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Intrinsic connectivity between the hippocampus and posteromedial cortex predicts memory performance in cognitively intact older individuals

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Abstract

Coherent fluctuations of spontaneous brain activity are present in distinct functional-anatomic brain systems during undirected wakefulness. However, the behavioral significance of this spontaneous activity has only begun to be investigated. Our previous studies have demonstrated that successful memory formation requires coordinated neural activity in a distributed memory network including the hippocampus and posteromedial cortices, specifically the precuneus and posterior cingulate (PPC), thought to be integral nodes of the default network. In this study, we examined whether intrinsic connectivity during the resting state between the hippocampus and PPC can predict individual differences in the performance of an associative memory task among cognitively intact older individuals. The intrinsic connectivity, between regions within the hippocampus and PPC that were maximally engaged during a subsequent memory fMRI task, was measured during a period of rest prior to the performance of the memory paradigm. Stronger connectivity between the hippocampal and posteromedial regions during rest predicted better performance on the memory task. Furthermore, hippocampal-PPC intrinsic connectivity was also significantly correlated with episodic memory measures on neuropsychological tests, but not with performance in non-memory domains. Whole brain exploratory analyses further confirmed the spatial specificity of the relationship between hippocampal-default network posteromedial cortical connectivity and memory performance in older subjects. Our findings provide support for the hypothesis that one of the functions of this large-scale brain network is to subserve episodic memory processes. Research is ongoing to determine if impaired connectivity between these regions may serve as a predictor of memory decline related to early Alzheimer's disease.

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Introduction

Functional magnetic resonance imaging (fMRI) studies have shown that spontaneous fluctuations of the blood-oxygen-level-dependent (BOLD) signal occur continuously in the resting state, in the absence of external stimuli, in human brain (Biswal et al., 1995). When examining the inter-regional correlation properties, termed “functional connectivity” or “intrinsic connectivity”, these spontaneous fluctuations demonstrate temporally coherent activity within widely distributed functional-anatomic systems (Biswal et al., 1995; Greicius et al., 2003; Seeley et al., 2007), which are thought to reflect the intrinsic functional architecture of the human brain (Vincent et al., 2007). Spatially distinct functional-anatomic networks underlying sensorimotor function, language, dorsal and ventral attention, executive control, and long-term memory have been identified by observing the topographic distribution of intrinsic connectivity (Biswal et al., 1995; Fox et al., 2006; Hampson et al., 2002; Lowe et al., 1998; Seeley et al., 2007; Vincent et al., 2006).

Importantly, recent studies have suggested that these coherent spontaneous fluctuations in distinct brain systems may have functional implications, and may be relevant to individual variability in human behavior. For example, the strength of spontaneous correlation between the posterior cingulate cortex (PCC) and medial prefrontal and ventral anterior cingulate cortices have been reported to predict individual difference in working memory performance (Hampson et al., 2006). Variance in prescan anxiety ratings and Trail Making Test performance has been linked to the variability of intrinsic connectivity within “salience” network and executive control network (Seeley et al., 2007). However, the functional significance of coherent spontaneous fluctuations in other functional-anatomic systems, such as the network supporting episodic memory, remains to be studied.

It has long been acknowledged that the hippocampus and surrounding medial temporal lobe structures are essential for episodic memory function (Squire et al., 2004). Emerging evidence from functional imaging further suggests that memory function may be subserved by a distributed network that includes not only the hippocampal memory system, but also medial and lateral parietal regions involved in the default mode or “core” network (Buckner et al., 2008; Spreng et al., 2009). For example, event-related fMRI studies in young subjects have revealed that activity within medial and lateral parietal regions can be specifically modulated during memory processes, resulting in “activation” in episodic memory retrieval (Wagner et al., 2005; Wheeler and Buckner, 2003), or in “deactivation” during successful encoding (Daselaar et al., 2004; Otten and Rugg, 2001). Furthermore, recent evidence suggests that the ability to flexibly modulate activity from encoding deactivation to retrieval activation in the PPC may be critical to memory success (Daselaar et al., 2009; Kim et al. in press).

Recent studies in older adults across the spectrum of normal aging, mild cognitive impairment (MCI), and mild Alzheimer’s disease (AD) have suggested that alterations in hippocampal activation are inversely correlated with changes in deactivation in posteromedial regions over the course of AD (Celone et al., 2006; Pihlajamaki et al., 2008; Pihlajamaki et al., 2009). The age-related memory impairment has been shown to be associated with loss of deactivation in the posteromedial cortices (Miller et al., 2008). These findings suggest that successful memory formation requires the coordinated modulation of neural activity among regions in a distributed memory network, in particular the hippocampus and posteromedial cortices, which may be particularly vulnerable in the process of brain aging.

In parallel with these findings from task-invoked activity response, the investigation of functional connectivity during the resting state has delineated a set of regions in parietal

cortex, including the precuneus, posterior cingulate cortex and bilateral inferior parietal lobules, as well as regions in medial prefrontal and lateral temporal cortices, which constitute an intrinsically correlated network associated with the hippocampus (Greicius et al., 2004; Kahn et al., 2008; Vincent et al., 2006). Notably, the intrinsic hippocampal connectivity map shows considerable overlap with default network map (Buckner et al., 2008; Vincent et al., 2006), and these network regions also closely correspond to regions responsive to episodic memory processing (Miller et al., 2008; Wheeler and Buckner, 2004). Interestingly, these regions are selectively vulnerable to early AD pathology (Sperling et al., 2009). These observations that the key nodes in the network identified by intrinsic connectivity overlap the regions required for successful encoding and retrieval suggest the possibility that coherent fluctuations of intrinsic activity between the hippocampus and the posteromedial regions of the default network might be related to the engagement of these regions in memory processes.

