Brain Struct Funct (2016) 221:3237–3258
DOI 10.1007/s00429-015-1098-4

ORIGINAL ARTICLE

Large-scale intrinsic functional network organization along the long axis of the human medial temporal lobe

Shaozheng Qin[1] · Xujun Duan[1,4] · Kaustubh Supekar[1] · Huafu Chen[4] · Tianwen Chen[1] · Vinod Menon[1,2,3]

Received: 28 November 2014 / Accepted: 20 August 2015 / Published online: 3 September 2015

Abstract The medial temporal lobe (MTL), encompassing the hippocampus and parahippocampal gyrus (PHG), is a heterogeneous structure which plays a critical role in memory and cognition. Here, we investigate functional architecture of the human MTL along the long axis of the hippocampus and PHG. The hippocampus showed stronger connectivity with striatum, ventral tegmental area and amygdala—regions important for integrating reward and affective signals, whereas the PHG showed stronger connectivity with unimodal and polymodal association cortices. In the hippocampus, the anterior node showed stronger connectivity with the anterior medial temporal lobe and the posterior node showed stronger connectivity with widely distributed cortical and subcortical regions including those involved in sensory and reward processing. In the PHG, differences were characterized by a gradient of increasing anterior-to-posterior connectivity with core nodes of the default mode network. Left and right MTL connectivity patterns were remarkably similar, except for stronger left than right MTL connectivity with regions in the left MTL, the ventral striatum and default mode network. Graph theoretical analysis of MTL-based networks revealed higher node centrality of the posterior, compared to anterior and middle hippocampus. The PHG showed prominent gradients in both node degree and centrality along its anterior-to-posterior axis. Our findings highlight several novel aspects of functional heterogeneity in connectivity along the long axis of the human MTL and provide new insights into how its network organization supports integration and segregation of signals from distributed brain areas. The implications of our findings for a principledunderstanding of distributed pathways that support memory and cognition are discussed.

Keywords Medial temporal lobe · Hippocampus · Connectivity · Network · fMRI · Memory

S. Qin and X. Duan contributed equally to this work.

Electronic supplementary material The online version of this article (doi:10.1007/s00429-015-1098-4) contains supplementary material, which is available to authorized users.

✉ Shaozheng Qin
szqin@stanford.edu

✉ Vinod Menon
menon@stanford.edu

1 Department of Psychiatry and Behavioral Sciences, Stanford University School of Medicine, 401 Quarry Rd, Stanford, CA 94304, USA

2 Department of Neurology and Neurological Sciences, Stanford University School of Medicine, Stanford, CA 94305, USA

3 Stanford Neuroscience Institute, Stanford University School of Medicine, Stanford, CA 94305, USA

4 Key Laboratory for Neuroinformation, School of Life Science and Technology, University of Electronic Science and Technology, Chengdu, People's Republic of China

Introduction

The medial temporal lobe (MTL) is a heterogeneous brain structure with multiple distinct roles in memory and cognition (Eichenbaum et al. 2007; Squire et al. 2004; Squire and Zola-Morgan 1991; Bird and Burgess 2008; Maguire et al. 2000). The hippocampus and parahippocampal gyrus (PHG) are two major anatomically distinct divisions of the MTL, spanning the dorsal and ventral aspects along its anterior–posterior axis (Squire and Zola-Morgan 1991; Squire et al. 2004). Studies on animals have shown that the

hippocampus and PHG subdivisions have different cortical and subcortical afferent and efferent projections (Goldman-Rakic et al. 1984; Kobayashi and Amaral 2003; Suzuki and Amaral 1994a), but very little is known about large-scale functional connectivity and network profiles of the human MTL at the whole-brain level. Knowledge of the large-scale functional organization of the hippocampus and the PHG is critical for understanding how each of the major MTL subdivisions makes distinct contributions to memory and cognition through their functional interactions with other distributed brain regions.

Most of our current knowledge of MTL circuitry is based on anatomical tract-tracing studies on animals (Aggleton et al. 2005; Suzuki and Amaral 1994a, b). Research in monkeys and rodents has demonstrated that the MTL receives widespread projections from multiple unimodal and polymodal association cortices. Most of these cortical inputs converge, via the perirhinal cortex (PRC) and the parahippocampal cortex (PHC) in the PHG, into the entorhinal cortex (ERC), which functions as the main interface between the hippocampus and neocortex (Van Hoesen et al. 1972; Krimer et al. 1997; Buzsaki 1996). The ERC, in turn, projects to the hippocampus, which is positioned at the top of a hierarchical circuitry within the MTL (Burwell 2000; van Strien et al. 2009; Powell et al. 2004; Sakai and Miyashita 1991). In addition to massive inputs from neocortical areas, the hippocampus also receives ascending projections from subcortical structures including the striatum and midbrain (Bird and Burgess 2008; Lisman and Grace 2005; Luo et al. 2011; Voermans et al. 2004). Thus, research in animal models has provided strong evidence that the hippocampus and PHG subdivisions (including PHC, PRC and ERC) have distinct patterns of anatomical connectivity.

The extent to which findings from histological tract-tracing studies on animals relate to the anatomical and functional organization of the human MTL is as yet unclear. To date, only a few studies have examined the structural and functional connectivity of the human MTL. Powell et al. (2004) used diffusion tensor imaging (DTI) to examine structural connectivity of the human PHG. They identified white matter pathways between the PHG and multiple cortical areas including the anterior and posterior temporal lobe, orbitofrontal cortex and extrastriate occipital lobe, as well as pathways linking the PHG and the hippocampus within the MTL (Powell et al. 2004). However, this study was restricted to connectivity of the anterior PHG along the ventral visual processing pathways, thus providing a limited view of MTL circuitry. Granziera and colleagues used diffusion spectrum imaging (DSI) to identify the hippocampus–mammillary body pathway via the fornix and connections between the lateral subiculum and the cingulate cortex (Granziera et al. 2011). Recently, Zeineh et al. (2012) combined high-resolution DTI with a detailed segmentation of the MTL to identify tracks representing the major pathways within the MTL, including the ventral cingulum bundle, the perforant pathways, subicular projections to the fornix and the ERC, and entorhinal projections to the PRC and the PHC. Due to the limited field of view used in these studies, connectivity outside of the MTL was not examined. Thus, the large-scale anatomical connectivity of the human MTL remains poorly characterized.

In contrast to the limited investigations of anatomical connectivity of the human MTL, a large number of task-related fMRI studies have focused on distinct contributions of the MTL subdivisions to different aspects of memory and cognitive processes, including item, associative and relational memory (Davachi et al. 2003; Henke et al. 1999; Davachi 2006; Qin et al. 2007, 2009; Staresina and Davachi 2010), recollection- and familiarity-based recognition memory (Diana et al. 2007; Ranganath et al. 2004; Yassa and Stark 2008), memory strength (Qin et al. 2011; Shrager et al. 2008; Song et al. 2011; Diana and Ranganath 2011), novelty detection and pattern separation (Kirwan and Stark 2004; Yassa and Stark 2008; Bakker et al. 2008). Within the anterior PHG, the PRC has been reported to be essential for item-based processing for objects and identities (Davachi et al. 2003; Henke et al. 1999; Qin et al. 2009; Staresina and Davachi 2010), while the anterior and posterior PHC (at the posterior PHG) preferentially contribute to domain-general and domain-specific (such as spatial-related) contextual information, respectively (Aminoff et al. 2007; Bar et al. 2008a, b; Litman et al. 2009; Engelien et al. 2000; Schon et al. 2004; Aminoff et al. 2013). Collectively, these studies point to material and context-specific functional distinctions along the anterior–posterior axis of the PHG. In contrast, functional dissociations along the anterior–posterior axis of the hippocampus are less well understood. Many functional neuroimaging studies have demonstrated that the hippocampus plays an important role in reward- and motivation-based learning due to its complex interaction with striatum, basal ganglia and dopaminergic midbrain regions (Shohamy and Wagner 2008; Wimmer and Shohamy 2012). While some fMRI studies have suggested that the anterior and posterior hippocampus both play domain-general roles in declarative memory (Davachi 2006; Spaniol et al. 2009; Diana et al. 2007; Eichenbaum et al. 2007), others have proposed that the posterior hippocampus is more important for recollective memory and spatial memory (Diana et al. 2007; Maguire et al. 2000; Ranganath et al. 2004) and that the anterior hippocampus plays a more dominant role in novelty- and emotion-related processes (Poppenk and Moscovitch 2011; Poppenk et al. 2008; Strange and Dolan 2006; Strange et al. 1999). How brain circuitry associated

with various MTL subdivisions supports these distinct mnemonic and cognitive functions is poorly understood. Here, we use intrinsic functional connectivity analysis in combination with brain network analysis to address critical gaps in our knowledge of human MTL circuitry.

