

Functional Connectivity of Hippocampal and Prefrontal Networks During Episodic and Spatial Memory Based on Real-World Environments

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ABSTRACT: Several recent studies have compared episodic and spatial memory in neuroimaging paradigms in order to understand better the contribution of the hippocampus to each of these tasks. In the present study, we build on previous findings showing common neural activation in default network areas during episodic and spatial memory tasks based on familiar, real-world environments (Hirshhorn et al. (2012) *Neuropsychologia* 50:3094–3106). Following previous demonstrations of the presence of functionally connected sub-networks within the default network, we performed seed-based functional connectivity analyses to determine how, depending on the task, the hippocampus and prefrontal cortex differentially couple with one another and with distinct whole-brain networks. We found evidence for a medial prefrontal-parietal network and a medial temporal lobe network, which were functionally connected to the prefrontal and hippocampal seeds, respectively, regardless of the nature of the memory task. However, these two networks were functionally connected with one another during the episodic memory task, but not during spatial memory tasks. Replicating previous reports of fractionation of the default network into stable sub-networks, this study also shows how these sub-networks may flexibly couple and uncouple with one another based on task demands. These findings support the hypothesis that episodic memory and spatial memory share a common medial temporal lobe-based neural substrate, with episodic memory recruiting additional prefrontal sub-networks. © 2014 Wiley Periodicals, Inc.

KEY WORDS: autobiographical memory; MTL; default network; sub-networks; fMRI

INTRODUCTION

The hippocampus has long been thought to play a role in episodic memory and in spatial memory (Scoville and Milner, 1957; O'Keefe and Nadel, 1978; Nyberg et al., 1996). The overlap between these abil-

ities and their mutual reliance on the hippocampus and other neural structures, however, is not fully understood and has been the subject of recent discussion (Maguire and Mullally, 2013; Nadel and Peterson, 2013). Some have proposed that the role of the hippocampus in spatial representations underlies its role in episodic memory (O'Keefe and Nadel, 1978; Kumaran and Maguire, 2005; Hassabis and Maguire, 2007; Maguire and Mullally, 2013; Mullally and Maguire, 2013), while others have proposed that the hippocampus plays a more general role in relational memory, of which episodic memory and spatial memory are two examples (Cohen et al., 1999; Eichenbaum and Cohen, 2001; Rosenbaum et al., 2009; Olsen et al., 2012).

In attempts to understand better the relationship between these types of memory, a number of recent studies have explored similarities and differences across episodic memory and spatial memory tasks by comparing them in highly matched neuroimaging paradigms, in order to determine the precise areas and amount of overlap in hippocampal activity. In the present study, we adopt this approach and extend it to address this question by examining functional connectivity of the hippocampus with the rest of the brain during spatial and episodic memory tasks. Examining the differential interactions among areas activated during episodic and spatial memory tasks, including the hippocampus, reveals differences and similarities between the neural substrates mediating episodic and spatial memory at the network level, in addition to those that are found in isolated regions of interest.

Several recent studies have demonstrated hippocampal activation that is common to episodic and spatial memory tasks. In two studies comparing episodic and semantic memories that were either spatial or non-spatial in content, there was greater hippocampal activation in response to spatial questions versus non-spatial questions, and also greater hippocampal activation in response to episodic versus semantic questions (Hoscheidt et al., 2010; Ryan et al., 2010). Of note, the greatest hippocampal activation was in response to questions that were both episodic and spatial. More recently, Nadel et al. (2013) and Evensmoen et al.

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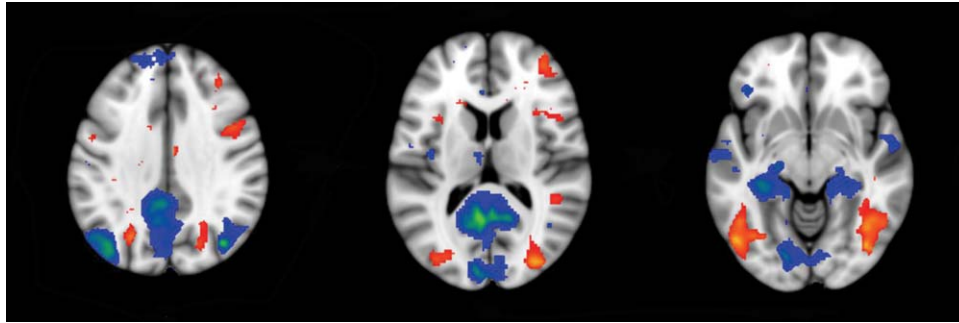


FIGURE 1. Patterns of neural activity common to episodic and spatial memory (Hirshhorn et al., 2012). Regions in cool colors indicate areas that showed activation common to the episodic, easy spatial, difficult spatial conditions, but not the vowel control condition. Regions in warm colors indicate areas that were active during the vowel control condition and not any of the memory conditions. Color-intensity represents the robustness of each voxel's contribution to this activation pattern. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

(2013) showed that the activated region of the hippocampus varied according to the grain of the spatial memory, with preferential activation of the anterior hippocampus by coarse spatial representations, and the posterior hippocampus by fine spatial representations (see also Poppenk et al., 2013).

In another previous study, participants made spatial and episodic memory-based judgments about real-world spatial stimuli from familiar environments (Hirshhorn et al., 2012). Participants were shown names of pairs of familiar landmarks in downtown Toronto, and either asked to make a spatial judgment which required drawing on knowledge of spatial relations among locations (i.e., which landmark is farther North?) or an episodic judgment which required retrieval of autobiographical memories pertaining to those locations (i.e., which landmark have you visited more recently?). When compared against a vowel counting control condition, the hippocampus showed increased activation across the episodic and the spatial tasks, with areas of common activity mostly in the middle and posterior hippocampus, and with other clusters being uniquely activated either by the episodic or spatial memory condition. Together, these studies provide robust evidence that although autobiographical episodic memory and spatial memory rely on a common hippocampal substrate, there also are differences between them. These studies were able to provide valuable insight into which areas were commonly active across spatial and episodic memory, and which areas differentiated between these types of memory. The studies, however, were limited by the fact that they did not address the interactions between these areas and how they changed according to memory type.

An important next question to address is whether areas that show common activation across tasks also differ in terms of their functional connections with the rest of the brain. There is evidence that autobiographical episodic and spatial memory tasks reliably engage a group of neural areas consistent with those that comprise the default network (Spreng et al., 2009). The regions in this network, however, do not always show

coordinated activity, and when they do, the activity may depend on the task being performed. For example, it has been shown that hippocampal activity synchronizes with the activity in other default network regions during memory retrieval, but not during encoding (Huijbers et al., 2011). Following from this, it is not known how the hippocampus relates to other parts of this network during memory retrieval tasks varying in content, or if components of this network couple differently with each other depending on task demands.