In the present study, we investigated the behavioral significance of coherent fluctuations during the resting state in a group of cognitively intact older individuals. We first determined the regions engaged in successful encoding during a cross-modal associative memory paradigm, and then measured the correlation between spontaneous BOLD signal fluctuations across these regions, acquired during a period of rest *prior* to the memory task. We hypothesized that the strength of intrinsic connectivity at rest within the distributed memory network, in particular, between the hippocampus and posteromedial cortices, might be predictive of individual performance on memory tests.

Materials and Methods

Participants

Seventeen healthy old adults (ages 62 to 83) participated this study. The subjects were drawn from participants in an ongoing longitudinal study examining cognitive aging and preclinical predictors of AD. Written informed consent was obtained from each subject and the study procedures were approved by the Human Research Committee at the Massachusetts General Hospital and Brigham and Women's Hospital. All subjects were screened for neurologic and psychiatric illnesses, and underwent neuropsychological assessment. Eligible subjects were cognitively normal (Clinical Dementia Rating (CDR) of 0.0) and had objective memory performance within 1.0 standard deviation of age-and education-adjusted normative scores. One subject was excluded from intrinsic connectivity analysis due to excessive head motion during resting-state fMRI scanning, but was included in the task fMRI analysis to identify regions of interest.

The neuropsychological test battery was administered within 3 months of the fMRI session, and included assessment of global cognition with Mini-Mental State Examination (MMSE), executive function with Trail-making Test B (Trails B), processing speed with Digit Symbol test (Digit Symbol), and episodic memory with Logical Memory Delayed Recall in Wechsler Memory Scale (WMS-LM DR) (see Table 1 for test scores).

Experimental design

This study consisted of a resting state fMRI experiment and an associative memory fMRI experiment. During the resting run, which was acquired prior to the fMRI memory task, subjects were instructed to fixate on a visual cross-hair centered on a screen. The resting run was six minutes and forty seconds in duration.

The associative memory paradigm used in this study was modified from previously published versions of face-name associative encoding task to incorporate a mixed block and event-related paradigm (Celone et al., 2006; Miller et al., 2008; Sperling et al., 2002).

Subjects were scanned while viewing 84 novel face–name pairs. Faces were displayed against a black background with a fictional first name printed in white underneath the face for 4.5 s. Each run consisted of three conditions: novel face-name pairs, repeated face-name pairs, and fixation. During the novel blocks, the "jittered" intervals of visual fixation on a white cross-hair, varying in length from 0 to 4 s, were presented prior to the presentation of each face-name pair. There were three longer blocks of fixation between the novel and repeated blocks, each lasting 25 s, as well as 5 s of fixation at the beginning and 6 s of fixation at the end for each run.

Before each run, subjects were explicitly instructed to try to remember the name associated with the face. During the presentation of each face–name pair, subjects were asked to press a button indicating a purely subjective decision about whether the name "fits" the face or not.

During post-scan recognition memory test, subjects were showed each of the faces seen during scanning, each paired with two names written underneath: one that was correctly paired with the face and one that was paired with a different face during scanning. Subjects were asked to indicate which of two names was correctly paired with each face and to indicate how confident they were in their decision (high vs. low confidence). Post-scan memory performance was evaluated by the number of "hits" (when the correct name was identified) and the confidence level (high confidence (HC) vs. low confidence (LC)), resulting in four response types: HC-hits, HC-misses, LC-hits, and LC-misses. The percentage of overall memory performance (All-hits, i.e. HC-hits + LC-hits), and that of successful memory encoding only (HC-hits) were used as the measures of each subject's episodic memory performance.

MR data acquisition

Subjects were scanned using a Siemens (Iselin, NJ) Trio 3.0 Tesla scanner with a twelve-channel head coil. Functional images were acquired for both resting state and memory task by using a gradient-echo echo-planar imaging (EPI) sequence (repetition time = 2000ms, echo time = 30ms, flip angle = 90°). Thirty slices were acquired in an oblique coronal orientation perpendicular to the anterior–posterior commissure line, with 5-mm thick slices and 1-mm gap and 3.125 × 3.125 mm in-plane resolution. The resting run generated 195 whole-brain volumes. For memory task scanning, six functional runs were acquired for each subject with 127 whole-brain volumes per run. Five "dummy" scans were collected at the beginning of each of task and resting runs to allow for T1 equilibration effect.

Data preprocessing

Both resting and task fMRI data were preprocessed in SPM2 (Wellcome Department of Cognitive Neurology). Resting scans were motion corrected to the first volume, normalized to the standard SPM2 EPI template, and resampled into 2-mm cubic voxels. An 8 mm full width at half maximum Gaussian smoothing kernel was then applied. The preprocessing provided a record of head motion within resting run, which was later included as a nuisance regressor in subsequent correlation analysis.