Intrinsic functional connectivity analysis has emerged as a powerful systems neuroscience approach for uncovering key architectural features of large-scale circuits associated with individual brain areas (Bressler and Menon 2010; Fox and Raichle 2007; Greicius et al. 2003). Since its first use in mapping the somatomotor system (Biswal et al. 1995), intrinsic functional connectivity analysis has been used to characterize multiple brain systems, including those involved in sensory processing, language, emotion, and attention (Greicius et al. 2003; Fox et al. 2006; Hampson et al. 2002; Lowe et al. 1998). The first such studies involving the MTL arose from findings that this region is part of the default mode network (Greicius et al. 2004; Buckner et al. 2008), a brain network supporting internally oriented processes and autobiographical memory (Raichle et al. 2001; Greicius et al. 2003; Buckner and Carroll 2007; Vincent et al. 2006). Combining resting-state fMRI with DTI, Greicius and colleagues showed functional and structural connections between the MTL and the retrosplenial cortex as well as connections between the medial prefrontal cortex and posterior cingulate cortex (Greicius et al. 2009). The next series of studies in the field examined the intrinsic functional organization of the human MTL in more detail by examining connectivity of different segments along its axis. Kahn and colleagues reported two separate pathways associated with the anterior and posterior segments of the MTL (Kahn et al. 2008). Specifically, the posterior PHC was correlated with lateral parietal cortex and posterior medial cortex, whereas the anterior hippocampus and the ERC were correlated with the lateral temporal cortex. Similar evidence has been provided by Poppenk and Moscovitch (2011) that the anterior and posterior subdivisions of the hippocampus are involved in two different pathways, with the posterior pathway supporting recollection memory and the anterior pathway being associated with social and emotional processes. Kahn and Shohamy (2013) recently identified robust functional connectivity between the hippocampus and mesolimbic pathways in humans. However, these studies did not directly contrast functional connectivity profiles associated with different MTL subdivisions, nor did they characterize differences in connectivity between the hippocampus and PHG with subcortical and mesolimbic pathways at the whole-brain level.

More recent studies have focused on intrinsic functional connectivity within the MTL. Lacy and Stark (2012) demonstrated that within the MTL, the hippocampal subfields and PHG regions have distinct functional connectivity profiles. They found that hippocampal subfields had relatively higher correlations with each other both within and across hemispheres but did not have strong correlations with other MTL cortices. Similarly, Libby et al. (2012) characterized distinct functional connectivity profiles of the PRC and PHC with hippocampal subfields. They reported dissociations between anterior–posterior functional connectivity for hippocampal subfields CA1 and subiculum. While these studies have provided important insights into the local organization of the MTL, they leave unclear the precise dissociation of large-scale functional connectivity patterns for the human MTL subdivisions at the whole-brain level and their differential connectivity profiles along the anterior–posterior axis of the hippocampus and the PHG. Critically, none of these previous studies have examined differential connectivity with cortical and subcortical structures that are important for emotion- and reward-related processes.

In the past decade, graph theoretical approaches have provided novel quantitative metrics for characterizing the intrinsic functional organization of complex brain networks (Bullmore and Sporns 2009; Bassett and Bullmore 2006; Supekar et al. 2009). Graph theory has been used to quantify structural and functional network properties at the macroscopic whole-brain as well as microscopic cellular levels in humans and animals (Bullmore and Sporns 2009). As with many other species, human brain networks demonstrate a small-world non-random topology (Bullmore and Sporns 2009). Human structural and functional brain networks, derived from structural and functional MRI, as well as DTI, data demonstrate short path length, high degree of clustering, and modularity with clusters linked by highly connected cortical 'hubs' (Bullmore and Sporns 2009; Bassett and Bullmore 2006). These properties have been widely used as quantitative metrics of global brain network organization (Bullmore and Sporns 2009; Di Martino et al. 2014; Supekar et al. 2008). Crucially, no previous studies have investigated quantitative network metrics and organization associated with the large-scale functional organization of individual MTL subregions.

To address key gaps in the literature and to gain a better understanding of the large-scale functional organization of the MTL, we conducted a comprehensive functional connectivity and graph-based brain network analysis of distinct divisions of the hippocampus and PHG. We used resting-state fMRI data acquired from 36 healthy young adults aged 19–22 using an optimized spiral in–out pulse sequence known to reduce signal dropout and increase signal-to-noise ratio (Glover 2012; Glover and Law 2001; Glover and Thomason 2004). We used two parallel arrays of nodes along the longitudinal axis of the hippocampus and the PHG in each hemisphere (Fig. 1a). Three nodes

were chosen in the hippocampus along its anterior, middle and posterior segments to characterize intrinsic functional organization patterns along the hippocampal anterior–posterior axis. Four nodes were chosen along the PHG axis—in the anterior PRC, in the transition area between ERC and PRC, in the anterior PHC and in the posterior PHC—based on their aforementioned distinct contributions to memory and cognition. These seven nodes, representing distinct subdivisions of the hippocampus and the PHG, allowed us to systematically characterize the large-scale functional connectivity of MTL. In addition, graph analytical metrics were used to quantify and contrast the relative importance of each of the seven subdivisions within the MTL functional connectivity network. Specifically, we used node degree and centrality, two complementary graph-theoretical measures that have been widely used to capture the relative importance of a node in a network (Bolland 1988; Bullmore and Sporns 2009). The node degree provides information about how densely each node connects with all other network nodes, and eigenvector centrality measures the influence of a node in a network (Bullmore and Sporns 2009). A node with high centrality plays a crucial role in efficient communication and information transfer (Bullmore and Sporns 2009). Crucially, nodes with high degree and centrality are thought to play a key role in facilitating information transfer across the entire network, and together these measures capture fundamental properties of network organization (Bullmore and Sporns 2009). We used these two metrics to characterize differences in the importance of each node in the MTL-based target network. Based on previous findings from anatomical and functional neuroimaging studies, we predicted that the PHG would show greater connectivity with unimodal and polymodal association areas, whereas the hippocampus would exhibit greater connectivity with subcortical and other limbic areas. We further predicted that the PHG and hippocampus would show heterogeneous patterns of functional connectivity along their anterior–posterior axes and that these patterns would be further reflected in distinct network measures of node degree and centrality.

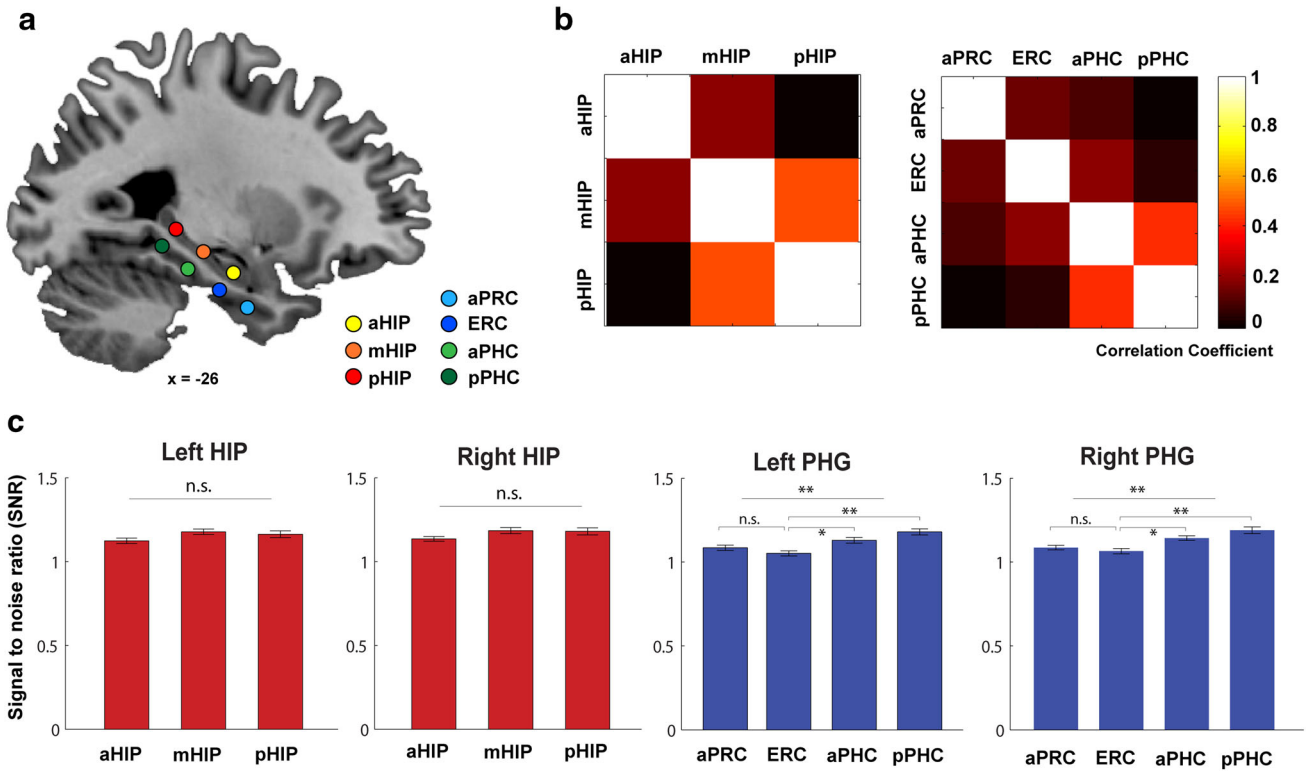

Fig. 1 Nodes of interest in the MTL and their inter-node correlation. **a** Sagittal view showing node locations along the long axis of the left hippocampus and parahippocampal gyrus (PHG). Nodes are superimposed on a high-resolution T1-weighted brain template in stereotaxic MNI space. **b** Correlation matrix maps indicating mean inter-node correlation computed by partial correlation between three hippocampal nodes and four PHG nodes, respectively. **c** The temporal signal-to-noise ratio for spontaneous BOLD signal fluctuations within the frequency band of interest over other frequency bands in the hippocampal and PHG nodes. *aHIP* anterior hippocampus, *mHIP* middle hippocampus, *pHIP* posterior hippocampus, *aPRC* anterior perirhinal cortex, *ERC* entorhinal cortex, *aPHC* anterior parahippocampal cortex, *pPHC* posterior parahippocampal cortex

Materials and methods

Participants

Thirty-six (17 males, 19 females) young, healthy, right-handed adults (mean age 20.58 ± 1.04) participated in this study after giving written, informed consent. All participants reported no history of neurological or psychiatric disorders. The study protocol was approved by the Stanford University Institutional Review Board.