Determining whether or not connectivity within this network differs according to task will provide important insights into how episodic memory and spatial memory relate to one another. In particular, though these memory tasks both result in activation of certain areas, including the hippocampus, this does not necessarily mean that all of the regions are functionally connected to the same networks, or play the same mechanistic role in the various types of memory. In the study by Hirshhorn et al. (2012), the areas commonly activated by the episodic and spatial memory tasks included not only the hippocampus bilaterally, but also medial frontal cortex, posterior cingulate gyrus and precuneus, as well as the lingual gyrus, superior temporal gyrus, and angular gyrus (see Fig. 1). This constellation of activated structures resembles that of the default network (Shulman et al., 1997; Raichle and MacLeod, 2001; Fox et al., 2005; Buckner et al., 2008; Buckner, 2012). Although the default network was originally found during baseline conditions in which participants were presumed to be inactive at rest, more recent research has associated activity in these areas with numerous tasks, including autobiographical memory, self-referential thought, prospection, navigation and theory of mind (Rosenbaum et al., 2004; Buckner and Carroll, 2007; Spreng et al., 2009; Andrews-Hanna et al., 2010; Buckner, 2010; Grigg and Grady, 2010a,b; Rabin et al., 2010; Spreng and Grady, 2010). Thus, it is not surprising that these areas would be engaged for both the episodic and spatial

memory tasks and not in the vowel baseline condition in Hirshhorn et al.'s (2012) study.

Other studies, however, have suggested that the default network is not as unified as previously thought, and that it may consist of distinct sub-networks (Andrews-Hanna et al., 2010; Andrews-Hanna et al., 2014). By examining functional connectivity with graph analytic techniques and hierarchical clustering analysis, using seeds in the medial prefrontal cortex and the parahippocampal cortex, Andrews-Hanna et al. (2010) found two subsystems within the default network, linked by a "midline core." The first subsystem was termed the "dorsal medial prefrontal cortex (dmPFC) subsystem" and included the dmPFC, temporoparietal junction, lateral temporal cortex and temporal poles. The second subsystem, the "medial temporal lobe (MTL) subsystem" included the ventromedial prefrontal cortex (vmPFC), the posterior inferior parietal lobule, retrosplenial cortex, parahippocampal cortex and hippocampus. Finally, the midline core consisted of the anterior medial prefrontal cortex (amPFC) and the posterior cingulate cortex (PCC), two network "hubs" with the strongest connectivity with each subsystem. The authors also found evidence for functional specialization of each sub-network, hypothesizing that the MTL subsystem is specialized for scene construction and imagery-related memory processes, and that the dmPFC system is related to thoughts about the mental states of oneself and others, and conceptual thinking. The midline core is thought to be related to representing self-relevant information. Large-scale studies using meta-analytic techniques and NeuroSynth (Yarkoni et al., 2011) have since replicated and supported the presence of these functionally-specialized subnetworks (Andrews-Hanna et al., 2014; Yeo et al., 2011).

This network organization was partially replicated in a study of autobiographical memory (St Jacques et al., 2011). Independent components analysis revealed four networks involved in retrieving and reliving autobiographical episodes, including an MTL network similar to the MTL subsystem proposed by Andrews-Hanna et al. (2010). They also found evidence for a dmPFC-PCC network, termed the medial PFC network, which may be similar to Andrews-Hanna et al.'s midline core network, though it differed in that the prefrontal area involved was more dorsal. The additional two networks identified were a left-lateralized frontal-parietal network and a cingulo-opercular network, thought to be involved in the strategic search and goal maintenance aspects of the paradigm.

Similar network organization was observed in a recent meta-analysis of studies involving autobiographical memory retrieval, which found a midline system (amPFC and PCC) relating to self-referential processing, and a temporal-parietal system relating to memory retrieval processes, consisting of the inferior parietal lobule, medial temporal lobe and lateral temporal cortex (Kim, 2012). The MTL and dmPFC sub-networks also exist in older adults, though when compared with younger adults, the older group showed weaker functional connectivity in the dmPFC subsystem (Campbell et al., 2013). In addition, connectivity studies of patients with amnesia due to MTL damage showed that while connectivity in the MTL subsystem was reduced in patients, con-

nectivity in the dmPFC subsystem and midline core was intact, or possibly increased, suggesting that the subsystems may be differentially impacted by age, disease or injury (Hayes et al., 2012). Taken together, a growing body of evidence points to distinct sub-networks making up the default network, especially a midline frontal-parietal network and an MTL subsystem. These networks may play unique roles in different types of memory and memory-related processes.

Based on these findings, we examined functional connectivity in the network of areas found to be active in Hirshhorn et al.'s (2012) study, using the same dataset but novel analysis techniques, in order to address several important issues. While Hirshhorn et al. (2012) demonstrated the areas that were commonly activated by the memory conditions, and those that distinguished between them, by using functional connectivity analyses we can see how some of these regions interact with one another, and their own respective sub-networks. Following the functional differentiation proposed by Andrews-Hanna et al. (2010, 2014) and others, we sought to determine how the functional connectivity of either of the sub-networks was similar or different based on the task conditions. If MTL areas are involved in episodic and spatial memory retrieval, it is possible that a sub-network of these areas would be crucial for both tasks, or alternatively, that different parts of the MTL are engaged for each. Evidence of the former could support the notion that episodic memory and spatial memory share a similar underlying mechanism, such as scene construction (Hassabis and Maguire, 2007, 2009; Maguire and Mullally, 2013), or relational binding (Eichenbaum and Cohen, 2001).

Other subsystems, including dmPFC and midline core networks reported by Andrews-Hanna et al. (2010) have been hypothesized to have different functions, relating more closely to representations of the self or one's mental states. If this is the case, we would expect the dmPFC sub-network to be preferentially recruited in an episodic memory task with an autobiographical component, though not necessarily in spatial memory tasks. In this way, we could address the broader question of similarities and differences across spatial and episodic memory tasks, and elucidate further how their neural substrates are related. To this end, we used partial least squares (PLS) seed-based connectivity analyses to examine the subsystems of the default network found by Andrews-Hanna et al. (2010) and others, and determine their roles in spatial and episodic memory retrieval. Using PLS to assess functional connectivity allows for simultaneous examination of whole-brain patterns of activity correlating with activity in multiple seeds. PLS analysis, therefore, is ideal for identifying unique networks related to specific brain regions.

MATERIALS AND METHODS

Participants

Fourteen right-handed, healthy, young adults (6 male; mean age = 26.43; SD = 2.68) participated in the study. Participants

had lived in Toronto for a minimum of five years ($M = 15.71$; $SD = 9.83$) and completed a survey prior to the experiment to ensure they had visited the landmark cues used in the study. In accordance with the research ethics review board at Baycrest Centre, participants provided written consent prior to participating in the study.

