From Hippocampus to Whole-Brain: The Role of Integrative Processing in Episodic Memory Retrieval

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Abstract: Multivariate functional connectivity analyses of neuroimaging data have revealed the importance of complex, distributed interactions between disparate yet interdependent brain regions. Recent work has shown that topological properties of functional brain networks are associated with individual and group differences in cognitive performance, including in episodic memory. After constructing functional whole-brain networks derived from an event-related fMRI study of memory retrieval, we examined differences in functional brain network architecture between forgotten and remembered words. This study yielded three main findings. First, graph theory analyses showed that successfully remembering compared to forgetting was associated with significant changes in the connectivity profile of the left hippocampus and a corresponding increase in efficient communication with the rest of the brain. Second, bivariate functional connectivity analyses indicated stronger interactions between the left hippocampus and a retrieval assembly for remembered versus forgotten items. This assembly included the left precuneus, left caudate, bilateral supramarginal gyrus, and the bilateral dorsolateral superior frontal gyrus. Integrative properties of the retrieval assembly were greater for remembered than forgotten items. Third, whole-brain modularity analyses revealed that successful memory retrieval was marginally significantly associated with a less segregated modular architecture in the network. The magnitude of the decreases in modularity between remembered and forgotten conditions was related to memory performance. These findings indicate that increases in integrative properties at the nodal, retrieval assembly, and whole-brain topological levels facilitate memory retrieval, while also underscoring the potential of multivariate brain connectivity approaches for providing valuable new insights into the neural bases of memory processes. *Hum Brain Mapp 38:2242–2259, 2017.* © 2017 Wiley Periodicals, Inc.

Key words: functional magnetic resonance imaging; graph theory; recall; medial temporal lobes; modularity

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INTRODUCTION

The human brain is a large-scale complex system comprised of diverse yet interconnected brain regions [Bullmore and Sporns, 2009]. Most existing neuroimaging research investigating the neural bases of cognitive processes has focused on the localization of specific functions using univariate activation methodologies. For example, consistently observed increases in hippocampal activity

during memory retrieval tasks for remembered versus forgotten items suggest that the hippocampus is critical for successful episodic memory retrieval [Kim, 2010, 2013; Rugg and Vilburg, 2013; Spaniol et al., 2009]. This corpus of work has focused on identifying particular brain regions thought to be involved in certain cognitive processes. However, individual regions, such as the hippocampus, can only support episodic memory by dynamically interacting with other diverse and spatially distributed brain regions [Geib et al., 2015; Jeong et al., 2015; Mišić et al., 2014; Watrous and Ekstrom, 2015]. In this study, we used graph theory measures to investigate how complex patterns of functional interactions at different topological levels underlie episodic memory retrieval for words.

Graph theory provides a particularly powerful framework for characterizing brain networks derived from functional neuroimaging data [Bullmore and Sporns, 2009; Rubinov and Sporns, 2010]. Using the mathematical formalisms of graph theory, networks of brain regions can be represented as graphs consisting of a set of nodes with the pairwise relationships between them, known as edges. In functional neuroimaging analyses, each node represents a discrete brain region, and the edges represent the measured functional connectivity between pairs of nodes.

There is general agreement that healthy and effective brain network architectures require both segregated and integrative processing [Bassett and Bullmore, 2006; Bressler and Menon, 2010; Medaglia et al., 2015; Sporns, 2013; Tononi et al., 1994]. Segregation refers to specialized processing within an individual brain region [Tononi et al., 1994] or within a small subset of tightly interconnected regions [Bullmore and Sporns, 2009]. In contrast, integration refers to the assimilation and transfer of information between specialized, spatially distributed brain regions [Rubinov and Sporns, 2010; Sporns, 2013]. In this article, we focus on the importance of integrative properties in functional brain networks during episodic memory retrieval.

Most graph theory analyses of functional neuroimaging data have investigated network topology during resting state [e.g., Buckner et al., 2009; Hayasaka and Laurienti, 2010; He et al., 2009; Moussa et al., 2012; Stevens et al., 2012; van den Heuvel et al., 2009], with relatively few studies having investigated alterations in network topology during cognitive tasks. Among the studies that have linked graph theory measures to cognitive performance on a task [e.g., Bassett et al., 2011; Braun et al., 2015; Cao et al., 2014; Meunier et al., 2014; Moussa et al., 2011, 2014; Stanley et al., 2014, 2015], only three have investigated patterns of functional network topology subserving episodic memory [Geib et al., 2015; King et al., 2015; Schedlbauer et al., 2014]. In particular, Schedlbauer et al. [2014] showed that a substantial proportion of the shortest topological paths between disparate brain regions pass through the hippocampus to support successful memory retrieval. King et al. [2015] showed that a subset of brain regions—a

priori identified from previous activation analyses as being involved in memory retrieval—become more strongly connected with one another to support successful remembering and that the strength of these connections is related to recollection accuracy. Lastly, Geib et al. [2015] showed that the hippocampus, embedded within the whole-brain network, reorganized its set of functional connections, displayed greater communication efficiency with the rest of the brain, and became a more convergent structure for information integration supporting vivid, compared to dim, retrieval of visual scenes. All of these studies underscore the importance of integrative processing for successful memory retrieval, expanding beyond prior emphasis on segregated processing.

To support episodic memory retrieval, recent work has shown that the hippocampus participates in more efficient communication with many other brain regions and serves as the critical integrative structure for the convergence and joint processing of information [Battaglia et al., 2011; Geib et al., 2015; Mišić et al., 2014; Watrous and Ekstrom, 2015]. However, this prior work has largely focused on the role of an individual node (i.e., the hippocampus) embedded within a larger network. This study builds on this prior work by characterizing network architecture at three different organizational levels: a nodal level, a subnetwork or retrieval assembly level, and the whole-brain network level. We maintain that the hippocampus serves as a critical integrative structure for successful memory retrieval, but we also suggest that the functional interactions of the hippocampus with a retrieval assembly facilitates efficient integrative processing and successful memory retrieval. We define a retrieval assembly as a subset of network nodes that become more strongly connected with the hippocampus during remembered trials compared with forgotten trials. Furthermore, prior work has also suggested that the extent to which the functional network as a whole exhibits certain integrative properties facilitates successful memory retrieval [Geib et al., 2015].

Specifically, we made three primary hypotheses in this study. First, extending prior work investigating topological properties of the hippocampus embedded within the entire functional brain network [Geib et al., 2015; Schedlbauer et al. 2014], we hypothesized that the hippocampus would exhibit an increase in its role in integrative processing (i.e., more efficient communication with the rest of the brain) for remembered versus forgotten items.

Second, we hypothesized that successfully remembering compared to forgetting items would be associated with stronger connectivity between the hippocampus and a subset of regions involved in memory retrieval, subsequently identified as a "retrieval assembly." More specifically, we hypothesized that certain subregions within the prefrontal cortex (PFC) and the ventral parietal cortex (VPC) would serve as nodes in this retrieval assembly. We do not include a manipulation to assess the expected contributions of these regions to memory retrieval; their

hypothesized roles in the retrieval assembly are based upon previous findings on similar kinds of memory retrieval tasks. The PFC is thought to support retrieval control processes, such as retrieval search and monitoring [Anderson et al., 2015; Preston and Eichenbaum, 2013; Wagner et al., 2005], and the VPC is thought to mediate attentional processes involved in memory retrieval [Cabeza et al., 2008; Ciaramelli et al., 2008]. There is also mounting evidence from bivariate functional connectivity analyses indicating that both PFC [Blumenfeld and Ranganath, 2007; Preston and Eichenbaum, 2013] and VPC [King et al., 2015; Robin et al., 2015] are functionally connected to the hippocampus during episodic retrieval. Additionally, we hypothesized that this retrieval assembly would exhibit increased integration with the rest of the brain for remembered compared with forgotten items.

Third, extending prior work showing that increased overall whole-brain integrative processing is closely related to cognitive performance [Cao et al., 2014; Geib et al., 2015; Meunier et al., 2014; Stanley et al., 2014, 2015; Stevens et al., 2012; van den Heuvel et al., 2009), we hypothesized that successful memory retrieval would be associated with a more globally integrated (and less segregated) network architecture across the entire brain. To address this question, we implemented data-driven modularity algorithms to assess the relative balance between segregated and integrative network architectures in remembered and forgotten episodic memory retrieval networks.

METHODS

Participants

Nineteen right-handed healthy young adult participants (mean age = 22.29 years, SD = 3.20, age range = [18, 30], 7 female, 12 male) completed the experiment. Participants with a history of neurological difficulties or psychiatric illness, alcoholism, drug abuse, or learning disabilities were excluded from the study. Due to technical problems during data acquisition, two subjects were excluded from the analyses: one lacked functional data, and the other lacked behavioral data. All analyses were performed on the remaining 17 participants. Written informed consent was obtained from each participant in accordance with a protocol approved by the Duke University Institutional Review Board. All participants were monetarily compensated for their time.

