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Anterior and Posterior MTL Networks in Aging and MCI

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Abstract

Two neuroanatomically dissociable, large-scale cortical memory networks, referred to as the anterior and posterior MTL (medial temporal lobe) networks have recently been described (Kahn et al 2008; Libby et al 2012) in young adults using resting-state BOLD-fMRI-based functional connectivity (fc-BOLD). They have been hypothesized to subserve distinct mnemonic, as well as non-memory cognitive functions, and are thought to be associated with differential vulnerability in neurological disorders (Ranganath & Ritchey 2012). In this paper, we demonstrate the existence of these functional networks in an older adult population, and in a cohort of patients diagnosed with amnesic mild cognitive impairment (MCI). Anatomical subregions of interest (ROI) in the MTL were defined using high-resolution T2-weighted MRI and used as seeds for defining the putative networks using fc-BOLD. While the literature has suggested that the posterior MTL network is particularly vulnerable to early Alzheimer's Disease, we show that both networks are affected in MCI, to varying degrees, compared to the control group. Further, cortical thickness in the brain regions defined by these networks was reduced in MCI.

Introduction

The medial temporal lobe (MTL) is a brain region that is known to mediate functions of episodic memory and learning (Squire et al 2004). It is an area with extensive bi-directional

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connections to the rest of the brain, and thus often thought to integrate complex sets of information from multiple sensory modalities. MTL is also an area vulnerable to several neurological disorders such as Alzheimer's Disease and Temporal Lobe Epilepsy (Huesgen et al 1993; Braak & Braak 1991; Berkovic et al 1991). As such, the MTL, which includes the hippocampal formation, as well as extra-hippocampal cortical regions, such as entorhinal cortex (ERC), perirhinal cortex (PRC), and parahippocampal cortex (PHC), has been one of the most widely studied brain regions both in animal and human experiments.

In human neuroimaging, the MTL has been studied using structural and functional MRI, both in experiments probing learning and memory function and those that look for non-invasive imaging-based biomarkers of disease processes (Dickerson & Eichenbaum 2010). The imaging technique of resting-state BOLD functional MRI, in particular, has become popular in describing connections projecting to and from the MTL at a network level, exploring how they may subserve differential brain function, and determining how they are affected in disease (Sperling et al 2010; Carr et al 2010; Filippi & Agosta 2011). For example, the MTL has been shown to be part of the widely-studied default mode network (Greicius et al 2003), which also is comprised of several cortical nodes, including the posterior cingulate, lateral inferior parietal, and medial prefrontal cortices. A number of studies have reported that the strength of the default mode network diminishes in patients with Alzheimer's Disease, and even in patients at the prodromal stages of the disease (Sperling et al 2010; Wang et al 2006).

More recently, functional connectivity of MTL has been studied in a more granular fashion, where distinct networks associated with specific subregions of the MTL have been described. In particular, a few studies have defined an "anterior MTL network" that connects the ventral and lateral temporal cortex, temporal pole and parts of orbitofrontal cortex to anterior regions of the MTL such as PRC, ERC and anterior hippocampus, as well as a "posterior MTL network" that connects posterior MTL regions such as the PHC and posterior hippocampus to dorsal-stream areas, including the inferior parietal lobe, as well as other nodes of the default-mode network including posterior cingulate (Kahn et al 2008; Libby et al 2012). These dissociable networks recapitulate to varying degrees anatomic connections described in rodents and primates. Further, these networks have been postulated to be dissociable, but interactive, in several cognitive domains, including episodic memory, perception, social cognition, and semantic cognition (Ranganath and Ritchy, 2012).

To our knowledge, the anterior and posterior MTL networks have only been described using anatomically defined seed-based analyses in young adults to date. However, one group did describe alterations in an anterior temporal network that was distinct from the default mode in older adults, MCI and mild AD patients (Gour et al 2011) using a data-driven method, Independent Component Analysis (ICA). The same group found an increase in anterior temporal network connectivity in early onset AD and decreased connectivity in late onset AD patients, in a separate study (Gour et al 2013) that used seeds based on previously reported MNI coordinates of networks nodes. Nonetheless, the existence of both networks in older adults defined explicitly using carefully labeled MTL subregions, their dissociable nature, and any differences in strength due to disease processes have not been studied.