Data acquisition

For the resting-state fMRI scan, participants were instructed to keep their eyes closed but not fall asleep and remain still for the duration of an 8-min scan. Whole-brain functional imaging data were acquired on a 3T GE Signa Scanner (General Electric, Milwaukee, WI) using a custom-built head coil with a T2*-sensitive gradient echo spiral in–out pulse sequence based on blood oxygenation level-dependent contrast (BOLD) (Glover and Law 2001). Specifically, we used an optimized spiral in–out pulse sequence with optimized parameter settings such as optimization of the B0 shim, reduced slice thickness, optimized slice orientation to the inhomogeneity gradients, and the use of shorter echo times. This has been demonstrated by a series of studies to reduce the effect of macroscopic susceptibility-induced field gradients generated near air–tissue interfaces and to increase both signal-to-noise ratio and BOLD contrast-to-noise ratio in T2*-weighted images (Glover and Law 2001; Glover and Thomason 2004; Glover 2012). A total of 29 axial slices (4.0 mm thickness, 0.5 mm skip) parallel to the anterior commissure–posterior commissure (AC–PC) line and covering the whole brain were imaged with the following parameters: 2000 ms TR, 30 ms TE, 80° flip angle, field of view 20 cm, 256 × 256 × 132, and matrix size 64 × 64, providing an in-plane spatial resolution of 3.125 mm. To reduce blurring and signal loss arising from field inhomogeneities, an automated high-order shimming method based on spiral acquisitions was used before acquiring functional images. A linear shim correction was applied separately for each slice during reconstruction using a magnetic field map acquired automatically by the pulse sequence at the beginning of the scan (Glover and Lai 1998).

Data preprocessing

Data were preprocessed using SPM8 software (http://www.fil.ion.ucl.ac.uk/spm). The first eight volumes were discarded to allow stabilization of the MR signal. Remaining functional images were realigned to correct for head motion, and any data affected by head motion over 2 mm or rotation more than 1° was excluded. The realigned images were corrected for errors in slice-timing, spatially transformed to standard stereotaxic space based on the Montreal Neurologic Institute (MNI) coordinate system, resampled every 2 mm using since interpolation, and smoothed with a 6-mm full-width half-maximum Gaussian kernel to reduce spatial noise. Voxel-wise time series were then filtered using a temporal bandpass filter (0.008–0.10 Hz).

Definition of MTL nodes of interest

We used two parallel arrays of nodes along the longitudinal axis of the hippocampus and the PHG. A total of 7 nodes were defined in the left hemisphere and a parallel set of 7 nodes were defined in the right hemisphere (Fig. 1a; Table 1). In each hemisphere, 3 nodes were located in the hippocampus: head (anterior, aHIP), body (middle, mHIP) and tail (posterior, pHIP). The other 4 nodes were located along the PHG axis in the anterior PRC, the ERC, the anterior PHC (aPHC) and posterior PHC (pPHC). The precise locations of the nodes were based on convergent evidence from previous studies on humans about distinct anatomical and functional profiles of the MTL subdivisions and functional heterogeneity along the hippocampal long axis. Specifically, the head, body and tail of the hippocampus were anatomically defined based on previous guidelines (Hackert et al. 2002; Greicius et al. 2003), suggesting the anterior 35 % of the coronal slices as 'head', the intermediate 45 % as 'body', and the remaining 20 % as 'tail'. The anterior hippocampus was defined by the uncal apex appropriately anterior to $y = -21$ mm in MNI space as suggested by Poppenk and Moscovitch (2011).

Table 1 Coordinates for seven seed regions of interest

	x	*y*	*z*
aHipp	(±) 24	−14	−20
mHipp	(±) 26	−26	−12
pHipp	(±) 26	−34	−4
aPRC	(±) 26	−4	−36
ERC	(±) 26	−16	−28
aPHC	(±) 26	−30	−20
pPHC	(±) 26	−40	−12

Coordinates for seeds in the right and left hemispheres were defined in the MNI stereotaxic space

aHipp mHipp and pHipp represent the anterior, middle and posterior hippocampus, respectively, *aPRC* anterior perirhinal cortex, *ERC* posterior perirhinal cortex proximate to entorhinal cortex, *aPHC* anterior parahippocampal cortex, *pPHC* posterior parahippocampal cortex

The MNI coordinates of the anterior, middle and posterior nodes of interest are listed in Table 1.

The four nodes in the PHG were based on anatomical landmarks and currently known models of its functional specialization based on human neuroimaging studies (Davachi 2006). The anatomical landmarks of the aPRC, ERC and PHC were defined in MNI-coordinate space according to guidelines provided by Insausti et al. (1998) and Pruessner et al. (2002). The location of the anterior PRC node was based on previous fMRI studies showing domain-specific object recognition and item memory (Kahn et al. 2008; Staresina et al. 2011; Libby et al. 2012), and the ERC node is at the transition area between the PRC and PHC (Insausti et al. 1998). The anterior and posterior nodes of the PHC were defined according to their functional dissociation in spatial and non-spatial contextual processing (Bar 2004; Aminoff et al. 2007). As shown in Fig. 1b, c, the correlation coefficients between pairs of nodes within the hippocampus and PHG ranged from 0.12 to 0.56, indicating that there is substantial non-shared variance between these nodes.

Signal-to-noise ratio in MTL nodes of interest

To quantify resting-state fMRI signals in the anterior and posterior MTL nodes and rule out gross differences arising from potential susceptibility artifacts, we computed the temporal signal-to-noise ratio (tSNR) of spontaneous BOLD signal fluctuations for the frequency band (0.008–0.1) of interest over other frequency bands for each node involved in our analysis. That is, $\text{tSNR} = S(x)/S(y)$, where $S(x)$ represents the power spectrum of frequency band of interest (0.008–0.1) and $S(y)$ represents the power spectrum of other frequency bands. As shown in Fig. 1c, we observed a very similar pattern of tSNR in 3 nodes in the hippocampus as well as 4 nodes within the PHG for each hemisphere, suggesting the robustness of BOLD fluctuations along the long axis of the hippocampus and PHG.

Functional connectivity analysis

For each node ROI, time series were extracted by averaging across all voxels. Each of the resulting ROI time series was used as a covariate of interest in an individual subject-level general linear model. A global time series computed across whole-brain voxels and 6 motion parameters were included as additional covariates of no interest to remove confounding effects of physiological noise and potential head movement-related artifacts. Separate functional connectivity analyses were first conducted for each ROI and subject.

Corresponding contrast images for each node's functional connectivity map from the individual level analysis were submitted to a second-level group analysis. Group-level functional connectivity of each node was statistically analyzed using one-sample t test with a stringent threshold of $p < 0.001$ with family-wise error (FWE) correction on a whole-brain level. Direct comparisons between functional connectivity maps of multiple nodes in the hippocampus and the PHG were performed using one-way analysis of variance (ANOVA), with a height threshold of $p < 0.001$ and an extent threshold of $p < 0.01$, corrected for multiple spatial comparisons using Monte Carlo simulations (Hayasaka et al. 2004; Nichols et al. 2005; Nichols and Hayasaka 2003).

To characterize functional connectivity patterns of each node to specific target brain regions, mean parameter estimates (β) of these regions were extracted from individual contrast parameter images using the MarsBar toolbox (http://marsbar.sourceforge.net). To avoid selection bias and circularity, 35 target ROIs were defined with a 6-mm sphere around peak voxels of significant clusters from a group-level analysis of functional connectivity for the hippocampus and PHG, collapsing across all 7 seed nodes along the longitudinal axis. Mean parameter estimates, representing connectivity strength of each node ROI with corresponding target masks, were then plotted using polar plots to summarize overall functional connectivity patterns throughout the whole brain—this included target ROIs in subcortical structures as well as motor, temporal, frontal, occipital and parietal cortices.

Network construction

The regional BOLD-fMRI time series were extracted for each of 49 regions (or nodes), consisting of 7 MTL seed nodes in the left hemisphere, 7 MTL nodes in the right hemisphere, and 35 target ROIs (see above) of the overall left and right MTL (collapsing across individual divisions). The BOLD time series of 49 nodes were then correlated (Pearson's r) region by region for each participant, creating a 49×49 correlation matrix. Fisher's z transform was applied to the correlation values to ensure normality. These correlations, representing functional connectivity between distinct ROIs, were used for network visualization and for graph theoretical analysis.