Stimuli and Procedure

Detailed descriptions of the stimuli and study procedure were reported in a previous article (Hirshhorn et al., 2012). The study was an event-related fMRI design, in which participants were shown pairs of names of well-known Toronto landmarks on each trial (e.g. the CN Tower and the Royal Ontario Museum). There were four conditions in the study, each requiring the participant to select one of the two landmarks as their answer.

In the *episodic condition*, participants were asked to indicate which of the landmarks they had visited most recently, requiring a judgment based on their own autobiographical memories. In the *easy spatial condition*, participants were asked to indicate which of the landmarks was farther North, South, East or West based on cardinal directional coordinates. In this condition, the landmarks were compared along the longest cardinal axis between them. In the *difficult spatial condition*, participants were again asked to indicate which of the landmarks was farther North, South, East or West based on cardinal directional coordinates, but in this case along the shortest axis between them, making this a more difficult judgment. Participants also completed a *vowel condition*, in which they were asked to indicate the landmark name that contained more vowels. This condition was used as a baseline, as it involved neither mnemonic nor spatial decisions.

The names of the landmarks and the question remained on the screen for the duration of the trial (12 sec). Each trial was separated by a 2-sec fixation cross. Participants completed four runs of 52 trials each. Participants were able to select their response by pressing “1” or “2” corresponding to the two landmarks presented on the screen, or “3” to indicate “I don’t know.” Only correct trials, or in the case of the episodic condition, recollected memories (as indicated by a post-scan interview), were used in the analyses. This resulted in the inclusion of an average of 48 trials per participant for the episodic condition, 48 trials for the easy spatial condition, 39 trials for the difficult spatial condition and 46 for the vowel condition.

Image Acquisition and Preprocessing

Anatomical and functional images were acquired with a 3T Siemens scanner and standard head coil at Baycrest Hospital. For the anatomical scans, a T1-weighted volumetric anatomical MRI (30 axial slices, $TE = 2.63$ ms, 5 mm thick, $FOV = 256$ cm) was acquired for each participant. The functional scans included twenty-six axial slides (5 mm thick), using a T2*-weighted pulse sequence with an echoplanar imaging (EPI) readout ($TR = 2,000$ ms, $TE = 30$ ms, $FOV = 20$ mm, 64×64 matrix). Brain activation was assessed

based on the BOLD (blood oxygenation level-dependent) signal.

Reconstruction and preprocessing were performed using the Analysis of Functional Neuroimages (AFNI, version 2.0) software package (Cox, 1996). The initial ten images from each run were discarded. After image reconstruction, images were then corrected for movement due to heart rate and respiration, slice-timing corrected to the first slice and motion corrected using a three-dimensional Fourier transform interpolation with a functional volume, minimizing motion to less than 1.5 mm. Files were then spatially normalized into MNI space and smoothed with a 8mm full-width-at-half-maximum (FWHM) Gaussian filter.

Partial Least Squares Analysis

We performed a seed-based Partial Least Squares analysis (PLS; McIntosh et al., 1996; McIntosh et al., 2004) to determine functional connectivity of two seed regions to one another, and to the rest of the brain, during the experimental conditions of interest. PLS is a multivariate, data-driven analysis technique that assesses covarying activity across voxels in the entire brain with no a priori contrasts. This technique allows the algorithm to detect whole-brain patterns of activity that covary with the experimental design without requiring subtraction or contrast analyses typical of univariate methods. In addition, in seed PLS, it is possible to specify a region, or regions, of interest and examine how the activity in these areas covaries with patterns across the rest of the brain across each experimental condition. As such, this technique is ideally suited to examine the functional connectivity of specific regions to the rest of the brain in a task-based experimental paradigm, such as ours.

To perform this analysis, we first chose two seed regions of interest. The areas selected were in the left hippocampus (MNI coordinates: $[-24, -22, -16]$) and the left prefrontal cortex (MNI coordinates: $[-2, 54, 34]$). We chose left hippocampal and medial prefrontal seeds in order to replicate the methods of previous work, which have used similar seed locations in the left parahippocampal gyrus and left dmPFC to generate the sub-networks of the default network (Andrews-Hanna et al., 2010; Campbell et al., 2013). The specific coordinates within each region in our study were chosen because they represented peaks of activity differentiating the three memory conditions from the vowel control condition in the original analysis of task-related activity (Hirshhorn et al., 2012). Since the activity in these seeds differentiated the spatial memory and episodic memory conditions from the vowel condition, and only the functional connectivity during the memory conditions is of interest in the present study, the vowel condition was discarded from all subsequent analyses. Seeds were chosen in the left hemisphere in order to be consistent with previous studies, and owing to the greater involvement of the left hippocampus in the episodic memory condition, as reported by Hirshhorn et al. (2012). In order to examine the interactions between the prefrontal and hippocampal seeds, which we hypothesized to

TABLE 1.

Brain Regions Showing Significant Functional Connectivity With the Prefrontal Seed Across all Task Conditions and the Hippocampal Seed in the Episodic Condition (LV1)

Brain region	<i>x</i>	<i>y</i>	<i>z</i>	BSR	Cluster size (voxels)
L Medial frontal gyrus (BA 9)	-4	54	32	-15.9067	2277
L Precuneus (BA 31)	-6	-60	30	-7.1476	1264
R Temporoparietal junction (BA 39)	48	-72	22	-6.1122	175
L Inferior frontal gyrus (BA 45)	-46	28	6	-5.8525	175
L Inferior frontal gyrus (BA 47)	-34	16	-14	-5.9395	98
L Middle frontal gyrus (BA 8)	-24	14	50	-4.5553	95
R Middle temporal gyrus (BA 20)	52	-14	-16	-5.0075	89
R Inferior frontal gyrus (BA 47)	34	20	-14	-6.679	87
R Cerebellum	18	-90	-30	-5.6188	81
L Middle temporal gyrus (BA 21)	-60	-20	-16	-5.5386	81

Clusters evident during TR 5 with a bootstrap ratio of greater than ±3 (equivalent to $P = 0.0027$) and a cluster size of minimum 80 voxels are reported.

be greatest in the episodic memory condition, we selected the lateralization associated with more consistent episodic memory activity.

We performed multiple voxel extraction to determine the mean activity for each condition and each participant in the voxels surrounding the selected coordinates for the hippocampal and prefrontal seeds. Mean activity was extracted from an 105-voxel cluster including the hippocampal seed, and a 94-voxel cluster including the prefrontal seed, based on a $5 \times 5 \times 5$ voxel cube with the seed at the center (voxels that fell outside the brain or in a ventricle were discarded). The location of the seeds was determined based on the timepoint that showed the peaks in neural activity in the original analysis, TR 4 (8–10 sec after task onset), and so activity in the seeds from this TR was entered into the analysis.