Experimental Design

Three-hundred sixty concrete nouns were chosen from the MRC Psycholinguistic Database (http://www.psy.uwa.edu.au/MRCDataBase/uwa_mrc.htm) and used as stimuli. During the encoding task, a total of 240 words was presented, equally divided across 4 functional runs.

Each run included five on-blocks (task being performed, 60 s each) and 6 off-blocks (rest, 15 s each). During each on-block, participants were presented with 12 words serially, for a duration of 2 s each. During the first two encoding runs, the participants were asked to make an animacy decision for each word (i.e., living/nonliving). Each word was presented in the center of the screen, and the living/nonliving choice was symmetrically placed to the left and right below each word. During the last two encoding runs of the four, participants were asked to read and remember each word and press the button corresponding to the location of the word "press" after they had completed reading the word. Again, the stimulus word was presented in the center of the screen and the two options for responding at the bottom of the screen ("press" and "xxxxx") were evenly spaced below each word. Button responses and response times were recorded using a magnetically shielded 4-button box held in the participant's right hand. Stimuli were separated with a jittered inter-stimulus-interval (ISI), which ranged from 1 to 4 s to facilitate deconvolution and extraction of the hemodynamic response. Off-block stimuli consisted of a continuously presented crosshair figure at fixation, which was also used for memory-task on-block ISI periods.

The encoding runs were followed by 20 min of anatomical and DTI scanning. Participants then completed a recognition test in the scanner. Across six retrieval runs, participants were presented with each of the 240 words that had been presented during encoding along with 120 new words. Word duration, ISI distribution, block length, and block order mirrored that of encoding. In response to each presented word, participants were asked to make an old/new judgment and indicate their confidence in that judgment (definitely old, probably old, probably new, definitely new). Again, words were presented one at a time in the center of a computer screen. The old/new confidence judgment was displayed below each word, and participants pressed a corresponding key to indicate whether the word was definitely old, probably old, probably new, or definitely new. This study was based on retrieval trials for the encoding trials for which they were explicitly told to remember the word (i.e., runs 3 and 4).

Data Acquisition and Preprocessing

Imaging data were collected on a 3T GE scanner. Following a localizer scan, functional images were acquired using a SENSE spiral-in sequence (TR = 2000 ms, TE = 27 ms, FOV = 24 cm, 34 oblique slices with voxel dimensions of 3.75 × 3.75 × 3.8 mm). Stimuli were projected onto a mirror at the back of the scanner bore, and responses were recorded using a 4-button fiber optic response box. Scanner noise was reduced with ear plugs and head motion was minimized with foam pads. A high-resolution anatomical image (96 axial slices parallel to the AC-PC plane

with voxel dimensions of 0.9 × 0.9 × 1.9 mm) was collected following the functional scanning.

Following acquisition, each participant's volumes were slice-time corrected, realigned to the first volume, and normalized to a standard EPI template in SPM8. Single-trial beta estimates of the event-related hemodynamic responses were computed using a method recently developed by Mumford et al. [2012] that better represents true activation magnitudes in fast event-related designs. This method estimates a first-level model for every trial such that the trial of interest serves as one regressor and all other trials serve as another regressor. Single-trial estimates also included six motion regressors (x-dim, y-dim, z-dim, roll, pitch, and yaw) in addition to block-wise run regressors. Following single-trial estimation, each voxel's time series was winsorized at three standard deviations above and below the mean. Overall translational movement (Euclidian distance from the origin) was minimal $M = 0.31$ (SD = 0.16 mm). Additionally, only 5% of the volumes had motion exceeding 1 mm and <1% of the volumes had motion exceeding 2 mm. Therefore, the effects of motion were negligible.

Generating Whole Brain Networks

To create episodic retrieval networks, we used a beta time-series analysis, which assumes that two regions are functionally coupled during a task if their activity is significantly correlated across trials [Fornito et al., 2011; Rissman et al., 2004; Schedlbauer et al., 2014]. Each beta value reflected the magnitude of the hemodynamic response evoked by a particular trial during the retrieval phase of the procedure. These observed beta values were then sorted for each individual participant separately in accordance with memory performance during the corresponding trial during the retrieval phase of the experiment. "Definitely old" responses to old items constituted the remembered-trial category. "Probably new" and "definitely new" responses to old items were used together to constitute the forgotten-trial category. "Probably old" responses were not included in order maximize the memory signal and to ensure that the number of remembered-trials was not significantly different from the number of forgotten-trials ($t(16) = -1.56, P > 0.10$). We focused on high-confidence hits and compared to misses to emphasize the contributions of the hippocampus in memory retrieval for the following reasons: (1) hippocampal activity is greater for definitely old than probably old, (2) only high-confidence responses activate the hippocampus, and (3) correct rejections elicit novelty-related activity in the hippocampus thereby subtracting out recollection-related activity [e.g., Daselaar et al., 2006]. Additionally, networks constructed using beta-series connectivity have been shown to have the advantage of being more sensitive to variability in the shape of hemodynamic response compared with psychophysiological-interaction analyses [Cisler et al.,

2014]; this advantage is particularly important for whole-brain connectivity analyses [Handwerker et al., 2004].

To measure functional connectivity between all regions simultaneously, the brain was first parcellated into 90 discrete anatomical regions of interest defined in accordance with the automated anatomical labeling (AAL) atlas (45 ROIs in each hemisphere with the exclusion of all cerebellar nodes) [Tzourio-Mazoyer et al., 2002]. This AAL template has been the most widely used nodal partitioning scheme in functional brain network analyses [Stanley et al., 2013], and it parcellates the cortex and subcortical structures by identifying gyral and sulcal boundaries. However, it is important to note that many other nodal partitioning schemes have been used in the literature, and the best possible method for defining nodes remains an open question [Stanley et al., 2013]. Each anatomical ROI from the atlas served as a network node. Pairwise Pearson correlations between regional mean beta series were computed to generate {90 × 90} functional connectivity matrices, with the correlation coefficients representing the strength in connectivity between any two nodes. These {90 × 90} cross-correlation matrices (i.e., adjacency matrices) serve as the fundamental starting point for any graph theoretic analysis of neuroimaging data. In this study, the adjacency matrices were not thresholded (i.e., weak connections were not removed), and each matrix constituted an undirected, weighted graph. Two separate whole-brain functional networks were created for each individual participant: a forgotten network constructed using the concatenated beta values from forgotten-trial category and a remembered network constructed using the concatenated beta values from the remembered-trial category. For display purposes, Figure 1 depicts remembered and forgotten adjacency matrices extracted from this approach, averaged across all participants.

Graph Theory Measures

Global efficiency

Global efficiency is a measure of the capacity for efficient information transfer throughout the entirety of a network. It is closely related to another widely used graph metric—path length. When computed for an individual node in the network, path length is defined as the average shortest distance between that node i and all other nodes in the network. In weighted functional brain networks, connections with higher correlation strengths are considered to be closer together, whereas nodes with lower correlation strengths are considered to be further apart. A node's global efficiency is defined as the average of the inverse characteristic path length between that node and all other nodes in the network [Rubinov and Sporns, 2010], such that higher global efficiency corresponds to shorter path lengths. In the formulation given below, d_{ij}^w represents the distance between two nodes in the network after taking into account the strength of each connection. The network-wide global efficiency is computed as an average of all nodal-wise global efficiency values.
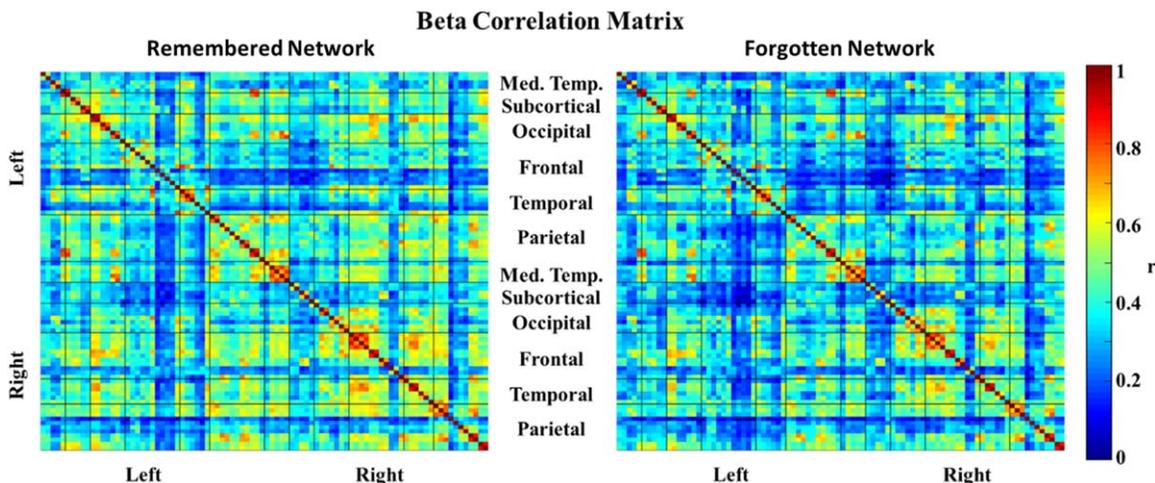
Figure 1.