Graph theoretical network analysis

A 49-node undirected weighted graph representing MTL functional connectivity network was constructed using the correlation matrix for each participant. We computed two node-level metrics—degree and eigenvector centrality—for each graph. The degree of every node was computed by

counting the number of edges incident on that node. Eigenvector centrality is a self-referential measure of centrality—that is, nodes have high eigenvector centrality if they connect to other nodes that have high eigenvector centrality. The eigenvector centrality of node *i* is equivalent to the *i*th element in the eigenvector corresponding to the largest eigenvalue of the adjacency matrix (Bullmore and Sporns 2009).

The Brain Connectivity Toolbox (http://www.indiana.edu/~cortex/connectivity_toolbox.html) was used to compute these metrics for each MTL subdivision. ANOVA was then used to examine differences in network metrics of the hippocampus and PHG along their respective anterior–posterior axes.

Results

Distinct functional connectivity profiles of the hippocampus and the PHG

We first focused on the left hemisphere and examined functional connectivity patterns of nodes of interest in the hippocampus and the PHG separately. We found that spontaneous activity in the MTL nodes was strongly correlated with activity in a widely distributed set of cortical and subcortical regions (Figure S1; Table S1 in the Supplementary Materials). We then examined differential connectivity between the hippocampus and the PHG. Compared to the PHG, the hippocampus showed greater connectivity with multiple subcortical structures, mainly the amygdala, caudate, putamen, thalamus, nucleus accumbens (NAcc), and VTA/substantial nigra (SN) (Fig. 2a; Table S2). In contrast, the PHG showed greater connectivity with multiple cortical regions, including multiple unimodal and polymodal association *areas* in occipital, parietal and temporal lobes, retrosplenial cortex, posterior cingulate cortex and precuneus, middle and anterior cingulate cortex, and insular cortex (Fig. 2a; Table S2). Parallel analysis of the hippocampus and the PHG in the right hemisphere revealed very similar functional connectivity patterns (Figure S2).

Additional analyses were performed using target ROIs associated with the hippocampus and PHG. Separate paired *t* tests on the mean functional connectivity strength of each of these target ROIs revealed that, compared to the PHG, the hippocampus had significantly greater functional connectivity with the thalamus, NAcc, amygdala and midbrain. In contrast, compared to the hippocampus, the PHG exhibited significantly greater connectivity with the posterior cingulate cortex/retrosplenial cortex (PCC/RSC), postcentral gyrus, fusiform gyrus and superior temporal gyrus (Fig. 2b; Table 2). These analyses confirmed distinct functional connectivity profiles associated with the hippocampus and PHG.

Inter-hemispheric differences in functional connectivity of the hippocampus and the PHG

To examine inter-hemispheric differences in functional connectivity of the hippocampus, we compared connectivity maps of the hippocampus between the left and right hemispheres. Compared to the right hippocampus, the left hippocampus showed significantly higher functional connectivity with the left hippocampus and left PHG as well as the bilateral NAcc (clusters colored in warm yellow; Fig. 3a). The right hippocampus showed significantly higher connectivity only with the right middle hippocampus (a cluster colored in cool blue).

For the inter-hemispheric differences in PHG functional connectivity, we found that the left compared to the right PHG showed significantly higher connectivity with several regions within the MTL along the left PHG long axis and extending into the amygdala, the left anterior temporal lobe, the middle temporal gyrus, the left retrosplenial cortex, the left medial prefrontal cortex, the bilateral midbrain and the cerebellum (Fig. 3b). In the opposite contrast (right > left), however, we found no reliable inter-hemispheric differences. These results suggest that the left hemisphere connectivity was stronger than the right in both the hippocampus and PHG.

Functional connectivity profiles along the long axis of the hippocampus

Next, we examined differences in functional connectivity across three nodes spanning the anterior–posterior axis of the left hippocampus. One-way ANOVA revealed a significant main effect of region (aHIP vs. mHIP vs. pHIP) in multiple cortical and subcortical regions. Cortical regions included anterior and posterior cingulate cortex, insular cortex, ventromedial prefrontal cortex, superior frontal gyrus, retrosplenial cortex, precuneus and widespread unimodal and polymodal association areas in occipital and temporal lobes. Subcortical regions of caudate, putamen, thalamus, NAcc and VTA/SN also showed a main effect of hippocampal subdivisions (Fig. 4a; Table S3). Parallel analysis for corresponding nodes in the right hippocampus revealed an almost identical pattern of results (Figure S3A).

Direct pairwise comparisons between the posterior, middle and anterior hippocampal nodes revealed that the pHIP, compared to the aHIP, had stronger connectivity with multiple cortical and subcortical regions (Fig. 4b; Table S3). Cortical regions included posterior cingulate cortex, retrosplenial cortex, precuneus, anterior and middle

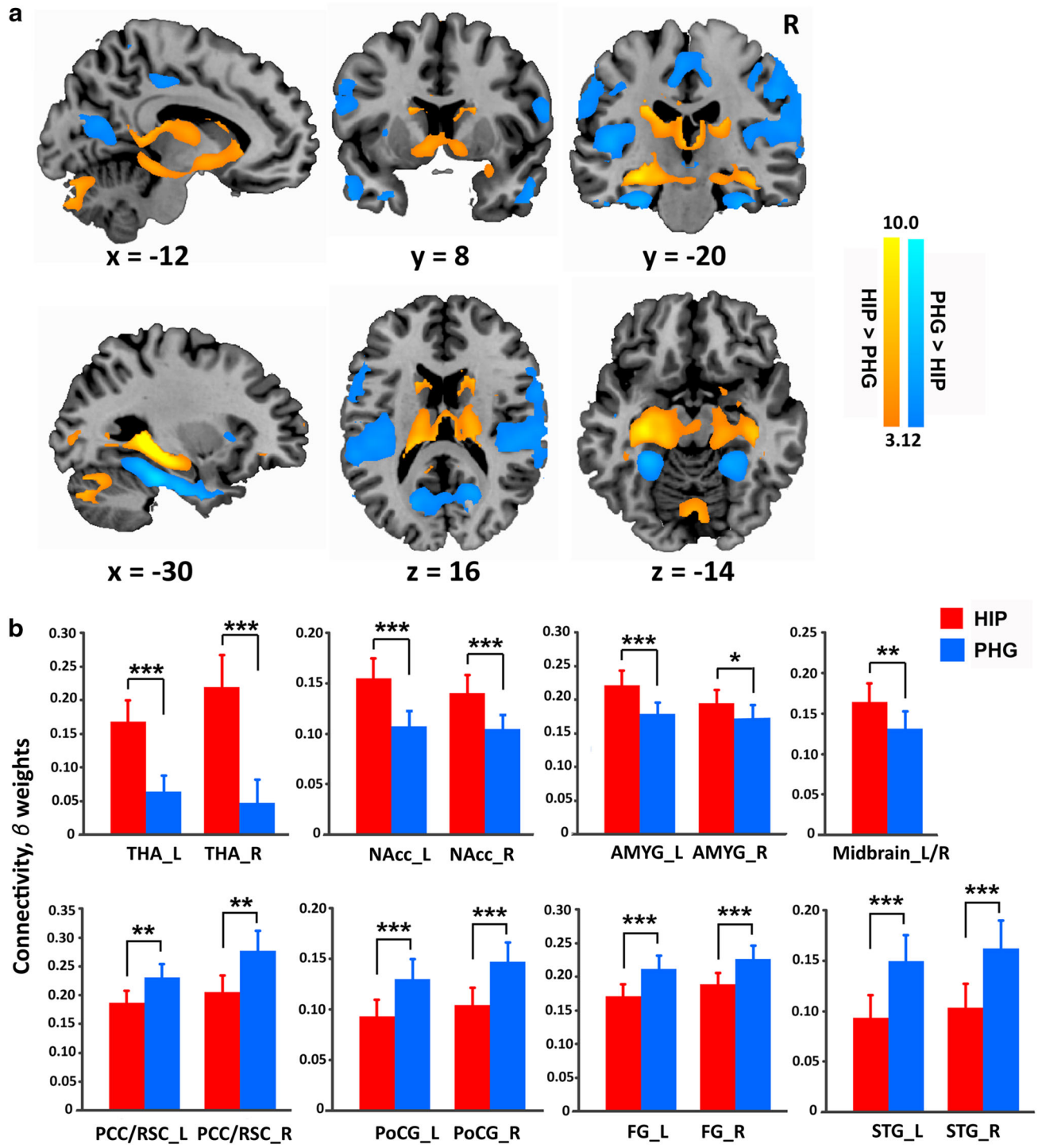

Fig. 2 Functional connectivity of the hippocampus and PHG. **a** Direct comparisons of functional connectivity associated with the entire hippocampus vs. the entire PHG. **b** Bar graphs show mean functional connectivity strength of the hippocampus (coded in *red*) and PHG (coded in *blue*) with four subcortical and four cortical target regions of interest (ROI). *Error bars* represent standard error of mean (SEM). *t* values were generated by paired *t* test. $*p < 0.05$; $**p < 0.01$; $***p < 0.001$. *HIP* hippocampus, *PHG* parahippocampal gyrus, *THA* thalamus, *NAcc* nucleus accumbens, *AMYG* amygdala, *PCC/RSC* posterior cingulate cortex/retrosplenial cortex, *PoCG* postcentral gyrus, *FG* fusiform gyrus, *STG* superior temporal gyrus, *R* right, *L* left

cingulate cortex, ventromedial prefrontal cortex, middle frontal gyrus, and visual association cortex in occipital and temporal lobes. Subcortical regions included NAcc, striatum, thalamus, VTA/SN and mammillary body and declive in cerebellum. A similar but relatively weaker pattern of results was observed when contrasting the mHIP