These data were then entered into a two-seed PLS analysis, so that the covariance between the activity in the two seeds was assessed, as well as the covariance between the activity of each seed and the patterns of whole-brain activity. In this analysis, the correlations between activity in each of the seeds and the brain activity at each voxel and time point are computed across subjects within each condition and then contrasted across the conditions of the study. Singular value decomposition (SVD) is performed on the correlation matrix, which produces a set of latent variables (LVs) which describe patterns of brain activity that covary together with the activity in the seeds across the experimental conditions over time, as well as the singular values corresponding to those LVs which are proportional to the amount of covariance accounted for by each LV, and the salience values, which represent how strongly each voxel is related to each LV.

TABLE 2.

Brain Regions Showing Significant Functional Connectivity With the Hippocampal Seed in the Difficult Spatial Condition (LV1)

Brain region	<i>x</i>	<i>y</i>	<i>z</i>	BSR	Cluster size (voxels)
R Superior parietal lobule (BA 7)	12	-70	54	5.7097	615
L Thalamus	-22	-16	20	6.3133	238
L Cerebellum	-24	-52	-46	5.5985	235
L Cerebellum	-2	-70	-24	5.1075	216
L Middle occipital gyrus (BA 18)	-32	-90	2	4.8411	184
L Middle frontal gyrus (BA 9)	-50	26	32	4.5363	178
L Precuneus (BA 7)	-20	-70	58	4.4829	152
R Cingulate gyrus (BA 31)	24	-20	44	5.0407	135
R Cerebellum	18	-40	-48	6.7684	124
R Middle frontal gyrus (BA 9)	42	34	32	4.9594	121
L Putamen	-26	-4	14	5.3337	118
R Putamen	24	-8	8	4.7777	97
L Inferior parietal lobule (BA 40)	-40	-46	44	3.9993	83

Clusters evident during TR 5 with a bootstrap ratio of greater than ±3 (equivalent to $P = 0.0027$) and a cluster size of minimum 80 voxels are reported.

TABLE 3.

Brain Regions Showing Significant Functional Connectivity With the Hippocampal Seed Across all Task Conditions and the Prefrontal Seed in the Episodic Condition (LV2)

Brain region	<i>x</i>	<i>y</i>	<i>z</i>	BSR	Cluster size (voxels)
R Hippocampus	36	-20	-14	15.5407	4450
R Cerebellum	36	-66	-46	13.5569	2004
L Parahippocampal gyrus (BA 35)	-22	-22	-16	20.9438	912
L Inferior parietal lobule (BA 40)	-50	-36	44	10.7506	811
L Middle temporal gyrus (BA 37)	-48	-58	6	5.5853	515
L Precentral gyrus (BA 6)	-38	-6	52	7.7004	484
L Precuneus (BA 39)	-36	-62	42	8.1925	377
L Cerebellum	-8	-74	-14	5.8804	194
R Precuneus (BA 31)	22	-52	34	6.9218	185
L Middle temporal gyrus (BA 21)	-60	-14	-8	6.9786	178
R Medial frontal gyrus (BA 6)	6	8	56	6.2217	174
L Thalamus	-16	-8	10	7.1427	167
L Inferior occipital gyrus (BA 18)	-28	-96	-10	8.1243	166
R Precentral gyrus (BA 9)	44	14	34	4.6694	157
R Caudate	10	2	6	6.7655	146
L Cerebellum	-18	-40	-30	6.2663	120
L Inferior parietal lobule (BA 40)	-48	-28	28	5.3507	102
L Middle occipital gyrus (BA 19)	-34	-78	26	4.4051	94
R Cuneus (BA 17)	14	-100	4	7.9087	80
L Medial frontal gyrus (BA 6)	-8	-4	54	4.7925	80

Clusters evident during TR 4 with a bootstrap ratio of greater than ± 3 (equivalent to $P = 0.0027$) and a cluster size of minimum 80 voxels are reported.

The significance and reliability of these results is computed by permutation testing and by a bootstrap estimation of the standard errors of the voxel saliences. In this study, 500 permutations were computed and the bootstrap estimation procedure was carried out 100 times. The permutation test determines the significance of each LV, while the bootstrap estimation of the standard errors of the salience values determines how robustly each voxel contributes to each of the LVs.

The LVs produced by PLS are orthogonal to one another, and each is associated with a linear contrast between the experimental conditions and images of the brain showing the regions that covary with the contrasts at each time point. In seed PLS, each LV identifies contrasting patterns of functional connectivity (warm- vs. cool-colored regions, in our figures). The contribution of each voxel to the LV is indicated by its bootstrap ratio (BSR), which represents the salience of each voxel divided by its standard error. The sign of the BSR indicates which

regions are coactive (same sign), or differentially active (opposing signs), although the positive/negative sign itself is arbitrary (i.e. negative BSR values do *not* represent deactivations, but rather a set of regions with functional connectivity that differs from that seen in regions with positive BSRs). Clusters of eighty or more voxels (2 mm isotropic voxels) in which bootstrap ratios (roughly equivalent to a *Z*-score) were greater than ± 3 are considered significant, and reported below (see Tables 1–4). The threshold of ± 3 corresponds to $P = 0.0027$, and is consistent with what is commonly used in PLS studies (Addis et al., 2012; Grigg and Grady, 2010b; Hirshhorn et al., 2012; Sheldon and Levine, 2013; Spreng and Grady, 2010). Furthermore, no correction for multiple comparisons is necessary, since PLS performs all calculations in a single computational step, protecting against an inflated family-wise error rate.

The degree to which each participant expresses the whole-brain patterns of activity associated with each LV, at each time

TABLE 4.

Brain Regions Showing Significant Functional Connectivity With the Prefrontal Seed in the Difficult Spatial Condition (LV2)

Brain region	<i>x</i>	<i>y</i>	<i>z</i>	BSR	Cluster size (voxels)
L Anterior cingulate (BA 32)	-2	38	16	-4.7825	148
R Middle frontal gyrus (BA 10)	44	44	10	-6.8825	128

Clusters evident during TR 4 with a bootstrap ratio of greater than ± 3 (equivalent to $P = 0.0027$) and a cluster size of minimum 80 voxels are reported.