Correlation analysis

Several additional preprocessing steps were carried out to optimize the resting state data for correlation analysis (Fox et al. 2006; Vincent et al. 2006). Firstly, temporal filtering (0.009 Hz < f < 0.08 Hz) was applied to the time courses of each voxel to remove low- and high-frequency components of resting fMRI data. Next, distinct sources of spurious variance along with their temporal derivatives were further removed from the data by linear regression: (1) six parameters generated from realignment of head motion; (2) the whole brain signal averaged from mask region in template space; (3) signal from regions of interest

(ROIs) located in the ventricles and deep cerebral white matter. Regression of each of these signals was performed stepwise and the residual time courses were retained for subsequent correlation analysis.

Two types of analyses were performed to test the hypothesis regarding intrinsic connectivity between regions engaged in memory task predicting individual memory performance: (1) a hypothesis-driven analysis in which the strength of intrinsic connectivity was measured between pre-specified ROIs in the hippocampus and posteromedial cortex derived from the memory task data and then this strength of connectivity was analyzed in relation to memory performance; and (2) exploratory analyses, aiming to investigate the spatial specificity of memory-related functional connectivity, that employed separate hippocampal and precuneus/posterior cingulate (PPC) seed regions and generated whole-brain correlation maps in which connectivity with the seed regions predicted memory performance. For computation of correlation strength between pairs of regions, the time courses from the resting data were extracted from pairs of ROIs defined by the associative memory task (see below) and the correlation coefficients were computed by using Pearson's product-moment formula. The correlation coefficients were converted to z values using Fisher's transformation and entered into connectivity-behavior analyses. Whole-brain correlation maps for each seed in the hippocampus and PPC were generated by computing the correlation coefficients between the averaged time course in each seed region and the time course of each voxel across the whole brain. The resulting correlation coefficients were converted to z values using Fisher's transformation and entered into a random effects one-sample t-test in a voxel-wise manner to generate seed-related connectivity maps.

Definition of regions of interest

To define the memory task-related ROIs carried forward to the resting state correlation analysis, the fMRI task data were analyzed using statistical parametric mapping (SPM2). The functional data were preprocessed using procedures similar to that used in resting state data, including realignment of head motion within and across functional runs, normalization to MNI template space and resampled to 3 mm cubic voxels, and smoothing with 8 mm Gaussian kernel.

Trials were categorized by recognition accuracy (hit vs. miss) and confidence (high confidence vs. low confidence), allowing for four possible conditions: HC-hit, HC-miss, LC-hit, and LC-miss. For each subject, all runs were concatenated and a general linear model (GLM) was constructed to characterize the hemodynamic responses for four experimental conditions. A train of delta functions representing each of the four experimental conditions was convolved with the SPM hemodynamic response function to generate the task model. No scaling was implemented for global effects. A high pass filter of 260 s was used to filter out low-frequency variations.

For each subject, HC-hits vs. Fixation contrast and Fixation vs. HC-hits contrast were created and were then entered into a second-level random-effect group analysis. Voxels were considered significant at $p < 0.001$ (uncorrected). Due to *a priori* hypothesis regarding the hippocampus and posteromedial regions based on our previous studies, region of interest analyses were performed by masking the group maps with MNI templates of the hippocampus and the PPC in each of two hemispheres to localize peak voxels engaged in the task within these regions. A total of four peaks were identified for each of the two regions for each of two hemispheres. Two 3-mm-radius spheres centered on the peak voxel in left and right hippocampus, as well as two 12-mm-radius spheres centered on the peak voxel in left and right PPC were created. Computations of 4 pairs of inter-regional correlation analyses were performed: left hippocampus vs. left PPC; left hippocampus vs. right PPC; right hippocampus vs. left PPC; right hippocampus vs. right PPC. Exploratory whole brain

connectivity maps were then generated using the activation peak from the right hippocampus and the deactivation peak from the right PPC as these regions demonstrated the greatest statistical significance (see Results).

Connectivity-behavior analyses

Connectivity-behavior analyses were carried out through hypothesis-driven ROI and whole brain exploration using seed-based correlation maps. To test the *a priori* hypotheses, the percentage of overall memory performance (All-hits) on post-scan memory test was correlated with the strength of connectivity in each pair of task-defined ROIs across subjects. To minimize the effect of correct guessing, the percentage of HC-hits was used as another measure of memory performance to correlate with the same set of connectivity measures. To further test the specificity of hypothesized relationship, the same set of connectivity measures were correlated with neuropsychological measures of episodic memory (WMS-LM DR), global cognition (MMSE), executive function (Trails B), and processing speed (Digit Symbol). Using a whole-brain regression analysis with the percentage of All-hits as a covariate on hippocampal connectivity maps, exploratory analyses were then performed to search for regions whose intrinsic connectivity with the right hippocampal ROI predicted overall memory performance (All-hits). The identical procedure was then applied to search for regions whose intrinsic connectivity with the right PPC ROI predicted overall memory performance (All-hits). The resulting maps were thresholded at $p < 0.001$ (uncorrected).

Results

Demographic information and memory performance with All-hits and HC-hits on the post-scan recognition test are presented in Table 1.