Table 2 Statistics of *T* and *F* tests from ROI analyses

Comparisons	Hemispheres	*T/F* values	*P* values
HIP > PHG			
Thalamus	L	$t(35) = 5.56$	<0.0001
	R	$t(35) = 6.05$	<0.0001
NAcc	L	$t(35) = 4.96$	<0.0001
	R	$t(35) = 5.11$	<0.0001
Amygdala	L	$t(35) = 4.81$	<0.0001
	R	$t(35) = 2.67$	<0.05
Midbrain	L/R	$t(35) = 3.48$	<0.005
HIP < PHG			
PCC/RSC	L	$t(35) = 3.33$	<0.005
	R	$t(35) = 3.37$	<0.005
PCG	L	$t(35) = 3.64$	<0.001
	R	$t(35) = 3.97$	<0.0005
FG	L	$t(35) = 4.42$	<0.0001
	R	$t(35) = 3.87$	<0.0005
STG	L	$t(35) = 4.08$	<0.0005
	R	$t(35) = 3.98$	<0.0005
aHIP vs. mHIP vs. pHIP			
Caudate	L	$F(2, 35) = 5.58$	<0.01
	R	$F(2, 35) = 6.05$	<0.005
Putamen	L	$F(2, 35) = 22.30$	<0.0001
	R	$F(2, 35) = 14.09$	<0.0001
NAcc	L	$F(2, 35) = 21.82$	<0.0001
	R	$F(2, 35) = 12.62$	<0.0001
Midbrain	L/R	$F(2, 35) = 15.16$	<0.0001
Amygdala	L	$F(2, 35) = 9.29$	<0.0001
	R	$F(2, 35) = 4.50$	<0.01
PCG	L	$F(2, 35) = 8.13$	<0.001
	R	$F(2, 35) = 8.21$	<0.001
Temporal pole	L	$F(2, 35) = 3.91$	<0.03
	R	$F(2, 35) = 4.58$	<0.01
MPFC	L	$F(2, 35) = 7.96$	<0.001
	R	$F(2, 35) = 14.01$	<0.0001
FG	L	$F(2, 35) = 7.94$	<0.001
	R	$F(2, 35) = 9.13$	<0.0001
PCC/RSC	L	$F(2, 35) = 3.91$	<0.03
aPRC vs. ERC vs. aPHC vs. pPHC			
PCC/RSC	L	$F(3, 35) = 25.02$	<0.0001
	R	$F(3, 35) = 16.07$	<0.0001
Angular gyrus	L	$F(3, 35) = 3.86$	<0.012
	R	$F(3, 35) = 9.36$	<0.0001

NAcc nucleus accumbens, *PCC* posterior cingulate cortex, *RSC* retrosplenial cortex, *PCG* postcentral gyrus, *FG* fusiform gyrus, *MPFC* medial prefrontal cortex, *STG* superior temporal gyrus

with the aHIP (Fig. 4d; Table S3). Compared to the mHIP, however, the aHIP showed significantly greater connectivity with the amygdala, insula, temporal pole, fusiform gyrus, lingual gyrus, superior temporal gyrus and motor cortex (Fig. 4d; Table S3). These results suggest that the pHIP shows the strongest connectivity with multiple cortical regions, the aHIP shows stronger connectivity with the bilateral anterior medial temporal lobe (including the anterior hippocampus, the entorhinal and perirhinal cortices extending into the amygdala) and the left temporal pole, and the mHIP shows intermediate patterns of connectivity (Fig. 4a–d). Parallel analysis for the above comparisons in the right hippocampus revealed an almost identical pattern of results (Figure S3).

Additional ROI analyses were then performed for major target ROIs associated with the three hippocampal nodes. Repeated measures ANOVA confirmed significant differences in connectivity between anterior, middle and posterior hippocampal nodes and the caudate, putamen, NAcc, midbrain, amygdala, postcentral gyrus, temporal pole, medial prefrontal cortex, fusiform gyrus and PCC/RSC (Table 2). These results confirm that the functional connectivity of the hippocampus is characterized by decreasing connectivity strength along the posterior-to-anterior gradient with multiple posterior midline and subcortical structures. Compared to posterior and middle subdivisions, the anterior hippocampus showed stronger connectivity only with the bilateral anterior medial temporal lobe and the left temporal pole.

To better visualize differential connectivity patterns associated with the three hippocampal nodes, we created schematic polar plots of each node with target regions that demonstrated stronger connectivity with the posterior hippocampus. As shown in Fig. 5, several subcortical structures (including striatum, thalamus and midbrain) and cortical regions (including midline prefrontal and posterior structures) showed increasing functional connectivity strength along the anterior-to-posterior axis of the hippocampus. Interestingly, there were also several areas including the amygdala, post central gyrus and temporal pole that showed a U-shaped pattern, with the mHIP showing the lowest connectivity compared to the pHIP and the aHIP.

Functional connectivity profiles along the long axis of the PHG

We examined differences in connectivity across four nodes spanning the anterior–posterior axis of the PHG. One-way ANOVA for functional connectivity of the four PHG nodes yielded a significant main effect in the default mode network (DMN) regions, including precuneus, retrosplenial cortex, ventromedial prefrontal cortex and bilateral angular gyrus (Fig. 6a; Table S4). Direct comparisons between functional connectivity of the four PHG nodes revealed a gradient of decreased connectivity along the posterior-to-anterior axis in these DMN regions (Fig. 6b–d; Table S4). Thus, compared to the PRC, the pPHC showed the

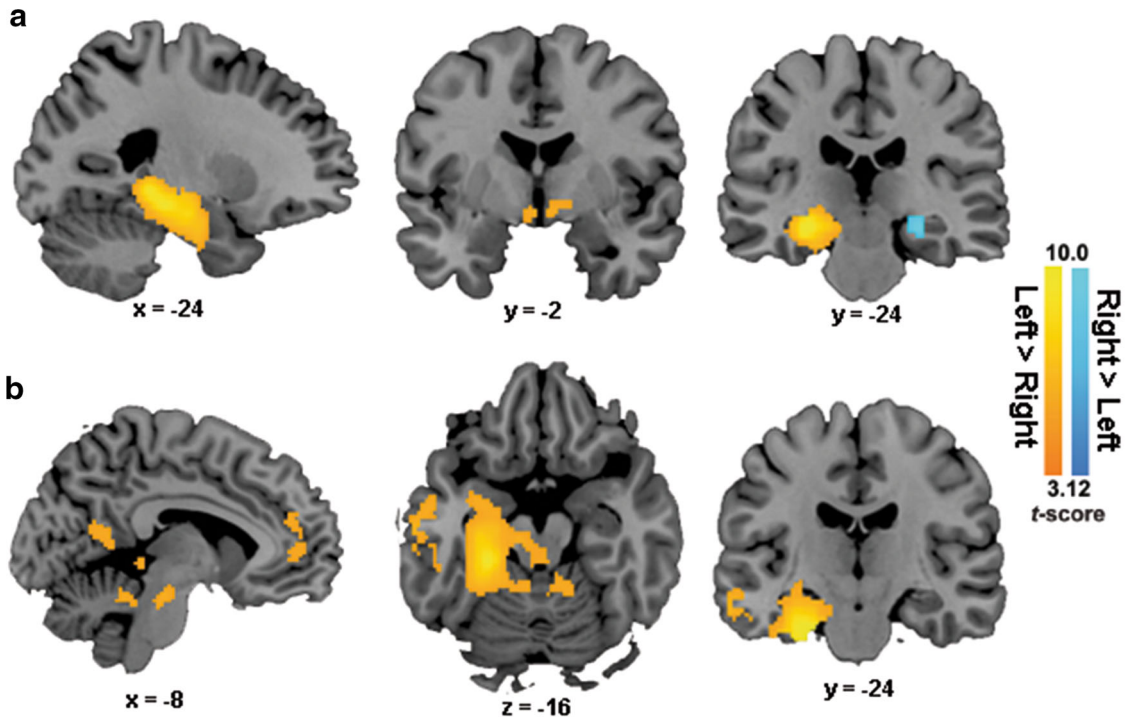

Fig. 3 Inter-hemispheric differences in functional connectivity of the hippocampus and the PHG. **a** Clusters showing significant differences in functional connectivity between the left and right hippocampal nodes; **b** clusters showing significant differences in functional connectivity between the left and right PHG. *HIP* hippocampus, *PHG* parahippocampal gyrus

strongest connectivity with these regions, and the ERC and aPHC showed intermediate levels of connectivity with these target DMN regions. Parallel analysis for corresponding nodes in the right PHG revealed an almost identical pattern of results (Figure S4A-D).