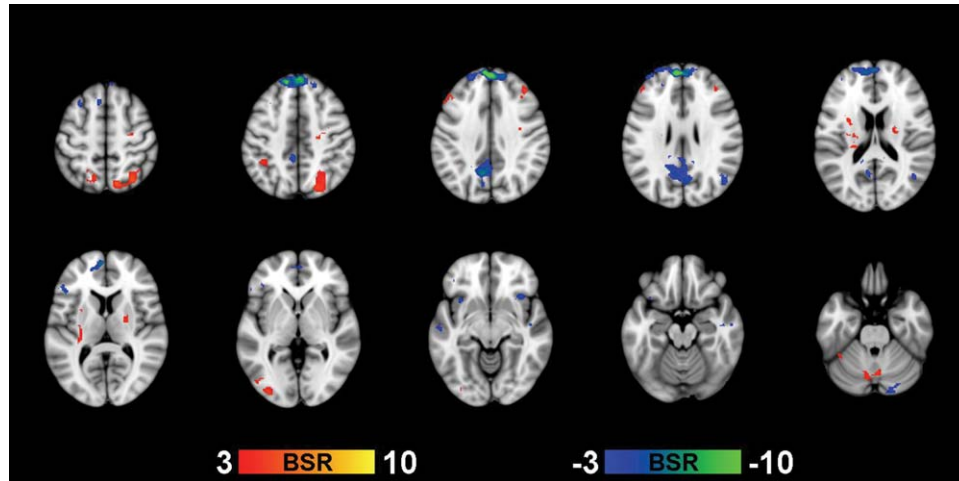


FIGURE 2. Areas of neural activity functionally connected to the prefrontal and hippocampal seeds (LV1) at TR 5 (10–12 sec after stimulus onset). Regions in cool colors (corresponding to negative BSR scores) indicate significant functional connectivity with the prefrontal seed across all task conditions (episodic, easy spatial, difficult spatial), and significant functional connectivity with the hippocampal seed in only the episodic condition. Regions

in warm colors (corresponding to positive BSR scores) indicate significant functional connectivity with the hippocampal seed in the difficult spatial condition only. Color-intensity represent the relative strength of the correlation (threshold of $BSR = \pm 3$, $P < 0.003$). [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

point, is expressed by a “brain score.” The correlation between the participants’ brain scores and the mean activity of each seed region was computed for each of the three conditions of

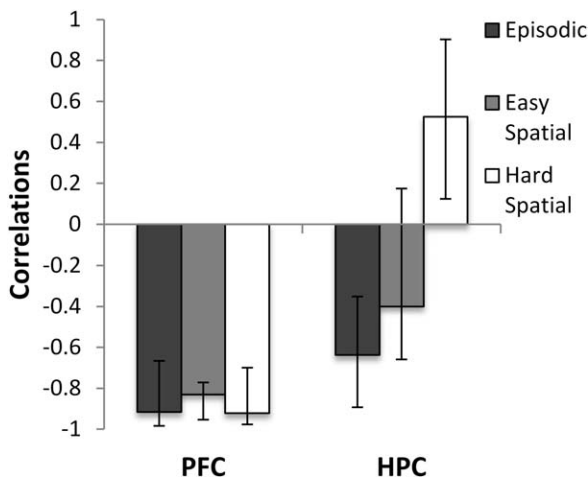


FIGURE 3. Correlations of prefrontal and hippocampal seeds with whole-brain networks of activity (LV1). Regardless of the task condition, activity in the prefrontal seed (PFC) was highly correlated with the associated whole-brain network (see Fig. 2). For the hippocampal seed (HPC), activity only correlated with activity in the PFC seed and the accompanying whole-brain network in the episodic condition. In the difficult spatial condition, activity in the HPC seed was negatively correlated with activity in the PFC seed and correlated instead with an orthogonal set of brain areas (see Fig. 2). In the easy spatial condition, activity in the HPC seed did not significantly correlate with activity in the PFC seed or either whole-brain network (as shown by the confidence interval, which includes zero). Error bars reflect 95% confidence intervals.

interest. A high correlation between activity in the seed region and the brain scores for the given pattern of activity indicates that activity in the seed and those brain regions correlate across participants for a given condition, and, therefore, these areas are functionally connected in that condition.

By referring to the patterns of neural activity (BSR values) in conjunction with the correlations between brain scores and seed-region activity for each condition, this analysis shows, for each experimental condition, which areas of the brain are reliably functionally connected to the seed regions of interest, across all participants. The significance of the correlation is shown by its 95% confidence interval, which is derived from the bootstrap resampling procedure; correlations whose confidence intervals do not include zero are considered to be significant. A significant positive or negative correlation indicates that activity in the seed covaries with one of the two orthogonal patterns of brain activity represented by the LV (positive correlation indicates covariance between seed region activity and the areas with positive BSR values, represented by warm colors in figures; negative correlation indicates covariance between seed region activity and areas with negative BSR values, represented by cool colors in figures). If the confidence intervals for two separate correlations do not overlap, this indicates that these correlations differ from one another.

RESULTS

This analysis resulted in two significant LVs accounting for 32.58% ($P < 0.001$) and 26.59% ($P < 0.003$) of the covariance in the dataset, respectively.

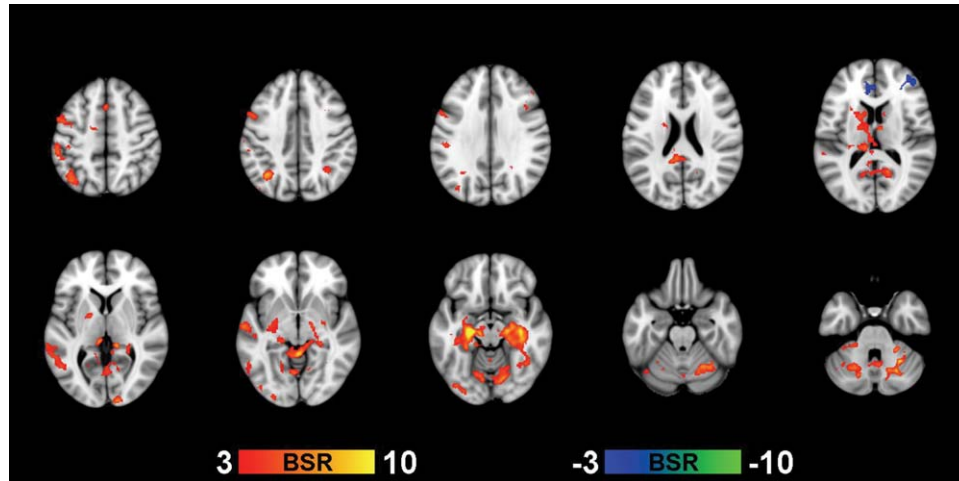


FIGURE 4. Areas of neural activity functionally connected to the prefrontal and hippocampal seeds (LV2) at TR 4 (8–10 sec after stimulus onset). Regions in warm colors (corresponding to positive BSR scores) indicate significant functional connectivity with the hippocampal seed across all task conditions (episodic, easy spatial, difficult spatial), and significant functional connectivity with the prefrontal seed in only the episodic condition.