Average (across participants) adjacency matrices derived from beta series correlations are represented for remembered and forgotten networks and split by hemisphere (right and left). For ease of visualization, regions of interest are sorted in accordance with the procedure implemented by Salvador et al. [2005]. [Color figure can be viewed at wileyonlinelibrary.com]

$$E^{\mathrm{w}} = \frac{1}{n} \sum_{i \in N} \frac{\sum_{j \in N, j \neq i} \left(d_{ij}^{\mathrm{w}} \right)^{-1}}{n-1}$$

Negative connections were not included in the global efficiency analyses (for reasons noted in Telesford et al. [2011] and Cao et al. [2014]). It is important to note that we are not using the term "distance" in a Euclidian sense. Distance here is a measure of how easily information may get from one node to another. Given this particular interpretation, using correlation strength as a measure of distance is reasonable, because information is more likely to travel (with less added noise) between two nodes that are strongly correlated.

Degree centrality

Degree centrality indexes the overall strength of a given node's connections by summing the weights of all its connections [Bullmore and Sporns, 2009]. Nodes with high degree centrality tend to directly interact with many other nodes in the network and are likely to play an important role in the flow of information throughout the network. To better compare results between global efficiency and degree centrality, only positive connections were included in the calculation of degree centrality for each network node. However, for all other computations, negative connections were retained in the functional brain networks.

Nodal change score

Nodal change scores [Geib et al., 2015] index the extent to which a node's graph theory metric changes relative to other nodes in the network and are computed by z-scoring graph theory measures within subjects and then subsequently computing the normalized difference between remembered and forgotten networks. This procedure was implemented for global efficiency and degree centrality. A large nodal change score indicates that a node has become more central to the network between conditions independently of large-scale network changes.

First step reorganization (FSR)

Metrics such as global efficiency and degree centrality assess a node's capacity for information transfer, but they do not provide information about the extent to which a node reorganizes its set of direct connections. Observed differences in nodal network properties (e.g., global efficiency) can only be explained by appealing to two factors: (1) a reorganization of first step (direct) functional connections and/or (2) a reorganization of indirect functional connections (beyond first step) that influence the value of the graph metric computed for the node of interest. FSR [Geib et al., 2015] can be used to partially disambiguate the extent to which direct versus indirect functional connections contribute to observed differences in graph theory metrics across conditions by determining whether direct (first step) functional connections significantly change between conditions (e.g., remembered and forgotten retrieval networks). More specifically, FSR is a network-normalized, negative, Fisher-transformed correlation computed between two columns of an adjacency matrix. Mathematically, FSR is computed as follows:

$$\mathrm{FSR}^{\mathrm{w}} = z\mathrm{score} \left\{ -\mathrm{arctanh} \left(\frac{Cov(A_i, B_i)}{\sigma_{A_i} \sigma_{B_i}} \right) \right\}$$

where A_i is the connectivity profile of node i in network A, B_i is the connectivity profile of node i in network B,

and the connectivity profile of node i is defined as its distinct set of weighted connections (i.e., the column in the adjacency matrix representing that particular node's connections with all other nodes in the network). Due to the normalization procedure (z-score), the FSR_i^w value obtained for a given node is always relative to those FSR values obtained for the other nodes in the network. Traditional parametric statistics can then be applied at the group level in order to identify nodes that consistently exhibit a reorganization of direct connections across participants.

Modularity (Q)

Modularity is computed using an optimization algorithm that identifies subsets of nodes that are more densely interconnected among themselves than with other nodes in the network [Blondel et al., 2008; Newman, 2006; Newman and Girvan, 2004]. The extent to which the network can be subdivided into nonoverlapping modules is quantified by the modularity Q statistic. Networks that can be clearly divided into nonoverlapping modules, or functional communities, have larger Q values and are considered less integrated (i.e., more segregated) with the rest of the functional brain network. In contrast, networks that are not so clearly divided into distinctive functional communities have smaller Q values and are considered more integrated with the rest of the functional brain network. The modularity value assigned to a given partition of the entire functional brain network is:

$$Q = \sum_{i=1}^{k} \left[\frac{e_{ij}}{M} - \left(\frac{a_i}{M} \right)^2 \right]$$

where $e_{i,j}$ is a measure of within module connections in module i, a_i is the total degree (summed strength of all connections that a node has) of module i, and M is equal to the degree of the entire network. Modularity algorithms are designed to maximize the value of Q, by separating the network into nonoverlapping subsets of nodes that maximize within-module connectivity and minimize between-module connectivity. In the current study, in order to find the maximal value of Q, the weighted undirected Louvain algorithm was run 10 times on each individual subject's remembered and forgotten network [Blondel et al., 2008].

In contrast, a node's modular assignment was determined by running the Louvain algorithm 1,000 times on the averaged (across participants) remembered network. The averaged remembered network was used, as opposed to a general retrieval network that includes both remembered and forgotten trials, because the condition of interest is successful memory retrieval as opposed to a more general retrieval processing mode. The resulting 1,000 partitions were then divided into two groups based upon the number of modules discovered (i.e., networks with 5 modules and networks with 4 modules). These groups were

then separately analyzed using the Jaccard Index (JI) to determine to the consistency of the module assignments across different iterations of the algorithm. The most consistently identified modular partition and the Q value itself were both considered in order to identify the best partition for further analyses.

Participation coefficient (PC)

The positive PC measures the proportion of connections a node has within its own module versus other modules in the network [Guimerà and Nunes Amaral, 2005]. Nodes with higher PCs are more strongly connected to nodes in other modules in the network, thereby facilitating communication between functional communities; in contrast, nodes with lower PCs are predominantly connected to nodes within the module to which they were assigned. Formally, a node's PC is defined as:

$$1 - \sum_{m \in M} \left(\frac{k_i^w(m)}{k_i^w} \right)^2$$

where M is the set of modules, and k_i^w is the weighted number of links between node i and all the other nodes in module m. The PC is computed independently for positive and negative connections, and we only report results from the positive PC. After we first identified the best modular partition using the averaged (across participants) remembered network, we then used that modular partition as a fixed template when computing PCs within each individual participant's functional brain networks.

Retrieval Assembly Construction

To further investigate changes in graph theory metrics computed for the hippocampus, we identified a **retrieval assembly** defined as a set of regions (i.e., nodes) whose bivariate connectivity with the hippocampus was stronger during remembered than forgotten trials. These retrieval assembly nodes were identified by finding regions with a significant within-subject change in connectivity strength (t-test, alpha = 0.01, one-tailed, unc.) with the hippocampus. We intentionally used a relatively liberal, fixed alpha level, because these analyses were exploratory in nature. Additionally, compared to the remembered network and the forgotten network, which were constructed for each individual participant and comprised all nodes in the 90-node AAL atlas in addition to all of their pairwise connections, the retrieval assembly is only comprised of the subset of those 90 nodes that alter their connectivity with the hippocampus between remembered and forgotten conditions. Consequently, there is only one retrieval assembly, because the assembly represents the subset of nodes with connections that change between remembered and forgotten conditions.

Statistical Testing of Graph Theory Measures

We used the permutation framework developed by Simpson et al. [2013] in conjunction with the Jaccardized Czekanowski Index [Schubert, 2013; Schubert and Telcs, 2014] to assess significance for potential differences in each graph theory measure between remembered and forgotten memory retrieval conditions. This framework is based on the JI, which computes a ratio between two discrete data sets based upon the size of the intersection and union between those two sets. The permutation framework developed by Simpson et al. [2013] can accommodate continuous values (numeric values) and utilizes a permutation procedure to access significance. This permutation framework is non-parametric, and we report median values and interquartile ranges (IQR) for global efficiency, degree centrality, modularity (Q), and PC. Violin plots were used to visualize these distributions mapped on top of box plots. For all box plots the middle band represents the median, the top of the box the 75th percentile, the bottom of the box the 25th percentile, and whiskers extend to an additional 1.5*IQR.