In the context of early AD pathology, this type of analysis may be particularly valuable, given the specificity of MTL subregional involvement. Early AD pathology does not uniformly involve all of the MTL substructures. Indeed, the first MTL region with neurofibrillary tangle pathology is the medial wall of the PRC (BA 35), with then further progression into the lateral ERC and then Cornu ammonis 1 (CA1) (Braak & Braak 1991; Delacourte et al 1999). As noted above, the PRC and ERC have been described as nodes of the anterior MTL network. Thus, one might expect the anterior network strength to be affected in the earliest stages of AD. In contrast, it is the network strength in parts of the posterior MTL network, particularly connectivity between the hippocampus and nodes of the default-mode network, such as posterior cingulate, that has often been shown to be decreased in mild AD and MCI (often conceptualized as largely reflecting ‘prodromal AD’) populations. Indeed, a recent review of the anterior and posterior medial temporal networks noted that both anterior and posterior hippocampal structures are affected in AD, but that cortical structures of the posterior network are associated with more severe dysfunction, as evidenced by such measures as glucose metabolism (Ranganath & Ritchey 2012). Nonetheless, these authors predict that pathologic changes in MTL regions associated with different neurodegenerative conditions may be reflected more broadly with dysfunction in these dissociable networks. However, more specific interrogation of the integrity of the anterior network is actually quite limited in AD and, thus, merits additional attention in light of the significant early involvement of its MTL node.

In this study, we first describe the anterior and posterior MTL networks in cohorts of older healthy controls and patients diagnosed with MCI. This is done by computing functional connectivity of three anterior (hippocampal head, entorhinal cortex and perirhinal cortex) and two posterior (hippocampal tail and parahippocampal cortex) MTL subregions. After defining these networks for the first time in these populations, we then investigate group differences in the strengths of the two networks between controls and MCI. We find that both networks are affected to a degree in MCI, with lower MTL connectivity. Finally, we perform an additional group analysis based on cortical thickness measurements to show that the average thickness over the regions belonging to both networks is lower in MCI than in controls, suggesting that both networks also undergo structural atrophy by the prodromal stage of disease.

Methods

Subjects and Image Acquisition

The study population consists of age- and education-matched older healthy controls (OHC, n=39) and amnesic MCI patients (n=30). All participants were recruited from the Penn Memory Center (PMC), a specialty memory clinic at the University of Pennsylvania and the clinical core of the NIA-funded Alzheimer’s Disease Center (ADC). The study was approved by the University of Pennsylvania’s Institutional Review Board and consent was signed by each subject. Patients underwent extensive evaluation by a neurologist, psychiatrist, or gerontologist including physical and neurological exam, history from both patient and informant, and psychometric testing. Diagnosis was made based on a consensus conference at the PMC using standard criteria for MCI (Petersen et al., 1999, 2004). All had

at least the following psychometric battery within 3 months of their scan: Mini-Mental Status Exam (MMSE; (Folstein et al 1975)); Digit Span subtest of the Wechsler Adult Intelligence Scale III (Wechsler 1987); Category fluency (animals) (Spreen 1998); Consortium to Establish a Registry for Alzheimer's Disease (CERAD) Word List Memory (WLM) test (Morris et al 1989); Trail Making Test (TMT) A and B (Reitan 1958); and a 30-item version of the Boston Naming Test (BNT; (Kaplan et al 1983)). Table 1 lists the demographic characteristics of the study cohort.

Images were acquired on a 3T Siemens Trio scanner. The imaging protocol included the following sequences: 1 mm³ T1-weighted structural MRI, high-resolution T2-weighted structural MRI (0.4×0.4×2.0 mm³ with 0.6 mm gap) with a partial field of view covering the entire MTL angulated perpendicular to the long axis of the hippocampus, and 3×3×3 mm³ resting-state BOLD fMRI covering the entire brain (TR/TE = 4000/30 ms; Matrix = 64×64; 40 axial slices).

