impaired precision of memory for spatial locations (Gilbert, Kesner, & DeCoteau, 1998) as well as other accounts of spatial navigation performance in humans such as the PBM (Yonelinas, 2013) which posits that the hippocampus is critical for “high-resolution” binding in space, predicting that hippocampal patients should have poorer spatial memory precision. These accounts may not generalize to all domains of information, however, as some evidence shows hippocampal damage relating to impairment in the quantity of information which can be remembered, rather than the quality (or precision) of the information when testing hippocampal patients on color information (Warren, Duff, Cohen, & Tranel, 2015).

In regard to compound relations involving identity-location information (e.g., swaps and cycles), it has been proposed previously that a lack of memory for identity-identity and identity-location relations in hippocampal patients may result in more identity-identity swapping (Watson et al., 2013). However, the present data demonstrated no group difference in swaps or cycles after accounting for overall location accuracy. The reason for this discrepancy is likely a combination of: 1) a difference in mathematical formulation of swapping (i.e. not using accuracy as a prerequisite for a successful swap results in an over estimate of the number of swaps) and 2) the inability of hippocampal patients to represent a sufficient amount of relational information to commit compound-relational error such swaps (which requires memory for two locations and their positions relative to one another and/or the environment but no information about item-location relations) more than by chance. Specifically, on the second point, if hippocampal patients are not maintaining identity-location information, their ability to have group-wise reassignment errors will be limited because they do not have specific knowledge of the constituents of the group. These compound swap/cycle errors do occur in both patients and controls (although patients uniquely commit them at very small set sizes), but once the set size is sufficiently high (i.e. once the comparison group actually makes identity-location errors) the groups do not differ in the frequency of their occurrence. Said differently, just as identity-location errors seem to account for a substantial proportion of patients' overall misplacement errors, the

disproportionate occurrence of swap and cycle errors at small set sizes in patients can also be attributed to their overall deficit in identity-location binding.

What causes this sudden increase in identity-location errors in comparison participants at higher set sizes? One possibility requires consideration of accurate identity-location placements in isolation of other metrics. Across all set sizes, hippocampal patients make approximately one accurate identity-location placement. This accuracy could be due, in part, to a maintenance of a single identity-location relation in working memory across the relatively short time span between study and test. Comparison participants, on the other hand, make accurate identity-location placements proportional to the set size.

When we consider how hippocampal patients may be able to maintain item-environment and item-item spatial relational information, it is interesting to consider alternate representations which may be able to maintain those relations. Previous work suggests that hippocampal damage may not impair shape information in SR task performance, as hippocampal patients may be able to represent shapes via an alternative, “unitized” representation, which can be formed via Gestalten perceptual features, i.e. configural features which constitute parts of a unified whole, rather than relations (Corsi, 1972; Kessels et al., 2000; Uttal & Chiong, 2004). The present data provide a suggestive look at this assertion from a purely vertex-oriented definition of shape, as the patients and comparisons did not differ in the number of locations (i.e. vertices) in which they accurately placed an item (independent of item identity), nor did they differ in the amount of global misplacement (i.e. misplacement that is systematically shared by all items) of the entire item set. This suggests that, at least in this highly restrictive definition of shape being defined via vertices, a similar amount of shape-like information is present in both comparison participants' and hippocampal patients' reconstructions. That said, using global misplacement transformations as a measure of shape is not necessarily the optimal method for investigating this issue, even with shape being defined solely via vertices. Topological Data Analysis techniques may prove to be a better analysis framework for determining the degree to which high-level relational information is preserved in a reconstruction (Carlsson, 2009; Ghrist, 2007). In Topological Data Analysis (TDA), large groups of vertex relations can be evaluated and compared directly with minimal assumptions by forming a more mathematically rigorous definition of the high-order structure of these relations. A similar technique to TDA has been used previously in spatial memory to analyze data from hippocampal damaged patients using a vMWM (Kolarik et al., 2016, 2017). It is unclear, however, if this technique scales well to a very small number of points, and, as such, these analyses are not included in this work; future investigations better suited to the technique should be considered.