Visualization of these results using polar plots of PHG connectivity confirmed that the four PHG nodes had a similar pattern of connectivity with most subcortical and cortical target regions except core nodes of the DMN. Statistical significance assessed with repeated measures ANOVAs revealed significant connectivity differences of the four PHG nodes from the posterior cingulate cortex, retrosplenial cortex and angular gyrus but not from any other subcortical/cortical target regions (Fig. 7; Table 2). Together, these results point toward a functional connectivity gradient, characterized by posterior-dominant connectivity with the DMN.

Functional gradients in network organization along the anterior–posterior axes of the hippocampus and the PHG

To further examine functional gradients and network organization properties along the long axis of the MTL, we conducted graph theoretical analysis of MTL-based target networks collapsing across two hemispheres (Fig. 8a–c). As shown in Fig. 8d–e, there is a clear pattern of gradient increases in node degree and centrality along the anterior-to-posterior axes of the hippocampus and the PHG in both the left and right hemispheres. Further analysis revealed a marginally significant gradient increase in node centrality in the right hemisphere [$F(2, 105) = 2.70, p = 0.07$] along the anterior-to-posterior axis in the right hippocampus, with significantly higher node centrality in the posterior relative to the anterior hippocampus [$t(35) = 2.99$, $p = 0.001$] and marginally significant higher centrality than the middle hippocampus [$t(35) = 1.75$, $p = 0.08$] (Fig. 8d). There is no significant effect for node degree [$F(2, 105) = 0.25$, $p > 0.50$] in either the left or right hippocampus nor is there significant effect for node centrality in the left hippocampus [$F(2, 105) < 1$]. These results provide novel quantitative evidence for gradients in functional network organization along the anterior-to-posterior axis of the hippocampus.

A parallel analysis conducted across the four nodes of the left and the right PHG separately revealed significant linear increases in node degree [left: $F(3, 140) = 5.04, p < 0.003$; right: $F(3, 140) = 2.61, p < 0.05$] and node centrality along the anterior-to-posterior axis [left: $F(3, 140) = 21.33$, right: $F(3, 140) = 12.30$, both $p < 0.001$], with the highest and lowest node degree and centrality in the most posterior and anterior nodes of the PHG, respectively (Fig. 8e). These

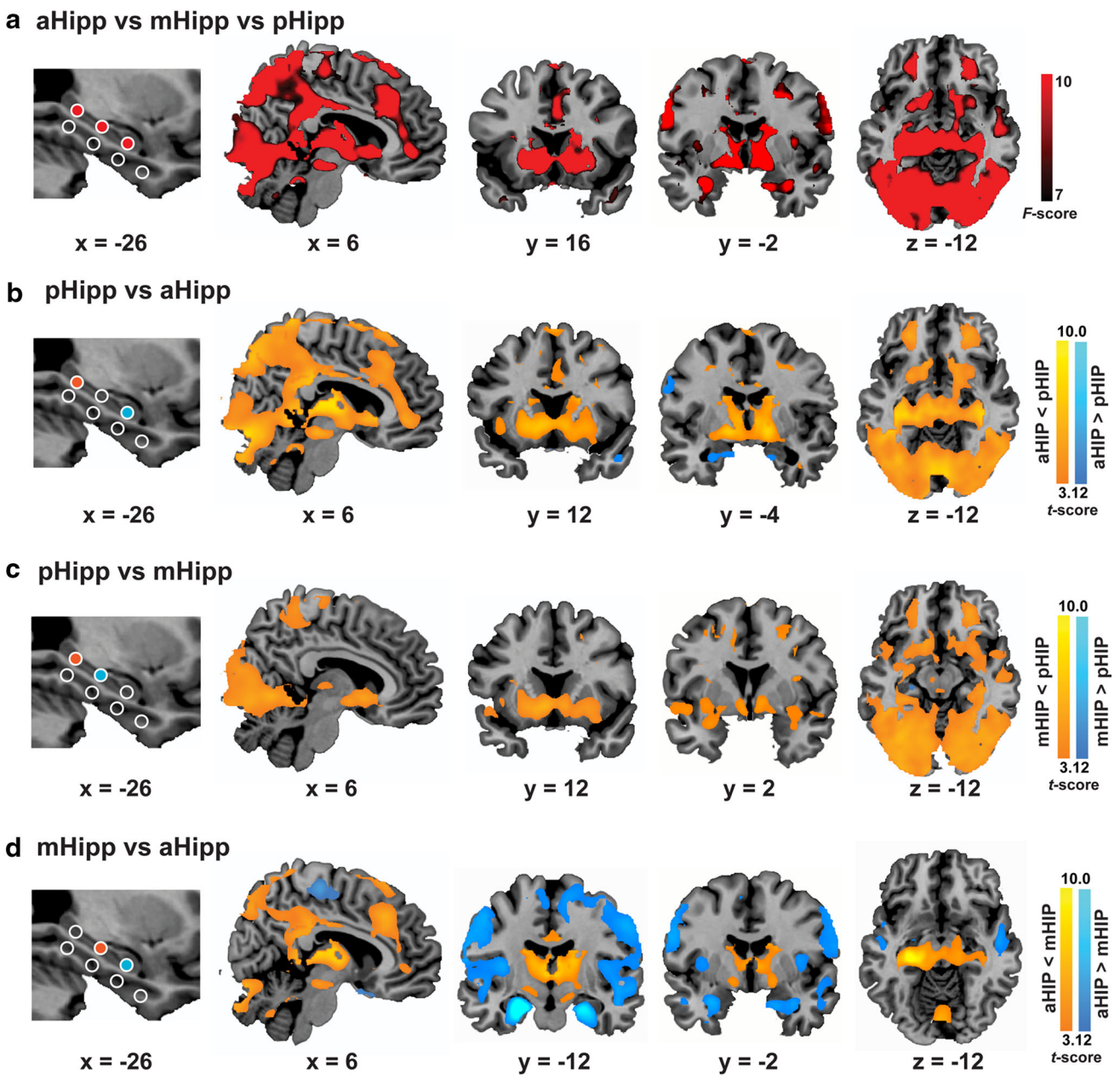

Fig. 4 Heterogeneous functional connectivity along the longitudinal axis of the hippocampus. **a** Main effect of hippocampal seed positions, generated by an omnibus F-contrast from one-way ANOVA (i.e., aHIP vs. mHIP vs. pHIP). **b–d** Direct pairwise comparisons for functional connectivity maps between distinct hippocampal seeds. Representative sagittal, coronal and axial slices of significant clusters were overlaid on high-resolution anatomical sections in the MNI stereotaxic space

results provide novel quantitative evidence for prominent gradient increase in functional network organization along the anterior-to-posterior axis of the bilateral PHG.

Discussion

This study investigated the large-scale intrinsic functional organization of anatomically distinct human MTL subdivisions using optimized spiral in–out functional imaging in combination with network and graph theoretical analyses. Several features of MTL connectivity emerged from our analysis of distinct hippocampus and PHG nodes (Fig. 9). First, we found a clear dissociation in connectivity between the hippocampus and the PHG. Compared to the PHG, the hippocampus showed stronger connectivity with subcortical regions including basal ganglia, midbrain, thalamus and amygdala, whereas the PHG showed significantly greater connectivity with multiple unimodal and polymodal association areas. Second, the hippocampus showed a