RESULTS

Behavioral Results

Indicative of accurate memory performance, there was a significant difference between the accuracy of high-confidence correctly recognized items and false alarms ($t(32) = 10.7$, $P < 0.0001$), as well as between all correctly recalled items and false alarms ($t(32) = 9.9$, $P < 0.0001$). Memory strength (d') across all correctly recalled items and false alarms was $M = 1.0$ (SD = 0.5). A summary of behavioral results is provided in Table I.

Network Results

Hippocampal integration is greater for remembered than forgotten items

Our first hypothesis was that the hippocampus would show an increase in its capacity for efficient integration with the rest of the network for remembered compared with forgotten items. Consistent with our first hypothesis, there was a significant increase in global efficiency ($P = 0.02$) and degree centrality ($P = 0.04$) for the left hippocampus from forgotten to remembered retrieval networks, as revealed by the permutation procedure developed by Simpson et al. [2013] in conjunction with the Jaccardized Czekanowski Index. Only the global efficiency result remained significant after Bonferroni correction for running tests on both the left and right hippocampus. In contrast, no significant differences in global efficiency or degree centrality were identified for the right hippocampus (both P's > 0.10; Fig. 2).

TABLE I. Provides a summary of the behavioral results

	New Items [Mean (SD)]		Old Items [Mean (SD)]	
	False Alarm	Correct Rejection	Miss	Hit
High Confidence	27% (15)	73% (15)	19% (14)	81% (14)
Low Confidence	30% (10)	70% (10)	57% (13)	43% (13)
All Trials	28% (12)	72% (10)	35% (12)	65% (12)

Only high-confidence hits were included in the remembered network, whereas both high- and low-confidence misses were included in the forgotten network. The forgotten and remembered networks were comprised of a similar number of total trials, on average (mean remembered = 54 (SD = 21, range = [25, 94]) trials, mean forgotten = 41 (SD = 15, range = [16, 68]). There was not a significantly different number of total trials ($t(16) = 1.56$, $P > 0.10$)

Even though stark shifts in nodal network properties can only be explained by appealing to the entire network architecture, these shifts occur because of (1) the reorganization of connectivity strengths for the set of first step (i.e., direct) connections and/or (2) the reorganization of connectivity patterns beyond first-step connections (i.e., indirect connections). The FSR analysis was used to clarify the extent to which direct changes in functional connectivity contribute to the observed changes in global efficiency for the left hippocampus. FSR was significant for the left hippocampus (FSR = 0.63, $t(16) = 2.37$, $P = 0.03$), indicating that the left hippocampus significantly reorganized its set of direct connections between remembered and forgotten conditions.

To test the specificity of the identified increases in global efficiency and degree centrality for the left hippocampus for remembered minus forgotten networks, nodal change scores for global efficiency and degree centrality were also computed. The magnitude of the nodal change score for global efficiency was higher than any other node in the network (rank = #1, $t(16) = 2.18$, $P = 0.04$) whereas the nodal change score for degree centrality was in the top 5% relative to all other nodes in the network (rank = #4, $t(16) = 1.88$, $P = 0.08$).

Low-confidence remembered responses were not included in the remembered networks for all analyses up to this point, because the hippocampus has been shown to be less sensitive to low-confidence responses [Kim, 2010]. To ensure that confidence was not confounding our results, high- and low-confidence networks were constructed from all retrieval responses, and left-hippocampal graph theory measures were computed. Global efficiency and degree centrality for the left hippocampus were not significantly different between the low- and high-confidence networks (both P's > 0.30), as assessed using the permutation procedure developed by Simpson et al. [2013] in conjunction with the Jaccardized Czekanowski Index, suggesting that confidence does not drive graph metric differences
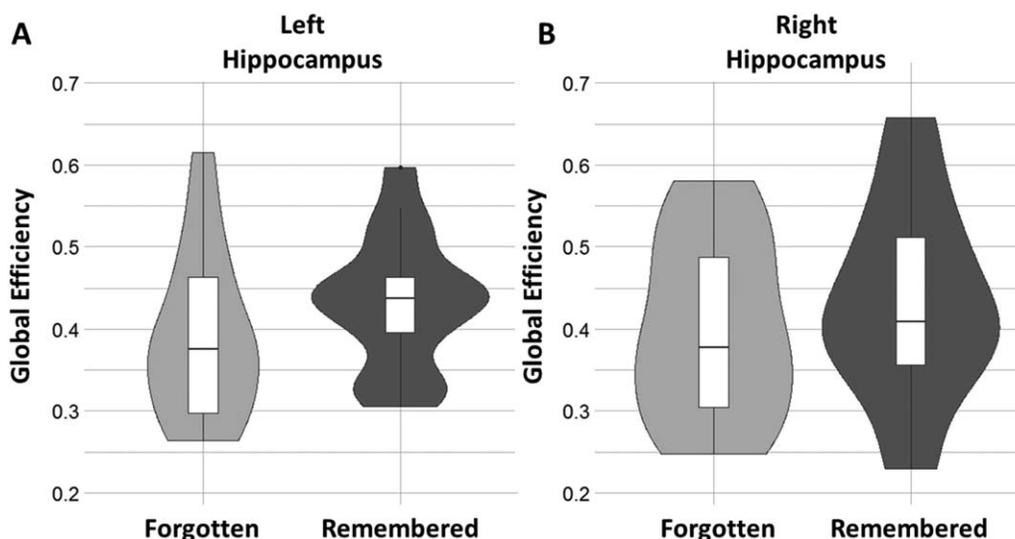
Figure 2.

Global efficiency of the left and right hippocampus for remembered and forgotten trials, respectively. The permutation framework developed by Simpson et al. [2013] in conjunction with the Jaccardized Czekanowski Index revealed that left hippocampal global efficiency was greater in the remembered than the forgotten condition ($P = 0.02$), while the right hippocampus did not reach significance ($P > 0.10$).

obtained for the hippocampus between our networks of interest.

Successful memory is supported by a hippocampal retrieval assembly

Our second hypothesis was that successful memory retrieval would be associated with stronger connectivity between the hippocampus and a subset of nodes comprising a "retrieval assembly." To investigate this hypothesis, we identified a group of regions whose bivariate (i.e., direct) functional connectivity with the left hippocampus increased from forgotten to remembered items (Fig. 3). A total of 12 brain regions showed an increase (within participants) in bivariate connectivity with the left hippocampus (t-test, $P < 0.01$, one-sided, unc.) from forgotten to remembered retrieval networks (Table II). No node showed a decrease in connectivity with the left hippocampus from forgotten to remembered retrieval networks in accordance with our set alpha level (t-test, $P < 0.01$, one-sided, unc.). The 12 regions identified as members of the assembly included the bilateral dorsal superior frontal gyrus, left middle frontal gyrus, left caudate, bilateral supramarginal gyrus, left precuneus, bilateral postcentral gyrus, right precentral gyrus, right inferior temporal gyrus, and right middle occipital gyrus.

Subsequent analyses using the permutation procedure developed by Simpson et al. [2013] in conjunction with the Jaccardized Czekanowski Index revealed that, on average, global efficiency and degree centrality were higher for

nodes in the retrieval assembly for remembered compared to forgotten networks (global efficiency: $P = 0.03$; degree centrality: $P = 0.03$; Fig. 4a). This was the case regardless of whether or not the left hippocampus was included as part of the assembly. To ensure that our finding was unique to nodes in the retrieval assembly, 1,000 random subsets of 13 network nodes were selected from the observed networks, and the average global efficiency of each randomly selected subset of 13 nodes was computed. The retrieval assembly we identified did in fact exhibit a greater magnitude change in global efficiency between remembered and forgotten networks than any other randomly selected subset of 13 network nodes. This same procedure was implemented for degree centrality, but the observed change in degree centrality was not among the largest changes in the network (rank 498 out of 1000). While there was a significant increase in degree centrality for the retrieval assembly as a whole between remembered and forgotten networks, there were also similar magnitude increases in degree centrality among many other subsets of nodes in the network. Table III summarizes the global efficiency and degree centrality values obtained for each node in the retrieval assembly in both remembered and forgotten retrieval networks taken separately. Importantly, while it is possible that the observed increase in global efficiency or degree centrality for the retrieval assembly was driven by increased bivariate functional connectivity to the left hippocampus, such a finding would still underscore the importance of the left hippocampus in facilitating integrative processing via the assembly.
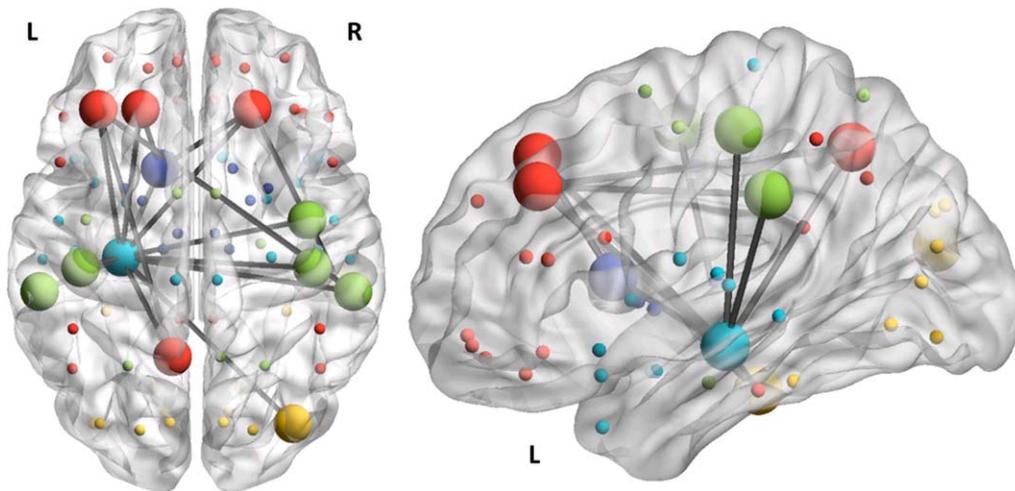
Figure 3.