Labeling of MTL Subregions

Subregions of the MTL were labeled on the high-resolution T2-MRI using an updated version of a previously validated automated segmentation method (Pluta et al 2012; Yushkevich et al 2010). Thirteen different regions including hippocampal subfields and extra-hippocampal cortices in the MTL are labeled. The hippocampus is macroscopically subdivided along the long-axis into head, body and tail regions (see protocol details in (Yushkevich et al 2010)). In addition, subiculum, posterior and anterior aspects of entorhinal cortex (hereafter referred to as ERC), Brodmann areas 35 and 36 that together constitute perirhinal cortex (PRC), and a region partially covering the parahippocampal cortex (PHC) is labeled. Five of these ROIs (Hippocampal head, Hippocampal tail, Brodmann Area 35 for PRC, PHC and anterior ERC) were used as seed regions for functional connectivity analysis. An example of seed regions defined in T2-MRI is shown in Figure 1. We note that the performance of the automatic segmentation algorithm was similar in both OHC and MCI subjects in an evaluation study as evidenced by no significant difference in Dice overlap metric between automated and manual labeling ($p > 0.05$ for all five ROIs used here by two sample t-tests). Mean Dice overlaps were as follows (OHC/MCI): Hippocampal head $0.87 \pm 0.04 / 0.88 \pm 0.03$, Hippocampal tail $0.83 \pm 0.09 / 0.82 \pm 0.08$, PRC $0.71 \pm 0.05 / 0.73 \pm 0.09$, ERC $0.79 \pm 0.05 / 0.79 \pm 0.06$, PHC $0.78 \pm 0.07 / 0.76 \pm 0.05$.

Preprocessing of BOLD fMRI data

The fMRI time series for each subject was realigned to the mean EPI image to correct for subject motion, and registered to the T1-weighted anatomical MRI using SPM5 (Friston et al 1995). The T2-weighted MRI where MTL subregions were labeled was also coregistered to the T1-MRI using the FLIRT rigid registration tool (Jenkinson & Smith 2001) with six degrees of freedom and the mutual information metric. Temporal filtering to extract signals in the 0.008–0.08 Hz frequency band was performed, followed by a linear regression to factor out mean global signal, average signal from white matter and average signal from ventricular cerebrospinal fluid regions. The GM, WM and CSF tissue labels were obtained using the Atropos segmentation tool (Avants et al 2011). The residual time series was used for subsequent functional connectivity analysis.

Defining Anterior and Posterior Networks

The residual fMRI time series following preprocessing was averaged within the following MTL subregions that were used as seed ROIs to define the two MTL networks: hippocampal head, BA35 (PRC) and anterior ERC (for anterior network); hippocampal tail and parahippocampal cortex (for posterior network).

In order to minimize effects of signal dropout and low signal-to-noise ratio (SNR) in the extrahippocampal cortex, a voxel selection method similar to (Libby et al 2012) was employed. Only voxels with a temporal SNR > 20 within each seed ROI were retained for analysis. Temporal SNR was generally lower in the anterior MTL regions, and lower in extrahippocampal cortex than in the hippocampus. Mean temporal SNR were as follows: Head=56, Tail=88, ERC=27, PRC=30, PHC=52.

Time series correlation maps were constructed for each seed ROI in each subject's native image space. Nonlinear spatial transformations were then applied to these correlation maps and resampled into the space of a custom-made optimal anatomical template constructed using ANTs (Avants et al 2008).

Once the respective correlation maps were transformed to the common template space, the anterior and posterior networks were defined by conducting voxel-wise one-sample t-tests for significant positive correlation within each cohort. Additionally, the head and tail correlation maps were directly compared using voxelwise paired sample t-tests in both cohorts. Multiple comparisons correction was done using false discovery rate (FDR) (Yekutieli & Benjamini 1999).