Task-defined regions of interest analyses

Brain regions demonstrating significant activation in the HC-hits greater than Fixation contrast for the group map included bilateral occipital cortices, bilateral fusiform gyri, bilateral temporal cortices, left inferior frontal cortex, left thalamus and bilateral hippocampi ($p < 0.001$). The region of interest analysis constrained by the MNI hippocampal mask identified significant clusters in right hippocampus with peak MNI coordinates 21 -6 -18 (Z score: 5.18) (Figure 1A) and left hippocampus with peak coordinates -24 -30 -6 (Z score: 5.14) (Figure 1B).

Brain regions demonstrating significant deactivation in the Fixation greater than HC-hits contrast included bilateral medial and lateral parietal cortices, bilateral occipital cortices and bilateral lateral temporal cortices ($p < 0.001$). The region of interest analysis constrained by the bilateral precuneus/posterior cingulate (PPC) MNI mask revealed significant deactivation in the right PPC with peak coordinates 3 -51 39 (Z score: 3.74) (Figure 1C), and in the left PPC with peak coordinates -9 -54 39 (Z score: 3.21) (Figure 1D).

ROI based correlational analyses

As shown in Figure 2, the greater intrinsic connectivity between the right hippocampus and right PPC ($r = 0.56$, $p = 0.02$) (Figure 2A) and between right hippocampus and left PPC ($r = 0.59$, $p = 0.02$) (Figure 2B) predicted better overall memory performance (All-hits). In addition, the intrinsic connectivity between the left hippocampus with left PPC and right PPC also showed a positive relationship with overall memory performance (All-hits), similar directionality to the results found with the right hippocampus, this was a much weaker effect, and was not statistically significant (left PPC: $r = 0.30$, $p = 0.26$; and right PPC: $r = 0.25$, $p = 0.25$). When examining the relationships between the same set of

connectivity measures and HC-his, the connectivity between right hippocampus and left PPC, as well as right PPC showed trend level correlation with HC-hits (left PPC: $r = 0.47$, $p = 0.06$; and right PPC: $r = 0.44$, $p = 0.09$); the connectivity between left hippocampus and left PPC, as well as right PPC showed no relationship with HC-hits (left PPC: $r = -0.13$, $p = 0.64$; and right PPC: $r = -0.08$, $p = 0.78$).

We then calculated correlations between the same set of connectivity measures and neuropsychological test scores of global cognition, executive function, processing speed and episodic memory. We found that only episodic memory (WMS-LM DR) performance was related to these connectivity measures (right hippocampus-right PPC: $r = 0.56$, $p = 0.02$; right hippocampus-left PPC: $r = 0.63$, $p = 0.01$; left hippocampus-right PPC: $r = 0.44$, $p = 0.08$; left hippocampus-left PPC: $r = 0.5$, $p = 0.05$). The non-memory domain measures (Trails B, Digit Symbol, and MMSE) did not demonstrate any significant relationships with hippocampus-PPC intrinsic connectivity. The correlations between intrinsic functional connectivity and all neuropsychological test scores are listed in Table 2.

In the whole-brain exploratory analysis with a threshold of $p < 0.001$, using the right hippocampal seed to examine the relationship of intrinsic connectivity to overall memory performance, an only significant cluster was found in the left PPC cortex (23 voxels with peak MNI coordinates -4 -48 34). When a more liberal threshold of $p < 0.005$ with an extent threshold of 10 contiguous voxels was applied, additional clusters located in the left angular gyrus (13 voxels with peak MNI coordinates -40 -66 28) and medial prefrontal regions (3 clusters: 11 voxels with peak MNI coordinates 16 48 2; 21 voxels with peak MNI coordinates 2 62 6; 18 voxels with peak MNI coordinates -4 62 24), as well as other regions were identified. Notably, 5 out of seven clusters were distributed in the regions constituting the default network (Figure 3A). The reverse exploratory analysis, using the right PPC seed to identify regions whose intrinsic connectivity predicted overall memory performance, revealed a small cluster located in the right hippocampus (14 voxels with peak MNI coordinates 24 -8 -20) (Figure 3B), at the more liberal threshold of $p < 0.005$ with an extent threshold of 10 contiguous voxels.

Discussion

These data demonstrate that individual differences in performance on an associative episodic memory task can be predicted by individual differences in intrinsic hippocampal-posteromedial cortical connectivity during the resting state. Specifically, the intrinsic connectivity between regions that are maximally engaged during successful memory performance was examined during quiet wakefulness prior to performance of the memory task. Stronger correlations between the spontaneous fluctuations in these regions at rest were associated with better memory performance. The specificity of the finding was enhanced by demonstrating that the hippocampal-PPC intrinsic connectivity also significantly correlated with the episodic memory measure on neuropsychological tests, but not with any of the non-memory domain measures. Exploratory whole brain analyses confirmed the spatial specificity of these findings that the hippocampal connectivity with the PPC and other posterior regions of the default network was related to memory performance in these older adults. The present results provide further evidence that the coherence of spontaneous fluctuations in the intrinsic activity of components of the default network is important for episodic memory, and support the view that one of the functions of this large-scale brain network is to subserve episodic memory abilities. More generally, these findings also lend the support to the hypothesis that the spontaneous fluctuations in intrinsic brain activity may be relevant to individual difference in behavior among older individuals.