Regions in cool colors (corresponding to negative BSR scores) indicate significant functional connectivity with the prefrontal seed in the difficult spatial condition only. Color-intensity represent the relative strength of the correlation (threshold of $BSR = \pm 3$, $P < 0.003$). [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

The first latent variable (LV1) corresponded to a pattern of activity with peaks in medial frontal and medial parietal areas (see cool-colored areas in Fig. 2). This network included areas in medial frontal gyri, precuneus, right temporoparietal junction, bilateral inferior frontal gyri, bilateral middle temporal gyri, and cerebellum. A list of significant clusters ($BSR > \pm 3$, $P < 0.003$, minimum size = 80 voxels) of functional activity is shown in Table 1. Activity in this network peaked at TR 5 (10–12 sec after stimulus onset), so data from this timepoint are reported in Figure 2 and Tables 1 and 2. Figure 3 shows how activity in each seed is correlated with the patterns of whole-brain activity for each task condition. Regardless of the task condition, activity in the prefrontal seed correlated strongly with this pattern of mostly midline frontal-parietal brain activity, $r = -0.92$ (bootstrapped confidence interval = -0.98 to -0.67), -0.83 (CI = -0.95 to -0.77) and -0.92 (CI = -0.98 to -0.70) for the episodic, easy spatial, and difficult spatial conditions, respectively. (Note: negative correlations still indicate increased functional connectivity since BSR scores for these areas are negative, see Fig. 3). However, activity in the hippocampal seed only correlated significantly with this pattern of activity in the episodic condition, $r = -0.64$ (CI = -0.89 to -0.35). Importantly, this also means that activity in the prefrontal and the hippocampal seed were only positively correlated with one another in the episodic condition. In the difficult spatial condition, activity in the hippocampal seed was significantly correlated with an orthogonal pattern of activity in the brain, $r = 0.53$ (CI = 0.12 to 0.90). This network included clusters in the right superior parietal lobule, thalamus, cerebellum, left middle occipital gyrus, left precuneus, bilateral middle frontal gyri and putamen (see

warm-colored areas in Fig. 2 and Table 2 for list of significant clusters in this pattern). Contrary to the episodic condition, activity in the hippocampal seed was negatively correlated with the activity in the prefrontal seed during the difficult spatial condition. In the easy spatial condition, activity in the hippocampal seed did not correlate significantly with either pattern of activity or with the prefrontal seed $r = -0.40$ (CI = -0.65 to 0.17 ; nonsignificant since the bootstrapped confidence interval contains zero).

The second significant latent variable (LV2) corresponded to a different pattern of neural activity, mainly located in the medial temporal lobes (see warm-colored areas in Fig. 4). This network included clusters in the hippocampi and the parahippocampal gyri, bilaterally, as well as areas in the cerebellum, left inferior parietal lobule and middle temporal gyrus, bilateral precuneus and precentral gyrus, as well as the thalamus and striatum. Table 3 provides a list of significant clusters of activity corresponding to this latent variable ($BSR > \pm 3$, $P < 0.003$, minimum size = 80 voxels). Activity in this network peaked slightly earlier than the pattern from LV1, at TR 4 (8–10 sec after stimulus onset), so data from this timepoint are reported in Figure 4 and Tables 3 and 4. Figure 5 shows how, for this second LV, activity in each of the seeds is correlated with the whole-brain patterns of activity, across task conditions. In contrast to the results from LV1, the functional connectivity of the hippocampus did not vary according to condition in this latent variable. Across all three task conditions, the activity in the hippocampus was significantly correlated with the activity in the network described above (for episodic: $r = 0.81$, CI = 0.69 to 0.95 ; for easy spatial: $r = 0.63$, CI = 0.41 to 0.88 ; for difficult spatial: $r = 0.85$, CI = 0.74 to 0.96), shown in warm

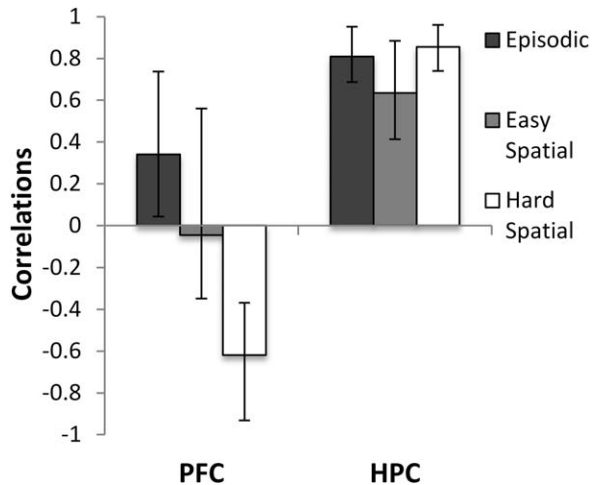


FIGURE 5. Correlations of prefrontal and hippocampal seeds with whole-brain networks of activity (LV2). Regardless of the task condition, activity in the hippocampal seed (HPC) was highly correlated with the associated whole-brain network (see Fig. 4). For the prefrontal seed (PFC), activity only correlated with activity in the HPC seed and the accompanying whole-brain network in the episodic condition. In the difficult spatial condition, activity in the PFC seed was negatively correlated with activity in the HPC seed and correlated instead with an orthogonal set of brain areas (see Fig. 4). In the easy spatial condition, activity in the PFC seed did not correlate significantly with activity in the HPC seed or either whole-brain network (as shown by the confidence interval, which includes zero). Error bars reflect 95% confidence intervals.

colors in Figure 4 and listed in Table 3. Interestingly, as with the first LV, activity in the prefrontal seed only positively correlated with activity in the hippocampal seed and its accompanying pattern of whole-brain activity during the episodic condition, $r = 0.34$ (CI = 0.04 to 0.74). Once again, during the difficult spatial condition, the connectivity patterns for the hippocampal seed and the prefrontal seed were markedly different. During the difficult spatial condition, activity in the prefrontal seed was correlated significantly with an orthogonal pattern of brain activity, including small clusters in the anterior cingulate gyrus and the right middle frontal gyrus, $r = -0.62$ (CI = -0.93 to -0.37). The areas in this pattern of activity are shown in cool-colored areas in Figure 4, and listed in Table 4. Finally, as in the first LV, during the easy spatial condition, activity in the prefrontal seed did not correlate significantly with either pattern of whole-brain activity, $r = -0.05$ (CI = -0.35 to 0.56 ; non-significant since the bootstrapped confidence interval contains zero).