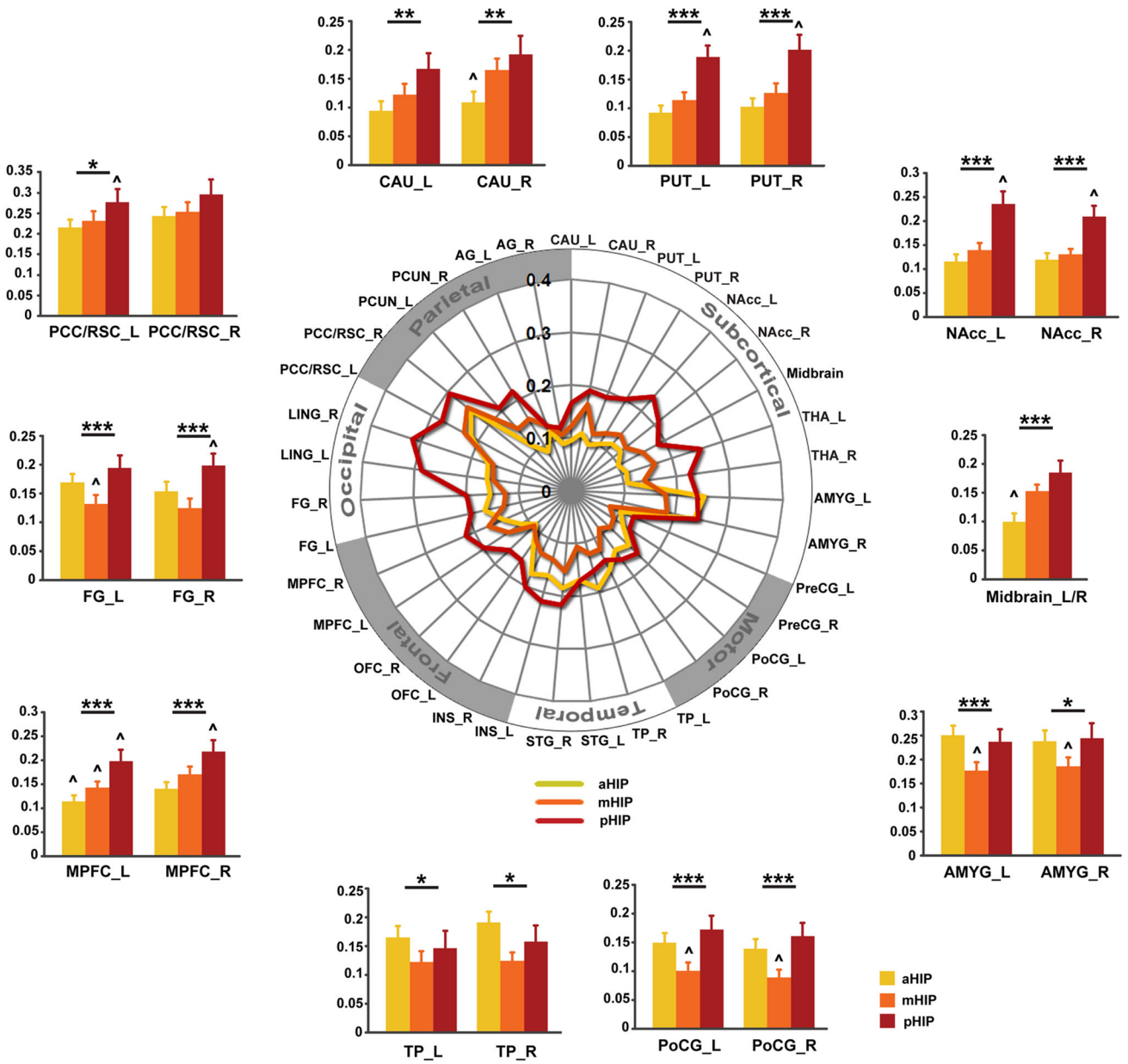

Fig. 5 Functional connectivity gradients of the anterior, middle and posterior hippocampus nodes. **a** Schematic polar plot illustrating connectivity patterns of three hippocampal nodes with target ROIs distributed across the whole brain. The *concentric circles* depict parameter estimates (β) representing the connectivity strength. **b** Bar graphs show mean connectivity strength of aHIP, mHIP and pHIP with representative target ROIs. *Error bars* represent SEM. $*p < 0.05$; $**p < 0.01$; $***p < 0.001$; ^, significantly from every others; *PCC/RSC* posterior cingulate cortex/retrosplenial cortex, *FG* fusiform gyrus, *MPFC* medial prefrontal cortex, *TP* temporal pole, *PoCG* postcentral gyrus, *AMYG* amygdala, *NAcc* nucleus accumbens, *PUT* putamen, *CAU* caudate, *R* right, *L* left

connectivity gradient along the anterior-to-posterior axis, with stronger connectivity of the posterior hippocampus with multiple cortical regions and stronger connectivity of the anterior hippocampus with the bilateral anterior medial temporal lobe extending into the amygdala and the left temporal pole. Third, along the anterior–posterior axis of the PHG, the PRC, ERC, aPHC and pPHC showed a similar topographical pattern of connectivity with most cortical and subcortical structures, except for one key feature: posterior PHG nodes showed much stronger connectivity with the DMN. Fourth, both the hippocampus and PHG showed increased network centrality along their anterior-to-posterior axes, suggesting a key role for their posterior subdivisions in integration of signals from large-scale brain networks. Fifth, the left and right hippocampus and PHG showed a remarkably consistent pattern of functional organization, except that left hemisphere connectivity was stronger in magnitude. These findings

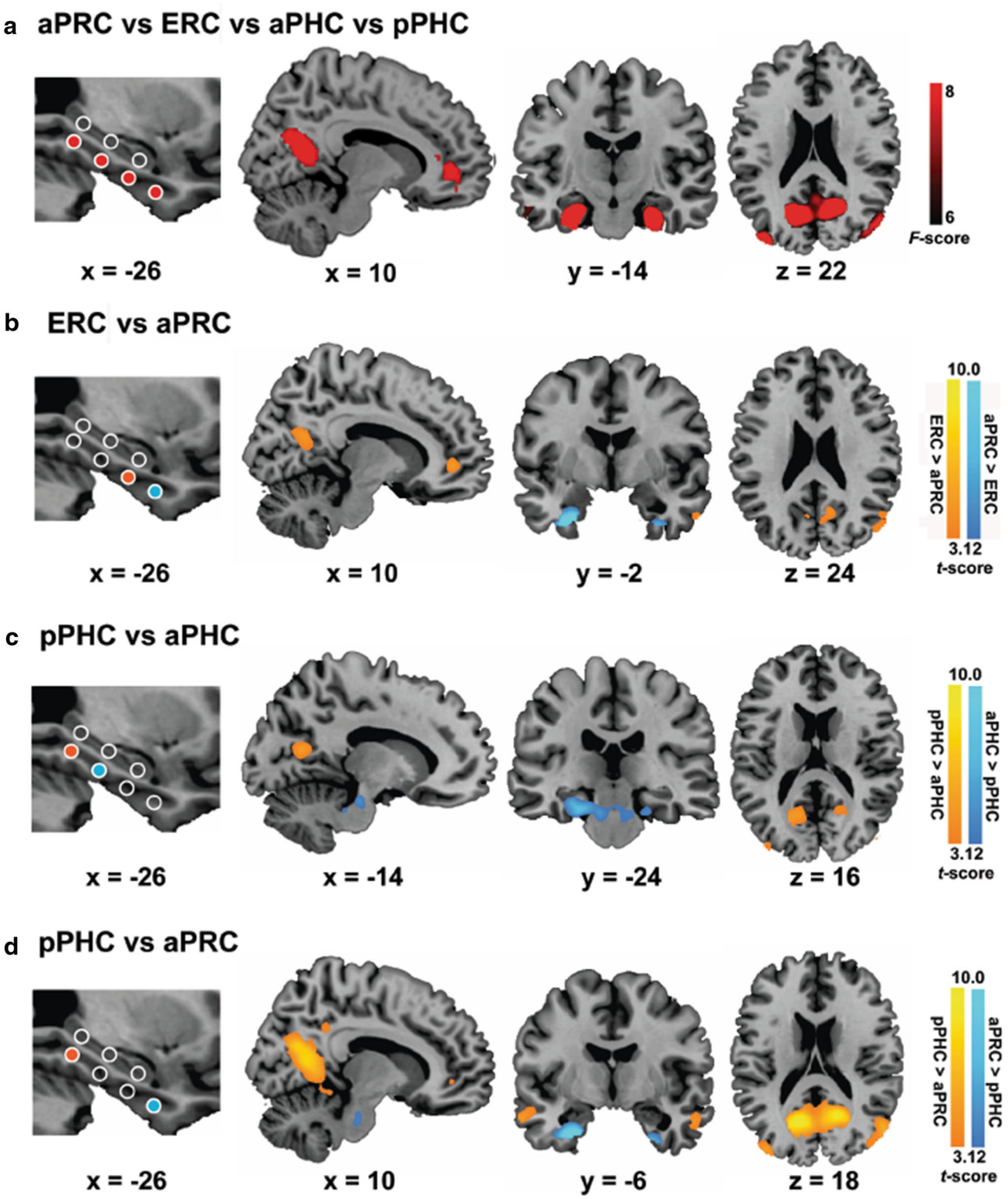

Fig. 6 Heterogeneous functional connectivity of the PHG nodes. **a** Main effect of PHG nodes, generated from one-way ANOVA with an omnibus *F*-contrast. **b–d** Direct pairwise comparisons for functional connectivity maps between distinct parahippocampal nodes: Representative sagittal, coronal and axial slices of significant clusters were overlaid on high-resolution anatomical sections in the MNI stereotaxic space