Group differences in network strength

Group differences of strength of functional connectivity within each network defined above were assessed using an exploratory voxel-wise analysis to find clusters of significantly different correlation between OHC and MCI subjects using two-sample t-tests. Permutation-based cluster analysis with FWER correction (Hayasaka & Nichols 2004; Nichols & Holmes 2002) was used to correct for multiple comparisons.

It has been shown that group differences in subject motion can confound group analysis of fc-BOLD data (Power et al 2012; Van Dijk et al 2012). We tested if group differences in motion parameters exist between control and aMCI subjects. Two sample t-tests between mean motion as defined by Van Dijk et al. was used for this purpose.

Group differences in cortical thickness

Cortical thickness was measured using an image-registration based method (Das et al 2009) that generates thickness maps in the native T1-MRI image space of the subject. As part of post-hoc analysis, these maps were transformed into the population template space and thickness values were integrated over the voxels defined as part of the respective networks. Two-sample t-tests were used to find significant difference in average thickness.

Results

Anterior and posterior MTL networks in aging

Hippocampal head, ERC and PRC were used as pre-selected seed ROIs for defining the anterior MTL network. Similarly, hippocampal tail and PHC were used for defining the posterior MTL network. Figures 2 (anterior) and 3 (posterior) show the putative networks defined this way with seeds in each hemisphere. Locations (MNI coordinates) of connectivity maximum of the largest significant clusters for each seed are listed in Supplementary Table S1.

The anterior networks in OHC as defined using the hippocampal (head) and extra-hippocampal (ERC, PRC) seeds largely overlap (Figure 1 (a), (c), (e), also see Figure 4), with the head showing generally more expansive connectivity. The network spans orbitofrontal and other ventromedial regions in the frontal lobe, parts of inferior temporal lobe, and large swaths of bilateral anterior temporal lobe, including temporal poles. These regions largely match networks described in young adults in (Kahn et al 2008; Libby et al 2012). From panels (b), (d) and (f) in Figure 1, the respective networks in MCI appear to have a reduced spatial extent for all six seed regions.

The posterior networks in OHC as defined using the hippocampal (tail) and extra-hippocampal (PHC) seeds largely overlap (Figure 3 (a),(c), also Figure 4), with the tail showing generally more widespread connectivity. The network spans parts of posterior cingulate cortex and precuneus, parts of superior temporal lobe, and inferior parietal/angular gyrus regions. These regions largely match posterior MTL networks described in young adults in (Kahn et al 2008; Libby et al 2012). Similar to the anterior network, panels (b) and (d) in Figure 3 show that the respective networks in MCI appear to have a reduced spatial extent for all four seed regions, with the difference being more noticeable in the tail network.

Figure 4 highlights the similarity of anterior and posterior networks defined by respective hippocampal and extrahippocampal seeds. Regions in purple indicate large spatial overlap of voxels belonging to networks defined by all seed ROIs.

Figures 2 and 3 visually demonstrate that the anterior and posterior MTL networks as defined by functional connectivity with hippocampal head vs. tail and ERC/PRC vs. PHC are spatially dissociable to a large degree. In order to directly test the dissociability, we performed voxel-wise comparisons of head vs. tail connectivity within each group. Figure 5 shows the areas of significant difference (FDR-corrected, $p < 0.05$) in connectivity with head vs. tail. Areas in the ventromedial frontal lobe, orbitofrontal cortex, inferior and anterior temporal lobes show stronger anterior (head) network connectivity in both groups. In contrast, posterior cingulate and inferior parietal regions show stronger posterior (tail) network connectivity. MCI shows less extensive statistical network difference than OHC.

Group difference in functional connectivity in the anterior and posterior MTL networks

Figure 6 shows results of voxel-wise group comparisons of anterior and posterior network strengths between OHC and MCI. In each case, the largest cluster of group difference is

shown in red, the second largest in green, followed by blue, yellow, cyan and magenta in decreasing order of size, defined with a threshold of $p < 0.05$. The posterior network showed decreased connectivity in the MCI cohort with the largest cluster of group difference (red) reaching significance (permutation-corrected $p < 0.05$) in the left tail network. This is expected based on default mode network differences reported by various groups (Wang et al 2006), which have shown that connectivity between the hippocampus and default mode nodes, such as posterior cingulate, is decreased in MCI.