Figure 3 provides an overview of the retrieval assembly and modular nodal assignments. All nodes in the assembly (depicted as the large nodes in the figure) showed significantly greater connectivity strength with the left hippocampus for remembered as compared to forgotten items (significant connections are depicted as dark lines; see **Table II** for further details). Significant connections within the assembly were determined by setting alpha to 0.01 (*t*-test, one-tailed, unc.) and removing deviant connection values (SD > 3.5). Five different functional communities (i.e., modules) were identified from the modularity analysis: occipital/temporal (yellow), fronto-parietal (red), parietal (green), medial temporal (light blue), and subcortical (dark blue). Note that the nodes comprising the retrieval assembly spanned all identified modules. [Color figure can be viewed at wileyonlinelibrary.com]

Successful retrieval is associated with an increase in integration across the whole brain

Our third hypothesis was that successful memory retrieval would be associated with increased integration (and a less segregated network architecture) across the entire functional brain network. To investigate this hypothesis, we computed modularity Q values for individual participants' brain networks. Q values represent the extent to which each network can be partitioned into densely interconnected communities of functionally cooperating brain regions. Although it did not reach the threshold of significance, these modularity analyses revealed that the whole-brain network was somewhat more integrated (i.e., had smaller Q values) during remembered (Median = 0.11, IQR = 0.05) than forgotten trials (Median = 0.13, IQR = 0.08, $P = 0.07$), as assessed using the permutation procedure developed by Simpson et al. [2013] in conjunction with the Jaccardized Czekanowski Index (Fig. 5a). While this difference in modularity did not reach significance, a subsequent individual-differences analysis revealed that the difference in the modularity Q statistic (remembered network Q minus forgotten network Q) was significantly and negatively related to memory performance assessed with d' ($r(15) = -0.72$, $P = 0.001$; Fig. 5b). Additionally, larger whole-brain modularity Q values in the forgotten networks were significantly related to better

TABLE II. Changes in hippocampal connectivity with nodes comprising the retrieval assembly

	ΔL. Hc Connectivity	
	Mean (SD)	*P*-value
L-CAU	0.14 (0.15)	0.0009
L-MFG	0.14 (0.17)	0.0021
L-SFGdor	0.16 (0.22)	0.0036
R-SFGdor	0.20 (0.21)	0.0007
R-MOG	0.15 (0.20)	0.0027
L-PostCG	0.12 (0.16)	0.0052
R-PostCG	0.12 (0.15)	0.0017
R-PreCG	0.11 (0.14)	0.0024
L-pCUN	0.12 (0.17)	0.0055
L-SMG	0.16 (0.25)	0.0094
R-SMG	0.15 (0.20)	0.0034
L-ITG	0.15 (0.22)	0.0085

Nodes included in the assembly exhibited a significant increase in connectivity with the left hippocampus from forgotten to remembered retrieval networks (*t*-test, $P < 0.01$, one-sided, unc.). [Legend: L-CAU (left caudate), L-MFG (left middle frontal gyrus), L-SFGdor (left dorsal superior frontal gyrus), R-SFGdor (right dorsal superior frontal gyrus), R-MOG (right middle occipital gyrus), L-PostCG (left post-central gyrus), R-PostCG (right post-central gyrus), R-PreCG (right pre-central gyrus), L-pCUN (left precuneus), L-SMG (left supramarginal gyrus), R-SMG (right supramarginal gyrus), L-ITG (left inferior temporal gyrus)].
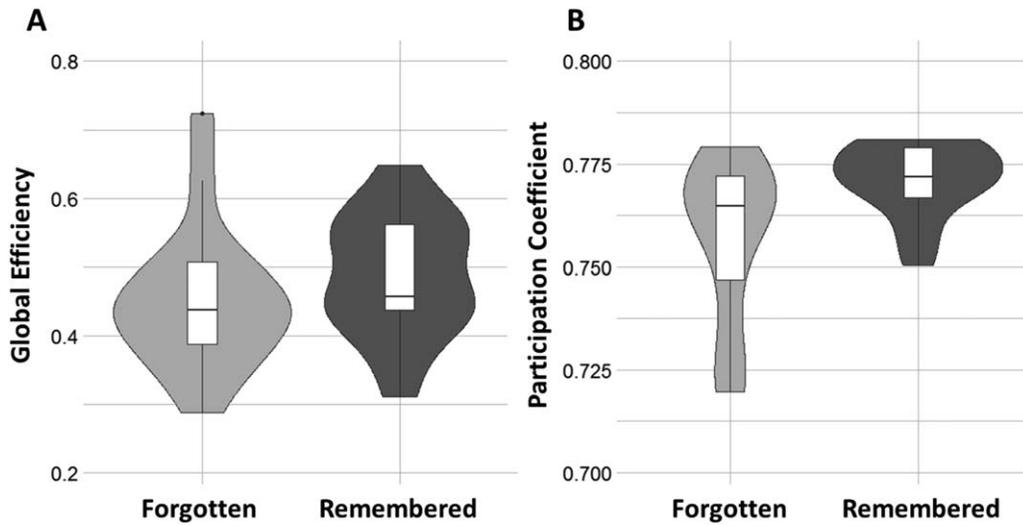
Figure 4.

A: Average global efficiency of all nodes in the retrieval assembly for both remembered and forgotten networks. The permutation framework developed by Simpson et al. [2013] in conjunction with the Jaccardized Czekanowski Index revealed that the global efficiency of the nodes comprising the retrieval assembly of the remembered network was greater than that of the forgotten network, regardless of whether or not the left hippocampus was included in the averaged global efficiency value (all P's < 0.05).

B: Average PC of all nodes in the retrieval assembly using the modular partition from the averaged remembered network as a template. The permutation framework developed by Simpson et al. [2013] in conjunction with the Jaccardized Czekanowski Index revealed that the average PC of nodes in the retrieval assembly in the remembered network was greater than that of the forgotten network, regardless of whether or not the left hippocampus is included in the average (all P's < 0.01).

TABLE III. Global efficiency and degree centrality for all nodes included in the retrieval assembly