There are alternate explanations for the ability to maintain item-environment and item-item spatial relations other than maintenance of shape-like information. It is possible individual relational information *is* being stored separately via a different brain region(s). For example, the parahippocampal place area has been shown to be involved in processing geometric information about scenes (Epstein, 2014), and the occipital place area has been related to processing of boundary relations between items and visible scene boundaries (Julian et al., 2016). If shape information were being used, regions such as the inferior temporal cortex could be involved in providing preprocessed representations of shape via shape selective

neurons identified in this region (Perrett & Oram, 1993). Alternatively, some heuristic approach to reconstruction could be used which takes advantage of hidden constraints in the task (i.e. it is unlikely for two items to appear on top of each other, which constrains the possible reconstructions). Should the hypothesis that shape-like information is being used to maintain these relations be investigated, different experimental paradigms could be used in which various levels of complexity of shape-like information are superimposed on a point set and presented to participants to be learned then reconstructed. In particular, edges between the locations could be drawn to avoid the need to infer some item-item relations which may contribute to a shape-like representation. We would predict that patients would perform similarly to comparisons for simple shapes and show deficits primarily in identity information for the vertices. Patients may also show performance deficits for more complex shapes, which are not as easily unitized (thus preventing a non-hippocampal representation from being as helpful).

Taken together, the evidence presented here defines the various *types* of relations present in a spatial-relational paradigm by applying a systematic framework that allows a more thorough investigation of the role of hippocampus in spatial-relational memory. Consistent with previous theories of the role of hippocampus in relational memory via the arbitrary binding of information (Cohen & Eichenbaum, 1993; Eichenbaum & Cohen, 2001), patients with hippocampal damage demonstrated specific deficits in arbitrary binding of identity-location relational information. Patients do not show a deficit in compound relational errors or location accuracy, suggesting that some types of relational information (in fact, the non-*arbitrary* relational information; i.e. information which has alternative derivations or redundancy) can be maintained by memory systems which are not hippocampally dependent. These results further clarify the role of the hippocampus in relational memory theory to be specifically in maintaining *arbitrary* relations, i.e. relations in which the constituent elements could have just as easily been anything. We have also proposed several possible alternate means through which other, non-arbitrary information may be maintained (such as a shape-like representation), which can be investigated in future research. We would predict, however, that because one benefit of representing arbitrary relations is in the ability to flexibly use those relations with changing task demands, whatever alternative means is being used to maintain these relations may not permit the same amount of flexibility.

SR tasks have proven enormously informative in that they provide sensitive measures of relational memory abilities that have been tied not only to hippocampal damage, but to more subtle hippocampally related measures such as subjective memory complaints (Lucas et al., 2016), spatial pattern separation (Clark et al., 2017), and medial temporal lobe viscoelasticity (Schwarb et al., 2017b, 2016). Precision and specificity of the metrics and the ability to distinguish between several different *types* of spatial relational errors will undoubtedly serve these lines of investigation well as it will allow a far more resolute picture of the specific impairments that may be tied to particular behavioral, functional, and structural phenotypes.

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Figure 1.

Magnetic resonance scans of hippocampal patients. Images are coronal slices through four points along the hippocampus from T1-weighted scans. Volume changes can be noted in the hippocampal region for patient 1846, and significant bilateral MTL damage including the hippocampus can be noted in patient 1951. A = anterior, P = posterior, NC = healthy comparison brain.

Figure 2.

A sample trial from the spatial reconstruction task; A, B, and C show different interpretations of the same reconstruction where the objects are in the reconstructed locations and the dots are the target locations from the study phase. (A) shows item-item and item-environment relations (dotted lines), which might be used to determine the locations of the dots. (B) shows reconstructed item to target location relations where gray shaded circles indicate a failure in placement of items to those locations (note that identity is ignored as, for example, the bus is not in its target location). (C) shows compound relations where some items roughly swap locations (although not necessarily precisely, in this case being a “partial swap”), some show cycle relationships (i.e. Bus Bed Bicycle Bus), and some show single-item placement in the correct target location.