DISCUSSION

In this study, we sought to characterize the neural relations between episodic and spatial memory by conducting a seed-based multivariate analysis of functional connectivity during memory tasks requiring episodic and spatial judgments (Hirshhorn et al., 2012). While Hirshhorn et al.'s (2012) original

study revealed neural areas of overlapping and non-overlapping activation during episodic and spatial memory tasks based on real-world landmarks, the current study extended these findings by demonstrating how areas that were commonly activated across tasks differed in functional connectivity with one another. We used as seeds the medial prefrontal cortex and the hippocampus, two regions of peak activity common to the spatial and episodic memory tasks, and determined the areas of the brain that covaried in activity with these regions of interest across each condition. This analysis yielded two sub-networks of functional connectivity, one including primarily medial prefrontal and medial parietal areas, and the other, consisting mainly of medial temporal lobe areas and medial parietal areas, which crucially, were functionally coupled with one another during the episodic memory condition but not during the spatial memory conditions.

It was first necessary to assess the similarity of the sub-networks found in the present study to the functional connectivity observed in previously reported sub-networks of the default and autobiographical memory networks (St Jacques et al., 2011; Kim, 2012; Campbell et al., 2013; Andrews-Hanna et al., 2010, 2014). The main clusters of activity correlating with the dmPFC seed in the first network (LV1) were in the dorsal anterior medial prefrontal cortex and medial parietal areas, including the posterior cingulate cortex and the precuneus, resembling the pattern in the midline core network, consisting of the amPFC and PCC (Andrews-Hanna et al., 2010). This network also included activation in the inferior frontal gyri and middle temporal gyri, bilaterally, and the right temporoparietal junction, areas that are consistent with the areas identified in the dmPFC network by Andrews-Hanna et al. (2010), but were found to couple with the amPFC-PCC core by Yeo et al. (2011). Thus, this network appears to show some similarity to both the dmPFC network and the midline core, as originally identified by Andrews-Hanna et al. (2010). St-Jacques et al. (2011) identified a “medial PFC” network comprised of the dmPFC, posterior cingulate and ventral parietal cortices. The more dorsal frontal activity, posterior midline activity and right temporoparietal junction activity found in LV1 closely resemble this pattern, though the authors did not find activity in the inferior frontal gyri and middle temporal gyri, as we did here.

The second network, found in LV2 to correlate in activity with the hippocampal seed, was comprised of large hippocampal and parahippocampal clusters of activity, as well as regions in the retrosplenial cortex, inferior parietal lobule, and lateral temporal cortices. This closely resembles the “MTL subsystem” that has been found consistently in the connectivity studies reviewed above (Andrews-Hanna et al., 2010; St Jacques et al., 2011; Kim, 2012; Campbell et al., 2013). One disparity between our network and those of previous reports is the absence of activation in the vmPFC, which has been found to be part of the network by some (Andrews-Hanna et al., 2010; St Jacques et al., 2011), but not others (Campbell et al., 2013; Yeo et al., 2011; Kim, 2012). Additionally, based on previous reports, the thalamic, cerebellar, and frontal (especially

precentral gyrus) activation was not predicted. Nevertheless, the main areas of activation closely resemble the areas found in previously reported MTL networks. Thus, taken together, the present study provides further corroboration of the presence of consistent sub-networks existing within a default network pattern of activity, including a medial prefrontal-parietal network and a posterior medial temporal-parietal network.

Having established the presence of these sub-networks, our primary aim was to examine the extent to which functional connectivity of these seeds and networks differed across episodic and spatial task conditions, or resembled one another. Many functional connectivity analyses have been conducted on resting state data (Fox et al., 2005; Greicius et al., 2009; Grigg and Grady, 2010b; Buckner, 2012; Spreng et al., 2012; Campbell et al., 2013), but examining functional connectivity during task conditions can reveal how areas of the brain couple or uncouple their activity with one another based on the task being performed (Andrews-Hanna et al., 2010; Grigg and Grady, 2010a; Cabeza and Moscovitch, 2013). Andrews-Hanna et al. (2014) propose that the differences in functional specialization among the sub-networks of the default network may be obscured by examining functional connectivity during unconstrained periods of rest, when presumably all subnetworks may become active. Our examination of patterns of correlations in activity of each seed with one another and the whole-brain networks, across each task condition, yielded important findings that reveal more about how the subnetworks of the default network interact.

First, we found that the activity in the prefrontal seed was coupled with activity in the medial prefrontal-parietal network, regardless of the task condition. Similarly, the activity in the hippocampal seed was coupled with activity in the MTL network regardless of the task condition. These results were not surprising given that in each case the seed was part of one of the main clusters in the network. This also indicates, however, that the functional connectivity within these two default network subsystems is stable, and expressed strongly across multiple cognitive processes, as well as at rest.

More interesting were the correlations in activity across the two networks and seeds of interest. The first LV demonstrated that activity in the hippocampal seed only correlated with activity in the medial prefrontal-parietal network during the episodic memory condition. This was replicated in the second LV, which showed the reverse pattern: activity in the prefrontal seed only correlated with activity in the hippocampus and its accompanying MTL network during the episodic memory condition. In contrast, during the difficult spatial condition, activity in the hippocampal seed was negatively correlated with activity in the prefrontal seed and its accompanying network, pairing instead with an orthogonal set of regions. This pairing represented a marked switch from the episodic condition to the difficult spatial condition. Once again in the second LV, during the difficult spatial task, activity in the prefrontal seed was negatively correlated with the hippocampal seed and the MTL network, and coupled with a separate set of regions. Finally, during the easy spatial condition, there was no relation-

ship between the prefrontal seed and the MTL network or the hippocampal seed and the medial prefrontal-parietal network.

These results not only confirm the presence of functionally distinct sub-networks within the default network areas (Andrews-Hanna et al., 2010; St Jacques et al., 2011; Kim, 2012; Campbell et al., 2013), but they also provide novel insight into how these networks coordinate their activity according to the nature of the task being performed. Our results indicate that during an episodic memory task, the activity across the two sub-networks was correlated, but during difficult spatial memory tasks the subsystems were uncoupled or even acted in opposition. This builds on the finding that functional connections *within* subnetworks may exist stably in the brain throughout the various tasks or even at rest, but that coordinated activity *between* the subnetworks only occurs under certain conditions. In this case, these results suggest that a common MTL subnetwork is shared by episodic and spatial memory tasks, but that autobiographical episodic memory recruits additional medial prefrontal-medial parietal areas. This could support the notion that episodic memory has an underlying spatial memory component, supported by the medial temporal lobes (O'Keefe and Nadel, 1978; Hassabis and Maguire, 2007; Bird and Burgess, 2008; Maguire and Mullally, 2013). Alternatively, the common MTL sub-network activation could relate more generally to associative or relational binding, which is common across episodic and spatial memory decisions (Eichenbaum and Cohen, 2001; Hannula and Ranganath, 2008; Rosenbaum et al., 2009; Ryan et al., 2010). More research is needed to elucidate whether the common activity in the MTL relates specifically to spatial representations, or to a more general associative mechanism. This novel finding shows the importance of examining functional connectivity during related task conditions, as suggested by the component process model (Moscovitch, 1992), in order to observe dynamics within complex neural networks, rather than simply the stable functional connections that exist over time (Cabeza and Moscovitch, 2013).