Although the literature on resting functional connectivity has been focused primarily on positive correlations between the posterior cingulate and the hippocampus (Greicius et al., 2004; Kahn et al., 2008), and the majority of the higher performing older subjects in our study demonstrated positive correlations between the hippocampus and the PPC, as well as other default network regions, we did observe that some low performing older subjects demonstrated negative or very low positive correlation values. There are several possible reasons for this observation. Previous work has also shown that aging is associated with reduced positive correlations between the hippocampi and several regions of the default network, and indeed that some older subjects demonstrate negative correlations, which typically results in low correlation strength among older subjects compared to young (Andrews-Hanna et al., 2007; Hedden et al., 2009). Our study suggests that lower positive correlations and especially negative correlations between the hippocampus and PPC are associated with poorer memory performance. Furthermore, as we defined the functional ROI based on the regions maximally engaged in successful encoding, which requires activation in the hippocampi and deactivation in the PPC, we may be especially detecting regions in which poor performing older subjects demonstrate impaired ability to rapidly modulate activity in these regions. In fact, two recent papers have suggested that the modulating from encoding deactivation to retrieval activation in the PPC may be critical to memory success (Daselaar et al., 2009; Kim et al. in press). We postulate that our finding of decreasing positive correlation between the hippocampi and PPC may be indicative of failing integrity of memory systems in some older subjects.

It has long been noted that humans demonstrate notable inter-subject variability in cognitive task performance. Previous fMRI studies revealed that such performance variability might be related to the differences in regional brain activity elicited by a given task (Ress and Heeger, 2003; Sapir et al., 2005; Wagner et al., 1998). It has been previously demonstrated that the variability in evoked brain activity can predict whether or not visual stimuli will be detected (Ress and Heeger, 2003), and whether verbal stimuli will be remembered. However, accumulating evidence has shown that performance variability in human behavior may also be determined by ongoing fluctuations of intrinsic activity in regions of corresponding functional networks (Boly et al., 2007; Eichele et al., 2008; Fox et al., 2007; Hesselmann et al., 2008a; Hesselmann et al., 2008b; Wig et al., 2008). For example, spontaneous fluctuations of BOLD signal in motor cortex have been reported to account for the variability on force of button press when subjects performed a cued button-press task (Fox et al., 2007); and prestimulus, baseline activity fluctuations in the thalamus and dorsal lateral prefrontal cortex predicted somatosensory perception (Boly et al., 2007); while prestimulus activity in the fusiform face area biases subsequent perceptual decision on ambiguous figures (Hesselmann et al., 2008a). Likewise, the coherent intrinsic activity in distributed functional-anatomic networks implicated in salience processing and executive control could modulate the variability in anxiety ratings and Trail Making Test performance (Seeley et al., 2007). The present results build on previous findings relating the strength of connectivity between nodes of large-scale brain networks to individual differences in behavior by demonstrating that such relationships exist for episodic memory.

Echoing the finding that intrinsic coherent activity can be relevant to performance variability in healthy adults, disrupted intrinsic connectivity has been associated with impaired cognitive ability. For example, the disruption of intrinsic connectivity between the medial prefrontal cortex and the PCC was related to declines in cognitive performance across executive, memory and processing speed in advanced aging (Andrews-Hanna et al., 2007). The strength in the hippocampal-PPC connectivity in these older adults was also significantly reduced when compared with results from young adults (Andrews-Hanna et al., 2007; Buckner et al., 2008). In the present study, we demonstrate that connectivity between two key nodes of a distributed memory network is predictive of episodic memory

performance in healthy older individuals. The hippocampus has been reported to be functionally connected with the cortical regions of the default network, and is sometimes included in the definition of the default network (Buckner et al., 2008; Greicius et al., 2004). Our previous work with task-related fMRI in older subjects has also suggested that alterations in PPC memory-related neural activity were evident in low-performing cognitively normal older adults, requiring paradoxical increases in hippocampal activity for successful memory encoding (Miller et al., 2008). Future work will be required to investigate whether longitudinal memory decline in aging is directly related to disruption of the hippocampal-PPC intrinsic connectivity. Furthermore, given that the amyloid-related functional disruption in the PPC is linked to the dysfunction in the medial temporal lobe memory system in cognitively normal and mildly impaired older individuals (Sperling et al., 2009), and also given that the disruption of intrinsic connectivity between these regions has been observed in patients with MCI and mild AD (Greicius et al., 2004; Wang et al., 2006), the measurement of the hippocampal-posteromedial network integrity may be particularly valuable in probing alterations in episodic memory network in the earliest stage of AD.

The current findings may have implications for our understanding of the functional role of spontaneous brain activity. The spontaneous BOLD signal fluctuations were thought to originate from a range of processes from intrinsic low-level physiological processes that are independent of mental activity, to spontaneous cognition (Buckner et al., 2008; Fox and Raichle, 2007; Larson-Prior et al., 2009; Vincent et al., 2007). Recent evidence, however, suggests that this “spontaneous” activity may be dynamically associated with preceding experience, or may serve a role in the consolidation of previous experience (Hasson et al., 2009; Lewis et al., 2009). Because the resting run in this paradigm was scanned prior to performance of the memory task, the intrinsic connectivity measured in the present study was unlikely to be modulated by the task or reflect the subjects’ “recapitulating” the task. In this case, given that the intrinsic connectivity correlated with the two episodic memory measures acquired minutes and 3 months within resting-state scanning, which may be reflective a persistent behavioral trait, the present results may suggest that the coherence of spontaneous fluctuations in intrinsic brain activity can be, at least in part, a reflection of the stable trait of the large-scale functional-anatomic network in these older adults.