In addition, we found generally decreased connectivity within the less-well studied anterior MTL network with some clusters reaching statistical significance consistent with the involvement of the disease in anterior MTL structures. In particular, the right ERC and right PRC networks showed significantly decreased connectivity (permutation-corrected $p < 0.05$) in MCI. Networks defined by left ERC/PRC and bilateral hippocampal head seed ROIs did not reach significant group difference using permutation-based analysis – however, these networks also had clusters of reduced connectivity in MCI in similar regions with a more liberal threshold, as indicated in Fig. 6. Table 2 lists the MNI coordinates of the centroids of permutation-based significant clusters of group difference for each network. A two sample t-test of motion parameters as suggested by (Van Dijk et al 2012) showed that there was no significant group difference in motion between OHC and MCI groups ($p=0.52$). Thus, it is unlikely that the group effects seen here are driven by subject motion.

Reduced cortical thickness in both MTL networks

We measured average cortical thickness over the regions defined to be part of the anterior and posterior MTL networks (Fig. 2 and 3). Thickness was significantly reduced in MCI both in the head network (left: OHC 2.74 ± 0.29 mm, MCI 2.57 ± 0.21 mm, $p = 0.005$; right: OHC 2.63 ± 0.29 mm, MCI 2.48 ± 0.20 mm, $p = 0.011$) and the tail network (left: OHC 2.46 ± 0.31 mm, MCI 2.31 ± 0.21 mm, $p = 0.017$; right: OHC 2.37 ± 0.31 mm, MCI 2.22 ± 0.21 mm, $p = 0.016$). Results were similar for the PRC, ERC and PHC networks. In contrast, in a region that is not associated with significant pathology in early AD, the calcarine sulcus in the occipital lobe, there was no significant group difference in thickness (left: OHC 1.34 ± 0.25 mm, MCI 1.37 ± 0.22 mm, $p = 0.67$; right: OHC 1.32 ± 0.32 mm, MCI 1.33 ± 0.26 mm, $p = 0.54$).

Discussion

In this paper, we have demonstrated that dissociable anterior and posterior MTL networks, as recently described by several authors in young adults, also exist in older healthy adults and patients diagnosed with MCI. Additionally, these data provide evidence that function and structure within both of these networks are affected in the prodromal stage of AD frequently associated with amnesic MCI. The finding that both networks are vulnerable to early AD has implications for the nature of cognitive impairment at this early symptomatic disease stage. Thus, this work extends the findings in young adults supporting the existence of these networks to an older population and provides evidence for their vulnerability in early AD.

We note that networks were defined in both OHC and MCI cohorts by using data from all of the subjects in the respective groups. Future availability of large datasets such as ADNI2 (Mueller et al 2013) will allow us to use networks defined in an independent cohort of subjects and test group effects in a different set of subjects. Doing so here would have decreased the power of such analyses given the relatively small sample size in our data. However, the group comparison presented here was done in a completely exploratory manner where no information – notably significant regions from within-group analysis – was used. This avoids a possible bias which would exist if ROI-based group analysis were carried out on regions predefined using the same set of subjects.

Choice of seed regions

Previous studies have used both PRC/ERC vs PHC and anterior vs posterior regions of the hippocampus as seed ROIs for defining the anterior and posterior MTL networks, respectively (Kahn et al 2008; Libby et al 2012). We specifically used a hippocampal head and tail seed because they have also been postulated to be dissociable nodes of the two networks by (Ranganath & Ritchey 2012) with relatively selective connectivity to PRC/lateral ERC and PHC, respectively. Additional motivation for use of hippocampus-based seeds were somewhat superior EPI signal quality within the hippocampus relative to the extra-hippocampal MTL cortices and that our automated segmentation routine made head and tail labels readily available. We also used ERC/PRC and PHC as alternative seed regions to define the networks, as other researchers have done (Kahn et al 2008). In order to mitigate effects of poorer EPI signal quality in MTL cortices, particularly in ERC/PRC (Olman et al 2009), we only used voxels within a seed ROI that had a temporal SNR>20, following criterion used by others (Libby et al 2012). It is worth noting that the rodent literature suggests segregation of the network within the ERC, with lateral ERC demonstrating greater connectivity with PRC while medial ERC is more strongly connected to PHC (Witter et al 2000; Ranganath & Ritchey 2012). Thus, our use of an ERC seed could be viewed as problematic given possible mixing of the networks. However, the ERC seed produced a similar spatial distribution of connectivity as the more “pure” anterior MTL seeds of the PRC and head of the hippocampus. As such, it remains unclear whether the same ERC segregation is observed in humans as described in the rodent literature and work using higher resolution imaging will need to be pursued to better address this issue.