	Global Efficiency: Median [IQR]			Degree Centrality: Median [IQR1		
	Remembered	Forgotten	P-value	Remembered	Forgotten	P-value
L-CAU	0.45 [0.38, 0.55]	0.39 [0.31, 0.46]	0.027	37.91 [27.53, 47.90]	31.32 [22.19, 38.33]	0.081
L-MFG	0.48 [0.40, 0.57]	0.45 [0.35, 0.49]	0.053	40.57 [32.06, 50.02]	37.28 [24.00, 42.95]	0.065
L-SFGdor	0.46 [0.44, 0.56]	0.44 [0.38, 0.51]	0.091	39.04 [32.97, 49.18]	36.97 [28.96, 42.52]	0.147
R-SFGdor	0.49 [0.46, 0.56]	0.43 [0.36, 0.52]	0.008	40.57 [38.05, 48.07]	34.63 [26.12, 44.01]	0.018
L-HC	0.44 [0.40, 0.46]	0.38 [0.30, 0.46]	0.021	36.35 [29.74, 40.60]	29.51 [21.37, 34.88]	0.039
R-MOG	0.43 [0.38, 0.61]	0.43 [0.36, 0.50]	0.308	36.20 [27.22, 53.61]	33.13 [25.42, 42.67]	0.524
L-PostCG	0.47 [0.43, 0.58]	0.44 [0.38, 0.53]	0.096	39.40 [33.88, 50.20]	32.32 [27.67, 46.58]	0.053
R-PostCG	0.53 [0.43, 0.57]	0.49 [0.39, 0.51]	0.080	43.39 [33.32, 50.68]	37.59 [27.69, 43.72]	0.139
R-PreCG	0.52 [0.41, 0.56]	0.48 [0.41, 0.52]	0.056	44.49 [33.08, 48.61]	39.06 [29.89, 43.97]	0.036
L-pCUN	0.53 [0.49, 0.63]	0.51 [0.45, 0.58]	0.259	43.83 [42.84, 56.03]	42.81 [35.62, 50.61]	0.09
L-SMG	0.45 [0.41, 0.54]	0.43 [0.35, 0.48]	0.098	36.43 [30.81, 47.20]	33.67 [24.76, 41.62]	0.064
R-SMG	0.46 [0.37, 0.51]	0.43 [0.34, 0.51]	0.352	36.72 [27.60, 45.78]	34.35 [21.04, 43.44]	0.256
L-ITG	0.53 [0.48, 0.60]	0.49 [0.41, 0.56]	0.038	45.91 [41.28, 52.91]	38.37 [32.56, 48.99]	0.024
Assembly	0.46 [0.44, 0.56]	0.44 [0.38, 0.51]	0.030	38.43 [35.55, 47.05]	34.76 [28.11, 42.00]	0.033

Statistical significance for changes in global efficiency and degree centrality between remembered and forgotten retrieval networks was assessed using nonparametric permutation tests using the framework developed by Simpson et al. [2013] in conjunction with the Jaccardized Czekanowski Index. [Legend: L-CAU (left caudate), L-MFG (left middle frontal gyrus), L-SFGdor (left dorsal superior frontal gyrus), R-SFGdor (right dorsal superior frontal gyrus), R-MOG (right middle occipital gyrus), L-PostCG (left post-central gyrus), R-PostCG (right post-central gyrus), R-PreCG (right pre-central gyrus), L-pCUN (left precuneus), L-SMG (left supramarginal gyrus), R-SMG (right supramarginal gyrus), and L-ITG (left inferior temporal gyrus)].
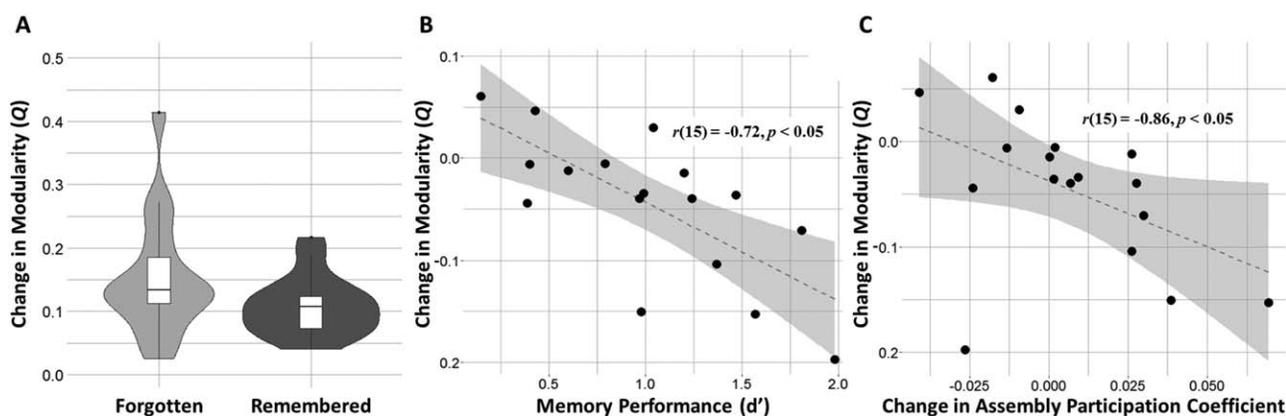
Figure 5.

Provides a summary of the modularity findings. **A**: The permutation procedure developed by Simpson et al. [2013] in conjunction with the Jaccardized Czekanowski Index revealed that modularity Q values were somewhat greater for the forgotten network than for the remembered network ($P < 0.10$), but this did not reach significance in accordance with our set alpha level.

B: The change in modularity between the remembered and forgotten networks was strongly correlated with individual variability in memory performance assessed with d' ($r(15) = -0.72$, $P = 0.001$). **C**: The relationship between the change in modularity (Q) and change in the retrieval assembly's PC for the remembered minus forgotten condition ($r(15) = -0.86$, $P < 0.05$).

memory performance assessed with d' ($r(15) = 0.54$, $P = 0.03$), suggesting that individuals with a more modular forgotten network have better memory performance. However, whole-brain modularity Q values in the remembered networks were not significantly related to memory performance ($P > 0.10$).

To identify the best modular partition to serve as a template, the modularity algorithm was run 1,000 times on the averaged (across participants) remembered network. Of these 1,000 different runs, 90.3% had 5 modules and the remaining 9.7% had 4 modules. The JI revealed that the 5 module networks were more consistent between iterations (in terms of the subsets of nodes comprising the different partitions) than the 4 module networks (5 Module Network $M = 0.87$ (SD = 0.12); 4 Module Network $M = 0.82$ (SD = 0.13); $t(9310) = 20.1$; $P < 0.0001$). The maximum Q values were nearly identical between the 5 module and 4 module networks (5 Module Max $Q = 0.0623$; 4 Module Max $Q = 0.0624$). Given that the Q values were nearly identical between 4 module and 5 module partitions, that the 5 module partition was identified more often than the 4 module partition, and that the 5 module networks were more consistently partitioned than the 4 module networks, the particular 5 module network with the highest Q value was used as the template partition for the averaged remembered network. While the averaged remembered network had a relatively low modularity Q, a series of random network rewirings [Rubinov and Sporns, 2010] revealed that modularity Q values in the observed networks were significantly greater than all Q values obtained from the corresponding randomized networks with equal density and degree distribution (1,000 permutations, range of Q values = [0.008, 0.0137]).

Interestingly, nodes comprising the retrieval assembly were distributed across all identified modules in the network (Fig. 3). This suggests that the hippocampus better facilitates information transfer across multiple network modules to support the successful retrieval of words. While this observation is largely qualitative in nature, it is consistent with the notion that the role of the hippocampus in episodic memory retrieval is to facilitate information integration between diverse brain regions and to enhance the convergence and joint processing of information across different components of the network, each of which is presumably contributing particular functions that facilitate memory retrieval.

Using the modular partition identified from the averaged (across participants) remembered retrieval network as a fixed template, we computed the PC of the nodes in the retrieval assembly for each of the individual participant's remembered and forgotten retrieval networks, respectively. While all nodes in the retrieval assembly had high PC in both remembered and forgotten retrieval networks, the permutation procedure revealed that the average PC of the assembly was higher in the remembered than the forgotten condition ($P = 0.008$; Fig. 4b). This was the case regardless of whether or not the left hippocampus was removed from the retrieval assembly. While one might argue that this result simply arises from the fact that the modules were defined using the averaged remembered network as a template, this seems unlikely because the modularity algorithm is designed to minimize the connectivity between different modules; thus, one would expect that a node's between module connectivity (indexed using the PC) would be lower in the network wherein the modular template was defined. A summary of

TABLE IV. PCs for all nodes included in the retrieval assembly

	PC: Median [IQR]		
	Remembered	Forgotten	*P*-value
L-CAU	0.786 [0.774, 0.789]	0.774 [0.762, 0.786]	0.047
L-MFG	0.759 [0.730, 0.765]	0.748 [0.669, 0.750]	0.001
L-SFGdor	0.767 [0.748, 0.771]	0.755 [0.739, 0.766]	0.074
R-SFGdor	0.767 [0.760, 0.777]	0.757 [0.744, 0.767]	0.035
L-HC	0.779 [0.767, 0.784]	0.771 [0.759, 0.783]	0.234
R-MOG	0.777 [0.764, 0.781]	0.776 [0.752, 0.778]	0.696
L-PostCG	0.781 [0.779, 0.785]	0.779 [0.757, 0.783]	0.006
R-PostCG	0.778 [0.776, 0.781]	0.776 [0.764, 0.778]	0.091
R-PreCG	0.780 [0.779, 0.783]	0.778 [0.766, 0.782]	0.057
L-pCUN	0.773 [0.767, 0.780]	0.773 [0.762, 0.777]	0.369
L-SMG	0.782 [0.774, 0.784]	0.774 [0.749, 0.781]	0.044
R-SMG	0.781 [0.769, 0.785]	0.771 [0.758, 0.778]	0.232
L-ITG	0.778 [0.769, 0.783]	0.773 [0.764, 0.777]	0.335
Assembly	0.772 [0.767, 0.779]	0.765 [0.747, 0.772]	0.008

Statistical significance for changes in PCs between remembered and forgotten retrieval networks was assessed using nonparametric permutation tests using the framework developed by Simpson et al. [2013] in conjunction with the Jaccardized Czekanowski Index. [Legend: L-CAU (left caudate), L-MFG (left middle frontal gyrus), L-SFGdor (left dorsal superior frontal gyrus), R-SFGdor (right dorsal superior frontal gyrus), R-MOG (right middle occipital gyrus), L-PostCG (left post-central gyrus), R-PostCG (right post-central gyrus), R-PreCG (right pre-central gyrus), L-pCUN (left precuneus), L-SMG (left supramarginal gyrus), R-SMG (right supramarginal gyrus), L-ITG (left inferior temporal gyrus)].

differences in PC for nodes within the retrieval assembly between remembered and forgotten networks is presented in Table IV.