The interpretation of current results may also have implications for our understanding of the neural mechanism underlying episodic memory, and the role of the default network or core network in supporting memory function. The PPC, as well as regions in the lateral parietal and medial prefrontal cortices, has been observed to show greater activity during resting state as compared with a variety of goal-directed tasks, thought to subserve the default mode of brain function (Raichle et al., 2001). Recent fMRI studies of episodic memory revealed that the PPC shows greater activity during successful episodic retrieval but during unsuccessful episodic encoding, suggesting that activity in key nodes of the default network is associated with retrieval success and encoding failure (Daselaar et al., 2004; Daselaar et al., 2009; Kim et al. in press). Our recent studies have suggested that successful memory formation requires coordinated activity between the hippocampus and the PPC in both young and older subjects (Miller et al., 2008). Whereas the present results showed that stronger temporal coupling of default network activity between the PPC and hippocampus was associated with better performance on the episodic memory task. Further studies investigating the relationship between correlated intrinsic activity in the default network activity and encoding/retrieval invoked activity in the PPC are needed. Furthermore, the hippocampus and PPC have also been found to be the components of the core network, hypothesized that a set of regions serves as the common neural underpinnings to support a broad number of cognitive domains, including autobiographical memory, prospection, navigation, theory of mind, and default mode (Spreng et al., 2009). Likewise, the present findings relating the intrinsic connectivity of two key nodes of the default network or core

network to individual memory performance may support the view that one of the functions of these large-scale brain networks is to subserve episodic memory abilities in healthy older adults (Buckner et al., 2008; Greicius et al., 2003).

There are several limitations to the present study. First, the current study includes a relatively small number of older subjects and because these subjects were well characterized and specifically selected to be cognitively normal, the ranges in behavioral measures were limited, both of which may be the factors requiring relatively liberal threshold (although a cut-off of $p < 0.001$ is commonly used in studies with older subjects or patients). Future studies including subjects with mild cognitive impairment are likely to have more statistical power to observe such relationships. Nevertheless, even with this small number of subjects, we also found that hippocampal-PPC intrinsic connectivity was correlated with two measures of episodic memory but not with any of the non-memory domain measures, including Trails B, Digit Symbol, and MMSE.

Second, it is important to note that the hippocampal-PPC intrinsic connectivity is likely only one of the factors contributing to episodic memory performance. The variance in observed connectivity-behavioral relationship might suggest that successful episodic memory is the result of integrated activity of multiple brain systems. For example, those subjects with relatively weak hippocampal-PPC connectivity may compensate a compromised episodic memory system by engagement of alternative prefrontal systems to maintain a relatively high memory score. Future studies examining the integrity of the prefrontal control systems may prove valuable in understanding the interactive or compensatory relationship between the executive control and episodic memory systems and how such a relationship can affect episodic memory performance in these older subjects.

Lastly, it is noteworthy that both inter-individual variability in human behavior and alterations of intrinsic functional connectivity in large-scale brain networks may be relevant to the activity of neurotransmitter systems. For example, activity in the striatal dopamine system, measured by dopaminergic D2 receptor binding, correlated with episodic memory performance in older adults (Backman et al., 2000). The experimental manipulation of dopaminergic neurotransmission could change the intrinsic connectivity in striatal cognitive and motor networks (Kelly et al., 2009; Li et al., 2000). Given that multiple neurotransmission systems, such as cholinergic, GABAergic and glutamatergic systems, are involved in the human memory network, and in particular, that the hippocampus and posterior cingulate are densely innervated with cholinergic fibres (Selden et al., 1998), the current connectivity-behavioral relationship remains to be fully understood by exploring the relationships of neurotransmission systems with hippocampal-PPC intrinsic connectivity, as well as with episodic memory ability in these older subjects.

In summary, the current findings provide further evidence for the hypothesis that coherent fluctuations of spontaneous brain activity may be relevant to individual difference in specific cognitive behavior among older adults. The localization of the relationship observed from intrinsic connectivity-episodic memory performance promotes our understanding of the default network functions, and the vulnerability of this network in the aging brain. Given the converging evidence that intrinsic connectivity between the hippocampus and PPC is critical for preserved memory function in older individuals, and the vulnerability of these regions to Alzheimer's disease pathology, longitudinal fMRI studies are crucial to determine whether impaired connectivity will serve as a sensitive predictor of memory decline related to early Alzheimer's disease.