In general, extrahippocampal seeds produced highly overlapping networks to those defined by head and tail respectively, although head/tail produced stronger network effects, perhaps because of better hippocampal signal (see Figures 2 and 3).). Furthermore, both sets of hippocampal and extra-hippocampal seed ROIs gave rise to distinct loci of connections, as also demonstrated in Fig. 5 by direct comparison of the two networks. This finding provides further support to the notion that these networks truly are dissociable and the present findings are remarkably similar to those reported in young adults by others (Kahn et al 2008; Libby et al 2012).

Involvement of anterior and posterior networks in MCI

While both the anterior and posterior MTL networks were clearly present in MCI, their spatial extent appeared diminished relative to that of the healthy older adults, likely

indicating that the connectivity is weaker, leading to smaller extent of suprathreshold regions of the test statistic. Direct comparison of the network strengths revealed that both the anterior and posterior networks are affected to some degree with MCI showing diminished network strength (Fig. 6). These findings were further supported by evidence of structural change within both networks as evidenced by significant cortical thinning in the MCI group. Given the small degree to which the MTL regions contribute to the spatial extent of these networks, this structural result suggests that network involvement is more broad than emanating purely from the significant MTL involvement expected in early AD. It is worth noting that the relationship between such cortical change and measures of functional connectivity remains uncertain, and, in turn, what the best approach is to try to account for or disentangle the relative effects in both.

It comes as no surprise that the posterior network would be involved in early AD given the frequent report in a number of fc-BOLD studies of impaired connectivity of regions that constitute this network, many of which are classically thought to define the default mode network (e.g. posterior cingulate and precuneus) that appears affected by pathology in early AD. Potentially more controversial is evidence of involvement of the anterior network, which has not been specifically studied in this population before with one exception (Gour et al 2011) (also see (Gour et al 2013) for a study in AD). However, as noted above, anterior MTL sites constitute the first regions associated with neurofibrillary tangle pathology, particularly PRC and ERC during Braak Stage I and II, respectively (Braak & Braak 1991; Delacourte et al 1999). As such, findings of involvement of this network in prodromal AD is consistent with these pathological studies. Indeed, in the only other report interrogating the anterior MTL network in MCI, Gour and colleagues, using ICA, extracted similar networks as described here and found a disease effect in MCI and mild AD; however, unlike the present results, they found an increase in network strength in the patients. The present results are also consistent with the hypothesis set forth by Ranganath and Ritchey (2012) that neurodegenerative changes in MTL structures could drive dysfunction more broadly in these networks.

From the perspective of episodic memory, the involvement of both of these networks is consistent with reports that both familiarity, or non-contextual item memory, and recollection, or associative memory, are affected at this early disease stage given the putative role of anterior and posterior structures in these memory processes, respectively (Wolk et al 2008; Wolk et al 2011b; Wolk et al 2011a; Wolk et al 2013; Ally et al 2009; Didic et al 2011; Algarabel et al 2009). As anterior extra-hippocampal involvement may be more specific to early AD relative to normal aging than in the hippocampus proper, which is affected to some extent by both processes (Jagust 2013; Small et al 2011), the anterior MTL network and its associated cognitive functions may be particularly useful in disease monitoring during prodromal and perhaps preclinical stages.