Having found, for remembered as compared with forgotten items, that the modularity of the network decreased and that the retrieval assembly, which spanned all modules, exhibited a larger PC as a whole, we then hypothesized that these increased PC values for nodes in the retrieval assembly would be related to a decrease in modularity Q across the entire network. Accordingly, the retrieval assembly's change in PC was compared to the change in the network modularity (Q) at the individual participant level. These measures were found to be closely related ($r(15) = -0.86$, $P < 0.001$; Fig. 5c). Follow-up analyses were run to determine if this significant correlation was unique to the nodes comprising the retrieval assembly. 50,000 random subsets of 13 nodes were selected from the full network, and the change between remembered and forgotten retrieval networks in the averaged PC of each set of 13 nodes was compared to the change between remembered and forgotten retrieval networks in the modularity of the entire network. Thus, we obtained 50,000 correlation coefficient values, one for each subset of 13 nodes randomly selected. The observed retrieval assembly PC difference was among the most closely related to the change in modularity (top 5%).

Univariate results

All univariate analyses were conducted using single-trial beta values. Univariate results estimated from the single-trial analyses were assessed for ROIs, as defined by the AAL atlas, and the univariate results were compared to graph theoretical results. This was done to ensure that graph theoretical results were not the product of differences in univariate activation. Within the retrieval assembly, no node exhibited a significant difference in univariate activation even before correction for multiple comparisons (Remembered minus Forgotten; $P > 0.10$). Additionally, none of the changes in graph theoretic measures were significantly correlated with changes in univariate activation even before correction for multiple comparisons ($P > 0.10$). Taken together, these results suggest that the graph metrics captured unique features of the data above and beyond what can be gleaned from examining univariate activity.

DISCUSSION

The purpose of this study was to investigate functional brain network architecture underlying episodic memory retrieval using graph theory measures at nodal, assembly, and whole-brain topological levels. This study yielded three main findings. First, the hippocampus displayed an increase in global efficiency and degree centrality for remembered compared to forgotten items, and it significantly reorganized its set of direct connections (FSR) between remembered and forgotten retrieval networks. Second, for remembered compared to forgotten trials, the hippocampus was more strongly connected with several network nodes comprising a retrieval assembly. This retrieval assembly included many regions previously linked to retrieval success, such as the PFC and ventral parietal regions. Collectively, the retrieval assembly exhibited greater integration with rest of the functional brain network for remembered compared with forgotten trials. Third, at the level of the whole brain, modularity analyses revealed that the entire network exhibited a less segregated modular organization for remembered compared to forgotten items, suggesting that integrative processing throughout the entire functional network supports the successful remembering of words. These three findings are discussed in separate sections below.

Hippocampal Integration: Increased Global Efficiency and Degree Centrality for Remembered Compared with Forgotten Items

Our results support our first hypothesis that the hippocampus would have a greater capacity for efficient integrative processing during remembered compared to forgotten conditions. The left lateralization of this effect builds upon results from previous univariate analyses showing that the

left hippocampus tends to be more sensitive to the retrieval of verbal stimuli while the right hippocampus is more sensitive to pictorial stimuli [Papanicolaou et al., 2002]. Our findings also complement recent multivariate functional connectivity results [Geib et al., 2015] showing that the right hippocampus exhibits a greater capacity for efficient information integration throughout the network for the vivid retrieval of scenes as compared to the dim retrieval of scenes.

The importance of segregated functioning during cognitive tasks has been extensively investigated using univariate activation methodologies. However, localized functional specialization alone cannot fully account for most aspects of brain function [Sporns, 2013]. Integrated and distributed processes that subserve cognition may instead benefit from a higher capacity for efficient information transfer across the brain as a whole, especially for more complex cognitive tasks [Sporns, 2013; Stanley et al., 2015; van den Heuvel et al., 2009]. Geib et al. [2015] demonstrated that the right hippocampus exhibits a greater capacity for global information integration to support the retrieval of scenes from memory. Similarly, our results here show that the left hippocampus exhibits a greater capacity for effective information integration to support the retrieval of individual words from memory. To further clarify why the hippocampus exhibits changes in global efficiency and degree centrality when items are remembered as opposed to forgotten, we computed FSR, which is a recently developed measure for investigating the extent to which an observed change in nodal graph theory measures might be dependent upon a reorganization of direct functional connections in the network [Geib et al., 2015]. There was a significant difference in FSR for the left hippocampus, indicating that successful memory retrieval involves a substantial reorganization of direct functional connections of the left hippocampus. This suggests that hippocampal changes in global efficiency and degree centrality are at least partly driven by the hippocampus reorganizing its set of direct functional connections. Finally, nodal change scores for global efficiency (rank = #1, $P < 0.05$) indicate that the left hippocampus increased its global efficiency more than any other node in the network from forgotten to remembered conditions. While nodal change scores for degree centrality were only trending toward significance (rank = #4, $P < 0.10$), they also emphasize that the left hippocampus increases in centrality from forgotten to remembered networks to a greater extent than the vast majority of other network nodes.

Univariate activation changes were uncorrelated with changes in graph theory metrics for all nodes of interest. However, changes in degree centrality and changes in global efficiency between remembered and forgotten networks were found to be positively correlated across nodes in each individual participant's network (smallest magnitude $r(88) = 0.71$, $P < 0.001$). While these two measures do capture different topological properties of complex networks, it is clear that they are explaining much of the same variance. Future studies will investigate when and why these measures diverge in functional and structural brain networks.

Assembly Organization: Successful Memory Is Supported by Increased Hippocampal Connectivity with a Retrieval Assembly

A retrieval assembly centered on the left hippocampus, which consisted of nodes with stronger connections to the left hippocampus for remembered compared with forgotten conditions, contained many brain regions previously shown to be involved in memory retrieval operations using different methodologies, such as the PFC [Lundstrom et al., 2005; Wagner et al., 2005] and VPC [Cabeza et al., 2008; Ciaramelli et al., 2008; Vilberg and Rugg, 2008]. Additionally, the nodes identified as comprising the retrieval assembly were located in spatially disparate regions of the brain, complementing prior work showing that long-distance connections may be particularly important for facilitating healthy cognitive functioning across diverse tasks [Cohen et al., 2014; Liu et al., 2013; Schedlbauer et al., 2014; Wang et al., 2010].

The importance of the PFC for episodic memory retrieval has been well-established using diverse methodologies. PFC damage is associated with impaired episodic memory [Davidson et al., 2006], and PFC activations are frequently observed during episodic retrieval and have been attributed to memory search and monitoring processes [Mitchell and Johnson, 2009; Reas and Brewer, 2013; Rugg and Vilberg, 2013; Wagner et al., 2005]. In this study, exploratory analyses revealed that the bilateral superior frontal gyri showed increased bivariate functional connectivity and increased global efficiency for remembered compared with forgotten conditions. These increases in connectivity are potentially due to the recruitment of these regions for memory search and monitoring to successfully retrieve items from memory.

Like the PFC, the VPC is commonly activated during episodic memory retrieval. The attention to memory model proposes that during episodic retrieval the DPC contributes to operations dependent on top-down attention, such as monitoring, whereas VPC contributes to operations dependent on bottom-up attention, such as recollection. Because we focused on high-confidence hits (vs. misses), the network we investigated is primarily associated with recollection rather than with monitoring. Monitoring-related activity can be identified by comparing difficult vs. easier retrieval conditions, such as familiarity vs. recollection or low- vs. high-confidence trials [Cabeza et al., 2008], which we did not investigate in the present study. According to another view, VPC activations reflect the maintenance of recovered multimodal information within working memory [Vilberg and Rugg, 2008]. The observed increase in this study in functional connectivity between

the hippocampus and the VPC for high-confidence hits is consistent with both views. However, further studies directly manipulating the capture of bottom up attention and maintenance of multi-modal information are needed to further elucidate the role of the VPC in the large-scale retrieval network.