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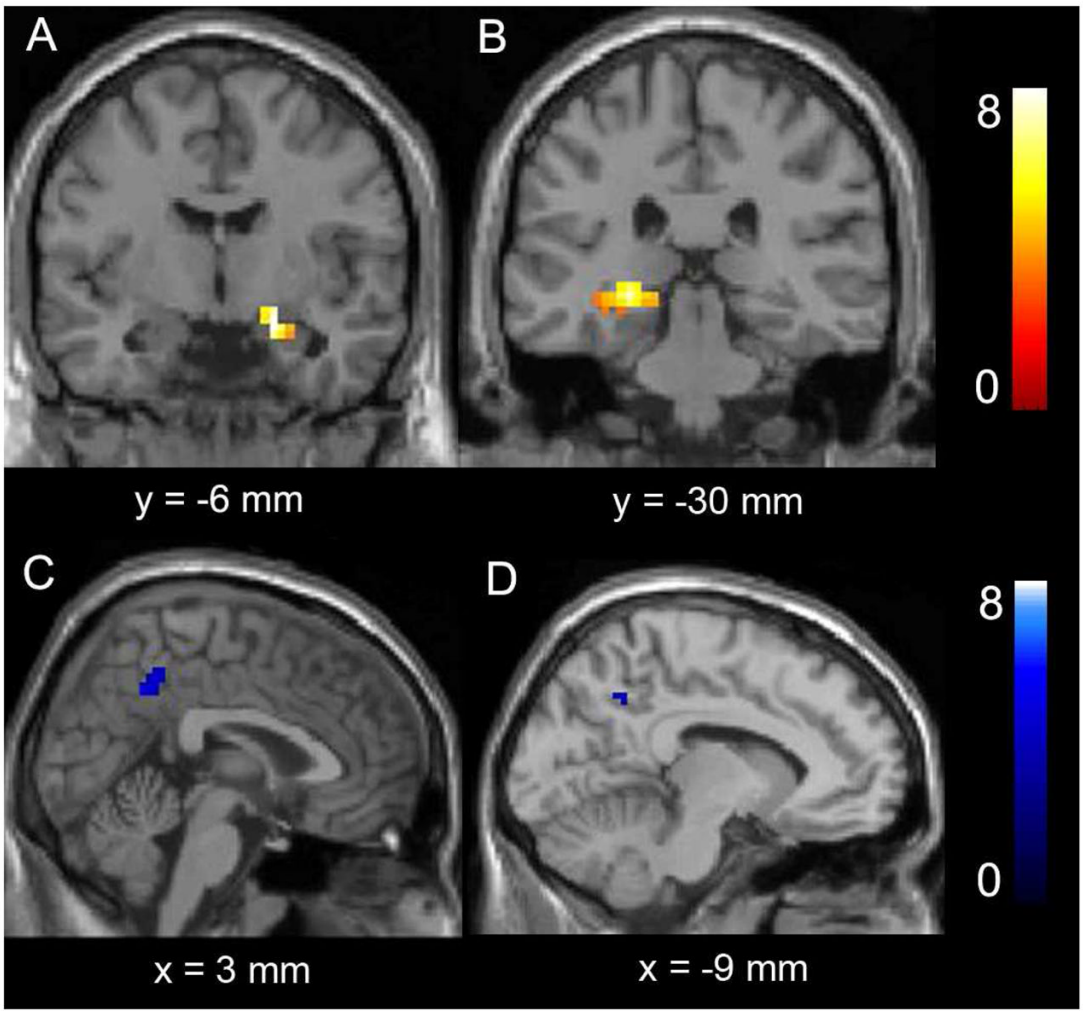

Figure 1.

Group data identifying the peak voxels of the activation in the hippocampi, and the peak voxels of the deactivation in the PPC. (A) and (B) show the clusters containing the right (MNI coordinates 21 -6 -18) and left (MNI coordinates -24 -30 -6) hippocampal activation peak, identified by the ROI analysis on the group result of HC-hits vs. Fixation, with a threshold of $p < 0.001$ (uncorrected), using MNI hippocampal templates, bilaterally. A sub-peak was chosen for the left hippocampus because the peak activation was localized at the far edge of the left hippocampus. (C) and (D) show the clusters containing the right (MNI coordinates 3 -51 39) and left (MNI coordinates -9 -54 39) PPC deactivation, identified by the ROI analysis on the group result of Fixation vs. HC-hits, with a threshold of $p < 0.001$ (uncorrected), using MNI precuneus and posterior cingulate cortex templates, bilaterally. Left indicates left side of brain.

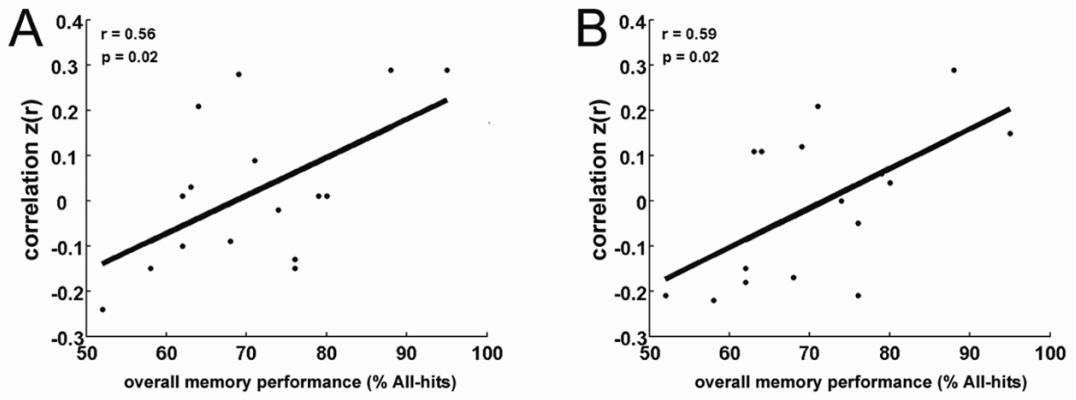

Figure 2.