Future work

Future work will relate assessments of the two networks with behavioral measures of memory and other cognitive functions. As these networks may be variably affected by aging, early AD, and perhaps other neurodegenerative conditions, study of their integrity in

reference to behavior and cognition will likely lead to greater insight into their normal functional role. It must be noted that the low resolution of EPI images here limit our ability to accurately localize BOLD signal within substructures. Coregistration of EPI data with the higher resolution T2-MRI where regions are labeled is the best approximation to localization we were able to do here. We are also collecting resting-state data at a higher resolution that may help map these networks with greater precision to specific MTL substructures. In future, improved signal quality in the inferior MTL regions will allow more reliable fc-BOLD analysis of extra-hippocampal MTL ROIs such as anterior PRC.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

Example of seed regions labeled in T2-MRI. Left: Oblique coronal brain slice with red inset enclosing right MTL. Right: Zoomed in MTL region and corresponding segmentations shown in a head and tail slice through the hippocampus.

Figure 2.
Areas of significant (FDR-corrected $p < 0.05$) functional connectivity, shown by group, using seed regions in hippocampal Head, PRC and ERC to define the anterior MTL network.

Figure 3.
Areas of significant (FDR-corrected $p < 0.05$) functional connectivity, shown by group, using seed regions in hippocampal tail and PHC to define the posterior MTL network.

Figure 4.

Overlap of networks defined by different seed ROIs as shown in Figures 2 and 3. Panels (a) and (b) show the anterior network. Red, blue and purple indicate voxels belonging to networks defined by one, two or all three seeds respectively, among hippocampal head, PRC and ERC. Panels (c) and (d) show the posterior network. Red, blue and green indicate voxels belonging to networks defined by hippocampal tail, PHC or both respectively.

Figure 5.

Areas of significant (FDR-corrected $p < 0.05$) difference in connectivity between the hippocampal head and tail networks, shown by group. Hot colors show greater connectivity to head, cool colors show greater connectivity to tail.

Figure 6.

Clusters of greater functional connectivity in OHC than in MCI. Different colors represent different sized clusters with red being the largest, followed by green, blue, yellow, cyan and magenta. Respective seed ROIs are indicated for each comparison. “**” indicates that the largest (red) cluster reaches a permutation-based FWER-corrected significance threshold of $p < 0.05$. Absence of “**” indicates that the clusters only reached significance at an uncorrected $p < 0.05$.

Table 1

Demographic Characteristics of Study Cohort

	OHC (N=39)	aMCI (N=30)
Age	70.62 (8.96)	71.60 (6.75)
Education	16.51 (2.86)	17.23 (2.43)
Female:Male	21:18	16:14
MMSE	29.46 (0.91)	27.40** (1.75)
Trails A (s)	30.38 (11.22)	45.97** (31.08)
Trails B (s)	70.31 (33.36)	128.57** (72.15)
Digit Span Forwards Max	6.91 (1.06)	6.57 (1.07)
Digit Span Backwards Max	5.26 (1.33)	4.57* (0.96)
Ten-Item word list immediate recall	24.03 (3.61)	17.34** (5.59)
(sum of three trials)		
Ten-Item word list delayed recall	8.23 (1.60)	3.20** (2.17)
Ten-item word list recognition (proportion of Hits)	9.82 (0.39)	9.10** (1.24)
Category Fluency (animals)	23.08 (5.28)	16.07** (4.90)
BNT Total	28.97 (1.29)	26.83** (3.30)

Standard deviations are in parentheses. MMSE: Mini Mental State Exam, BNT: Boston Naming Test; Note that 5 OHC and 2 MCI did not have digit span scores available, 1 MCI did not have sum of immediate recall recorded

* $P < 0.05$

** $P < 0.01$, aMCI versus OHC Comparison

Table 2

Locations of significant clusters of group difference

Network	MNI coordinate	Region
Right ERC	-17, 18, -18	Left orbitofrontal cortex
Right PRC	-53, -29, -2	Left middle, superior temporal gyrus
Left hippocampal tail	52, -26, 14	Right angular gyrus, superior temporal gyrus