Figure 3.

The analysis procedure as defined in the above sections. (A) shows the correct locations (dots with shadowed identities) and the reconstructed locations (items) along with shadowed dotted lines showing the original misplacement. Note that large amounts of misplacement error is accumulated via improper assignment of identities to locations. (B) shows the global remapping (dark dots are targets and light dots are reconstructed points) wherein identity is stripped away and a minimal one-to-one mapping is formed. (C) shows the global transformation (in this case a slight rotation and scaling error) where dark dots are targets, medium dots are reconstructed points, and light dots are post-transformation reconstructed points (i.e. points where the global error have been subtracted from the reconstructed points). (D) shows the binary accuracy evaluation on the post-transformed points (where the dark shaded circle signifies an inaccurate item). (E) shows the compound errors identified and labelled according to the previous steps (where shaded regions are considered “partial” groups where at least one item was inaccurately placed).

Figure 4.

Comparisons of Patient (HC) vs Comparison Participant (NC) groups for A) Misplacement Across Analysis Steps, i.e. misplacement magnitudes at each step of analysis and B) Reduction in Misplacement by High-Order Error Type, i.e. differences in misplacement accounted for by each step (i.e. the subtraction of A). For Patients, individual symbols are shown such that: Square is 1951, Triangle is 1846, and Circle is 2563.

Figure 5.

Comparisons of Patient (HC) vs Comparison Participant (NC) in the magnitude of the three types of global transformation error; A) the Translation magnitude, B) the Scaling magnitude (where 1 means no scaling, <1 means shrinking, and >1 means stretching), and C) the Rotation angle (in radians). For Patients, individual symbols are shown such that: Square is 1951, Triangle is 1846, and Circle is 2563.

Figure 6.

Comparisons of Patient (HC) vs Comparison Participant (NC) in the number of items in which itemlocation and identity-location was correct and incorrect. Note that items which were not placed in any studied location are collapsed together as 'Inaccurate Location'. For Patients, individual symbols are shown such that: Square is 1951, Triangle is 1846, and Circle is 2563.

Figure 7.

Comparisons of Patient (HC) vs Comparison Participant (NC) Item-location and identity-location accuracy across set sizes for patients vs comparisons. Note that items which were not placed in any studied location are collapsed together as 'Inaccurate Location'.

Table 1
Demographic, neuroanatomical, and neuropsychological characteristics of participants with hippocampal amnesia.

Demographics				NeuroAnatomy			Neuropsychological							
Sub.	Age	Edu.	Sex	Hand.	Etiology	Hipp.	Lesion	WAIS-III FSIQ	WMS-III GMI	WMS-III WMI	BNT	TT	CFT Copy	WCS Cat
1846	52	14	F	R	Anoxia	-4.23	Bilateral HC	84	57	85	43	41	28	6
2563	60	16	M	L	Anoxia	N/A	Bilateral HC	102	75	99	52	44	36	6
1951	63	16	M	R	HSE	-8.10	Bilateral HC + MTL	106	57	108	49	44	32	6
Mean	58	15	-	-	-	-	-	97	63	97	48	43	32	6

Hand. = Handedness. Ed. = years of education. HSE = Herpes Simplex Encephalitis. HC = hippocampus. + MTL = damage extending into the greater medial temporal lobes. HC Volume = hippocampal volumetric z-scores as measured through high resolution volumetric MRI and compared to a matched healthy comparison group (J. S. Allen, Tranel, Bruss, & Damasio, 2006; Buchanan, Tranel, & Adolphs, 2005). WAIS-III FSIQ = Wechsler Adult Intelligence Scale-III Full Scale Intelligence Quotient. WMS-III GMI = Wechsler Memory Scale-III General Memory Index. BNT = Boston Naming Test. TT = Token Test. CFT = Complex Figure Test; WCT = Wisconsin Card Sorting Task; Cat = Number of categories achieved out of six.