This result may also fit with previous accounts suggesting that the functional specialization of the medial prefrontal-parietal subsystem is related to self-referential or personally-relevant thought, whereas the medial temporal network is closely related to memory retrieval, imagery retrieval or scene construction (Grigg and Grady, 2010a; Kim, 2012; Andrews-Hanna et al., 2010, 2014). Based on these theories of the functional specialization of the sub-networks, it would follow that only the episodic task would require coordinated activity across the two networks in question. The episodic memory task involved determining one's most recent visit to a given landmark, and, therefore, would require self-reflection and accessing autobiographical memories and the location where they were acquired, whereas making spatial judgments about those same landmarks should not invoke a representation of the self and likely not specific autobiographical memories, either. This account converges with evidence from D'Argembeau et al. (2014), who reported a network including the dmPFC, inferior frontal gyrus, middle temporal gyrus, and angular gyrus that

was preferentially activated when participants engaged in an autobiographical reasoning task, requiring reflection on the meaning and self-relevance of personal memories. Thus, while these two networks were present regardless of the task, perhaps coordinated activity across the two was only necessary during the self-related episodic memory task in order to retrieve self-relevant, autobiographical memories related to a particular spatial location, instead of making purely spatial judgments.

Another point of note is that activity in the medial prefrontal-parietal network seemed to peak a few seconds later than activity in the MTL network (lag 5 vs. lag 4, respectively). While we did not have any specific hypotheses about the time course of the activations across the various networks in the present study, this evidence may point to interesting differences in the dynamics of the networks. Perhaps viewing the landmark-pair cues initiated activity in the MTL network first, owing to the spatial nature of the cues, but in order to complete the episodic memory task, the activity extended to the medial prefrontal-parietal network as well. This resembles the construction-elaboration model of autobiographical memory described in previous studies (Addis et al., 2007; McCormick et al., 2013). This additional recruitment of the medial prefrontal-parietal network for autobiographical event elaboration would not be necessary in the strictly spatial tasks. St-Jacques et al. (2011) also examined the time courses of the network activation in their study, but found that the medial PFC network activity preceded that of the MTL network. One possible explanation for this opposite finding is that the spatial cues in the present study generated MTL activation sooner owing to an automatic triggering of spatial representations, whereas in the procedure used by St-Jacques et al., the emotionally arousing auditory word-cues they used, which were not linked directly to the episode, may have initiated a more deliberate search of autobiographical memories, followed by a later elaboration of spatial and contextual details. This explanation is speculative, however, and more research will need to be done on the dynamics of interacting sub-networks, and how these dynamics relate to the nature of the tasks being performed.

Finally, this study also indicated possible other networks unique to the difficult spatial condition, acting in opposition to the sub-networks described above. In the difficult spatial condition, not only was activity in the two sub-networks uncorrelated, but orthogonal patterns of activity were functionally connected to the seeds of interest; this was not the case in the easy spatial condition. In the first LV, during the difficult spatial condition, the hippocampus was functionally connected to a set of regions including the right superior parietal lobule, thalamus, cerebellum, left middle occipital gyrus, and the bilateral middle frontal gyri. A number of these regions have been associated with visual or spatial processing. In the second LV, the prefrontal seed showed connectivity to a much smaller network, including only two small clusters: the anterior cingulate gyrus and the right middle frontal gyrus. It is possible that during the difficult spatial condition, rather than coupling with the medial prefrontal-parietal network, the hippocampus and its accompanying MTL network were correlating in activity

with a network of areas supporting the more difficult spatial processing. It is also possible that some of the areas recruited were not specific to spatial processing, and were due instead to increased attention or effort required for this condition, but the comparable RTs in the episodic and difficult spatial condition provide some evidence against this possibility (RT: 3,559 ms in difficult spatial condition, 3,759 ms in the episodic condition). Lastly, the inverse correlation of the hippocampal seed and the medial prefrontal-parietal network, and similarly, the prefrontal seed and the MTL network, may even represent a suppression of distracting self-related thoughts or memories in order to focus more closely on the challenging spatial judgment to be made. Consistent with this interpretation, these inverse correlations and connections with additional spatial processing areas were not observed in the easy spatial condition. The easy spatial condition was not as challenging, as reflected by higher accuracy scores and retrieval times that trend toward being slower for the difficult condition (accuracy: 93% in easy spatial condition, 75% in difficult spatial condition; RT: 3,380 ms in easy spatial condition, 3,559 ms in difficult spatial condition, see Hirshhorn et al., 2012 for full results). Participants may have been able to make the easier spatial judgments without requiring the additional spatial and/or attentional resources needed for the more difficult judgments, perhaps making the suppression of the medial prefrontal-parietal network and engagement of additional areas not necessary. Further research on the networks relating to easy and difficult spatial memory or navigation tasks is needed to address these questions.

CONCLUSIONS

The present study suggests that the subsystems of the default network can flexibly synchronize and desynchronize in activity, depending on the demands of the cognitive task being performed. Finding that networks couple or decouple under different task conditions has been previously shown with respect to other neural systems and cognitive tasks, such as the interactions between the default network, dorsal attention network and the frontoparietal control network during tasks requiring goal-directed cognition (Spreng et al., 2010; Gerlach et al., 2011). This study provides a novel demonstration of these network subsystem dynamics in episodic and spatial memory tasks. The results add to the literature focusing on the differences in hippocampal activations across these different types of memory task (Hoscheidt et al., 2010; Ryan et al., 2010; Hirshhorn et al., 2012) by suggesting that areas that are commonly engaged by episodic and spatial memory tasks may still differ in terms of their interactions, according to the nature and content of the task. In particular, this study supports the notion that episodic memory and spatial memory share a medial temporal-based system, but that episodic memory requires the concerted activity across an additional medial prefrontal-parietal system underlying the self-related aspects of the

memories. More generally, the results are consistent with a component process model (Moscovitch, 1992) in which regions form temporary alliances with one another, as well as rivalries, to accomplish the tasks at hand (Cabeza and Moscovitch, 2013). Future studies will be needed to continue to probe the composition and dynamics of the various memory networks in the brain, and how these interact to support different forms of memory and its underlying processes.

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