There is existing evidence from different methodologies suggesting that the caudate is involved in declarative memory retrieval processes [Scimeca and Badre, 2012]. Hart et al. [2013] have suggested that semantic memory retrieval is dependent upon a pre-SMA, caudate, thalamus circuit. Additionally, this circuit has been shown to be active in tasks involving episodic memory retrieval in both fMRI [Bastin et al., 2012] and PET [Wiggs et al., 1999] studies, and a circuit that just includes the thalamus and caudate has been shown to play a role in the retrieval of autobiographical memories [Burianova and Grady, 2007]. Damage to the caudate has also been associated with poorer declarative memory for verbal information [Mizuta and Motomura, 2006]. Finally, it is also possible that our results regarding the caudate are more closely associated with goal attainment during the retrieval process [Han et al., 2010].

Our exploratory findings suggest that the caudate may play an additional role in episodic memory retrieval by also serving a critical integrative function within the network, as evidenced by increased global efficiency, and a higher PC for remembered compared with forgotten conditions. These results indicate that the caudate has a greater capacity for efficient information transfer throughout the network when successfully retrieving memories. Additionally, given the known anatomical connections between the hippocampus and caudate [Robinson et al., 2012] and between the caudate and frontal cortex [Lehéricy et al., 2004], the caudate might serve as an intermediary node between the hippocampus and prefrontal nodes involved in retrieval control processes.

Assembly Integration: Global Efficiency Increases and PC Increases for Remembered Compared with Forgotten Items

For the subset of nodes comprising the retrieval assembly, global efficiency, and degree centrality were higher, on average, for remembered than for forgotten items. This suggests that increased integration within the assembly contributes to memory success. While previous studies have reported that average whole brain global efficiency is higher during the retrieval of vivid compared to dim memories of scenes [Geib et al., 2015], here we narrowed our analyses to a level of organization between the nodal and whole-brain levels to show that the integrative properties of the retrieval assembly also increase from forgotten to remembered conditions. In the case of global efficiency, this increase was greater in magnitude than any other randomly selected subset of nodes.

Furthermore, we found that the average PC of nodes in the retrieval assembly was greater for the remembered than for the forgotten trials. This finding suggests that the nodes in the assembly are increasing their extramodular functional connections. This kind of change in functional network architecture between remembered and forgotten conditions presumably facilitates integrative processing across many different functional communities in the network. Taken in conjunction with the hippocampal FSR result, this suggests that the overall hippocampal increases in integration may be driven by changes both in direct functional connections (e.g., FSR) and in indirect functional connections via the connections of nodes in the retrieval assembly.

Whole Brain Integration: Decreased Modularity for Remembered Compared with Forgotten Items

Modularity algorithms take into account the relative balance between integrative and segregated topological features within a network [Blondel et al., 2008; Newman, 2006]. While the retrieval assembly results show that increased integrative processing among a small subset of nodes in the network was important for successful memory retrieval, modularity algorithms provide a statistic describing the extent to which the entire network exhibits a more integrative or segregated functional architecture. Our results demonstrate that whole-brain modularity decreased from forgotten to remembered retrieval networks, suggesting that successfully remembering items was associated with a relatively more integrated than segregated functional network architecture. Additionally, the differences in modularity Q scores (remembered network Q minus forgotten network Q) across individuals were inversely correlated with their memory performance. This corroborates and extends findings from previous work showing that better cognitive performance, especially for more complex tasks, is associated with a more globally integrated network architecture in diverse cognitive domains, including: working memory [Stanley et al., 2014; Stevens et al., 2012], odor recognition memory [Meunier et al., 2014], episodic memory for visual scenes [Geib et al., 2015; Westphal et al., 2014], and cognitive control [Braun et al., 2015]. We additionally report that increased modularity in the forgotten network is related to memory strength (d'). One potential (but speculative) explanation for this result is that better performers on the task fail to remember items only for trials in which the network is highly segregated (i.e., not well integrated).

Furthermore, we found that the nodes identified as comprising the hippocampal retrieval assembly span multiple, different modules. This suggests that the hippocampus might be responsible for coordinating large-scale network interactions between differentially specialized and distributed subsystems. In fact, rapidly accumulating evidence

has shown that the hippocampus coordinates with a diverse set of brain regions that support complex representations, including: encoding retrieval similarity in the occipitotemporal cortex [Wing et al., 2015], predictive coding in the extrastriate cortex [Hindy et al., 2016], temporal sequences in the lateral PFC and medial PFC [Schapiro et al., 2016], and attentional orientation in the retrosplenial cortex [Aly and Turk-Browne, 2015]. Our results suggest that the hippocampus alters its connectivity profile from forgotten to remembered retrieval conditions to better interconnect nodes in different modules. In this way, the hippocampus appears to facilitate the communication and the distribution of information between modules when items are successfully remembered as opposed to forgotten.

Post-hoc analyses also revealed that nodes within the retrieval assembly exhibited increased PCs in accordance with an observed decrease in modularity (Q) for remembered compared with forgotten items. This suggests that the observed decrease in modularity Q for the entire network is closely related to the fact that nodes within the retrieval assembly increase their relative between module connectivity. Previous work [Geib et al., 2015] has provided evidence that both the hippocampus and entire brain become more integrated during successful memory retrieval. However, this work did not link these phenomena at a more intermediate level of network analysis. Here, we suggest that the retrieval assembly serves as the explanatory link between these phenomena. The retrieval assembly shows increased integrative processing during successful memory retrieval and facilitates between module communication across the network. Moreover, the extent to which the retrieval assembly increases its relative between module communication is closely related to the change in whole-brain integrative processing. We are not suggesting that all nodes in the network become more integrated (e.g., olfactory and auditory cortices should not become more integrated as a function of memory performance), but only that the network as a whole becomes more integrated.

Investigating the properties of retrieval assemblies provides a viable avenue for conducting future research on the neural instantiation of memory processes. Future work will investigate which components of the retrieval assembly are common across different kinds of retrieval tasks, which kinds of information are being shared between modules, and the temporal sequence of topological changes (e.g., does the retrieval assembly or hippocampus increase its efficiency first?). It is through the discovery of this intermediate level of organization that we can fully parse out how network interactions influence memory retrieval.

CONCLUSIONS

Recently, there has been growing interest in identifying network nodes that facilitate the integration of information between segregated, specialized communities of brain regions in order to support more complex cognitive processes [Bertolero et al., 2015; Fornito et al., 2015; Stanley et al., 2014]. Network nodes that interconnect many different network modules play a key role in subserving more complex cognitive tasks by allowing groups of nodes to perform specific, specialized functions yet still effectively interact with other brain regions performing other kinds of functions. Here, we incorporated a novel analysis method to show how a critical network node can change between two conditions of interest to better facilitate the integration of information between modules. Using this approach, we showed that the hippocampus occupies a more topologically critical position in the network to facilitate the flow of information between network modules for successful compared to unsuccessful memory retrieval. To facilitate the successful retrieval of items from memory, the hippocampus became more strongly connected with sensory motor regions, attention regions, frontal control regions, higher order visual regions, subcortical regions, and other default mode regions such as the precuneus. In general, to support successful episodic memory retrieval of semantic information, the hippocampus is likely to be strongly connected with prefrontal regions that mediate retrieval control process [Rugg and Vilburg, 2013; Wagner et al., 2005], ventral parietal regions serving attention functions [Cabeza et al., 2008], higher-order visual regions supporting sensory reactivation [Danker and Anderson, 2010], and the precuneus supporting internal mentation [Kim, 2016]. It is through the complex but coordinated interactions involving these regions that we are able to retrieve information from memory. Although our sample size is relatively small, our results are highly consistent with and complementary to this prior literature investigating the neural bases of memory using diverse methods.

Taken together, these findings suggest that memory retrieval is dependent upon a broadly distributed, yet interconnected, set of brain regions, as opposed to activations in single regions or activations across a set of regions that can be identified using univariate activation analyses. Notably, evidence was presented for increased integrative processing at the hippocampal, retrieval assembly, and whole-brain topological levels to support the successful remembering of words. While we maintain that the hippocampus is a critical structure for memory retrieval, the functionality of the hippocampus itself is only partly responsible for our ability to successfully retrieve items from memory. Identifying the ways in which the hippocampus is directly and indirectly functionally interacting with other brain regions to facilitate episodic memory retrieval provides a more complete account of the neural processes underlying this critical cognitive function.

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