Intrinsic connectivity between the hippocampus and posteromedial regions predicts overall memory performance in older adults. The z-transformed correlation coefficients (y axis) computed by correlating the spontaneous activity between the right hippocampal ROI and the right PPC ROI (A), and between the right hippocampal ROI and left PPC ROI (B), are plotted against individual overall memory performance (the percentage of All-hits, x axis) on the post-scan recognition task, respectively. The strength of intrinsic connectivity between right hippocampal ROI and right PPC ROI (A) ($R = 0.56$, $p = 0.02$), and between right hippocampal ROI and left PPC ROI (B) ($R = 0.59$, $p = 0.02$), predicts overall memory performance on this task in these older adults.

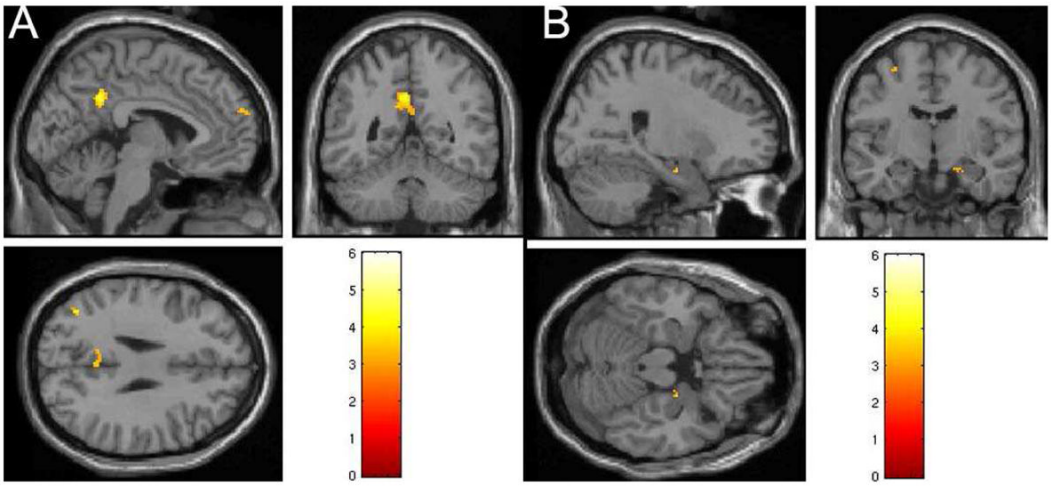

Figure 3.

Overall memory performance correlations with right hippocampal intrinsic connectivity (A); and right PPC intrinsic connectivity (B). The PPC, left lateral parietal region, and medial prefrontal region, where intrinsic connectivity with the right hippocampal seed predicts the overall memory performance on the post-scan recognition task in these older adults, were showed in (A). Notably, these regions are also the nodes constituting the default network. The right hippocampus, and a region in the left superior frontal gyrus, where intrinsic connectivity with the right PPC seed predicts the overall memory performance on the post-scan recognition task in these older adults, were showed in (B). The maps were thresholded at $p < 0.005$ (uncorrected) with an extent threshold of 10 contiguous voxels.

Table 1

Means and standard deviations of demographic information, memory performance on the postscan recognition test, and the neuropsychological data.

	All subjects (n = 17)
Age (range)	73.4 ± 6.0 (62–83)
M/F	3/14
Years of education.	16.5 ± 3.1
All-hits	71% ± 11%
HC-hits	42% ± 19%
MMSE	29.4 ± 1.0
LM-DR	11.1 ± 3.3
Trails B	71.4 ± 24.9
Digit Symbol	47.2 ± 14.3

MMSE = Mini-Mental State Examination, LM DR = Logical Memory Delayed Recall in the Wechsler Memory Scale.

Table 2

Correlations between the hippocampal-PPC intrinsic functional connectivity and memory performance on the post-scan memory task, as well as with neuropsychological measures

	R Hip vs. L PPC		R Hip vs. R PPC		L Hip vs. L PPC		L Hip vs. R PPC	
	r	p	r	p	r	p	r	p
All-hits	0.59	0.02	0.56	0.02	0.3	0.26	0.25	0.25
HC-hits	0.47	0.06	0.44	0.09	−0.13	0.64	−0.08	0.78
MMSE	−0.12	0.65	−0.13	0.63	0.29	0.28	0.17	0.53
LM DR	0.63	0.01	0.56	0.02	0.5	0.05	0.44	0.08
Trails B	0.12	0.66	0.3	0.25	−0.04	0.87	−0.1	0.7
Digit Symbol	−0.11	0.68	−0.32	0.21	−0.13	0.64	−0.04	0.87

Hip = hippocampus; R = right; L = left; MMSE = Mini-Mental State Examination; LM DR = Logical Memory Delayed Recall in the Wechsler Memory Scale