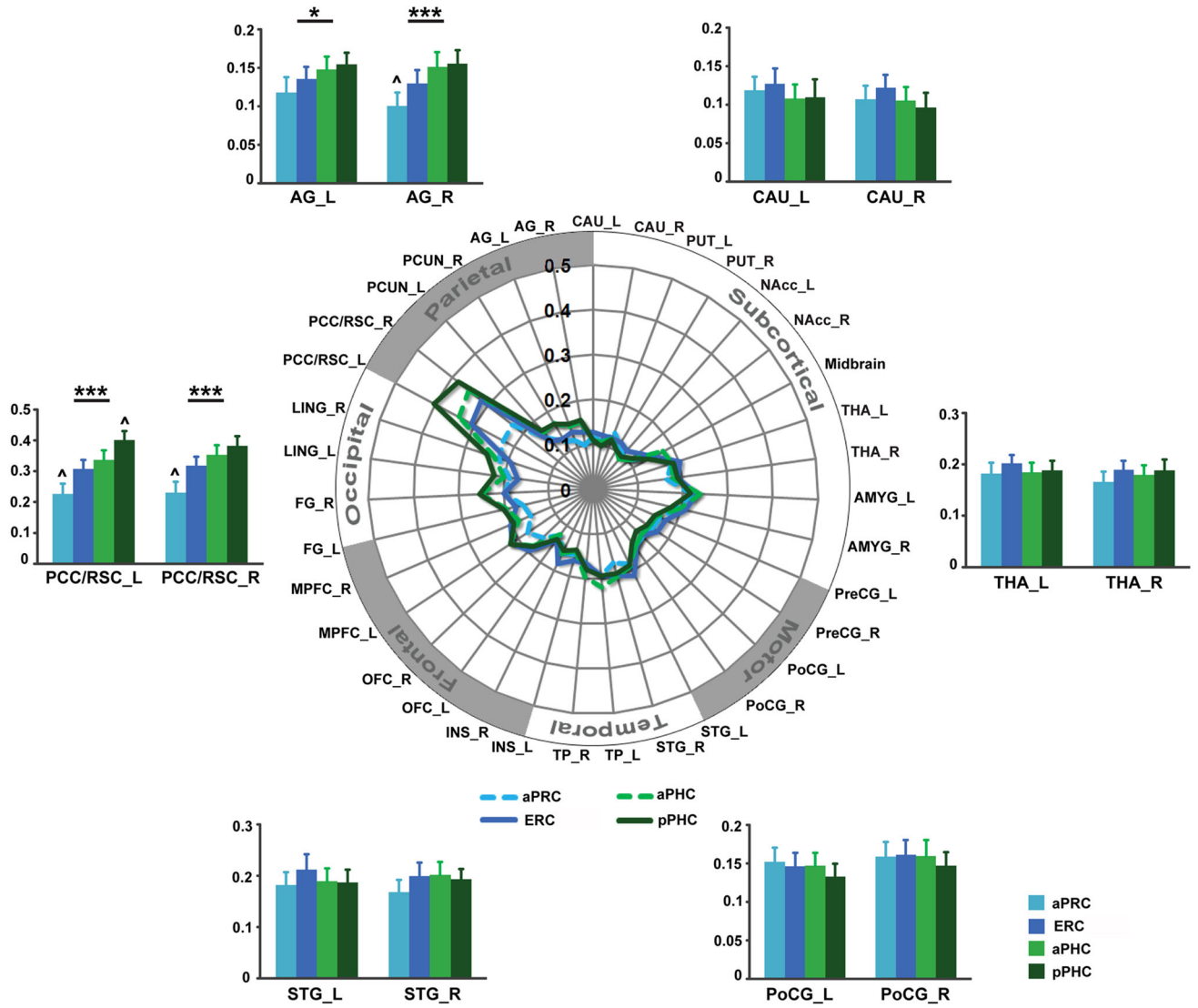

Fig. 7 Functional connectivity gradients of four distinct PHG nodes. **a** Schematic polar plot illustrating connectivity patterns of the parahippocampal seeds with target ROIs. The concentric circles depict the parameter estimates (β), which represent the strength of seed connectivity with target ROIs. **b** Bar graphs show mean parameter estimates (β) of aPRC, ERC, aPHC and pPHC connectivity with representative target ROIs. *Error bars* denote SEM. All abbreviations are same as Fig. 4. $p < 0.05$; $^{**}p < 0.01$; $^{***}p < 0.001$. ^, significantly from every other seed; *PCC/RSC* posterior cingulate cortex/retrosplenial cortex, *STG* superior temporal gyrus, *PoCG* postcentral gyrus, *THA* thalamus, *CAU* caudate, *AG* angular gyrus, *R* right, *L* left

highlight several key aspects of functional network organization within the human MTL. Below we discuss our findings in the context of previous fMRI studies of the MTL as well as histological tract-tracing studies on animals and current models of the MTL.

Distinct functional circuits associated with the hippocampus and the PHG

The hippocampus, compared to the PHG, showed preferential connectivity patterns with multiple subcortical regions, including dorsal and ventral striatum, VTA/SN and amygdala. The hippocampal connectivity with dorsal striatum provides novel evidence that the hippocampus and basal ganglia form interacting memory systems (Poldrack and Rodriguez 2004; Voermans et al. 2004; Delgado and Dickerson 2012). Functional interactions between these pathways may underlie skill and habit formation especially during the early phases of learning (Poldrack et al. 2001; Poldrack and Rodriguez 2004; Voermans et al. 2004; Dickerson et al. 2011; Delgado and Dickerson 2012). Notably, the hippocampus showed greater connectivity with the VTA/SN, consistent with the hippocampus–midbrain dopaminergic loop identified using tract tracing in rodents (Lisman and

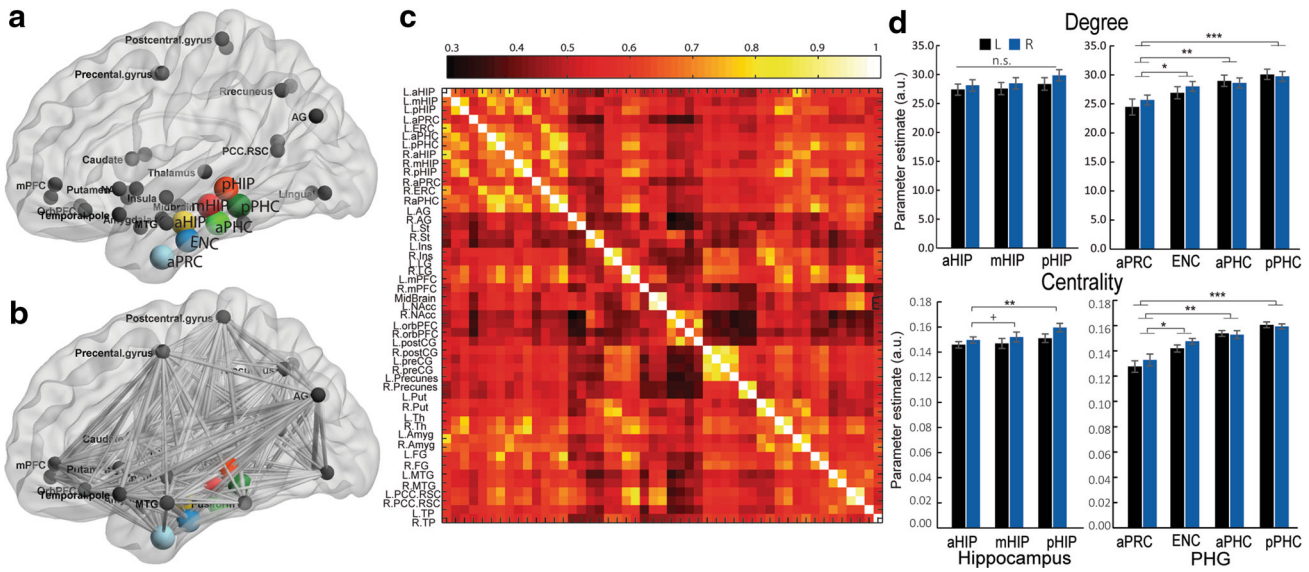

Fig. 8 Graph theoretical network construction and network organization profiles for nodes along the long axis of the hippocampus and the PHG. **a** Forty-two nodes within MTL-based intrinsic functional networks which consist of 7 seed nodes (*colored spheres*) and 35 unbiasedly defined target ROIs (*darken gray spheres*) across the whole brain; **b** edges (*gray lines*) among 49 nodes within MTL-based intrinsic functional networks; **c** network construction consisting of a 49-by-49 correlation matrix between nodes for each participant; **d** network organization properties including levels of the node degree to and centrality of connections separately for each seed. Abbreviations in (**c**) are listed in Supplemental Materials. *m.s.* marginally significant with $p = 0.07$ or 0.08; $^{*}p < 0.05$; $^{**}p < 0.01$; $^{***}p < 0.001$

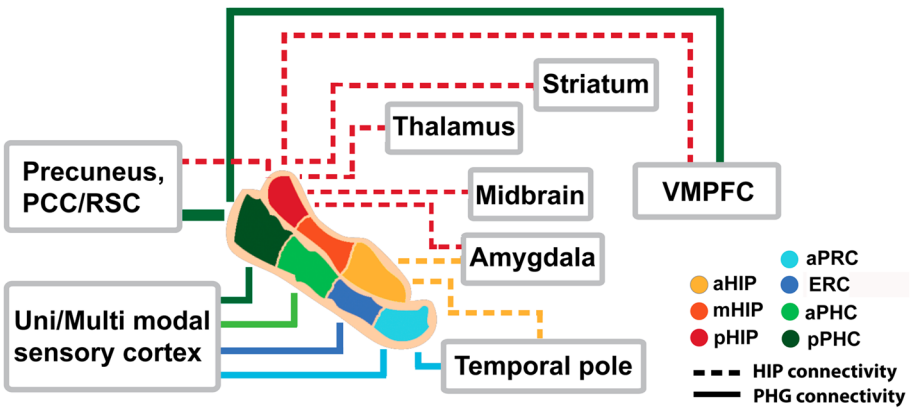

Fig. 9 A schematic view of distinct functional connectivity profiles of the MTL subdivisions. The PHG connectivity patterns are indicated by *solid lines* and hippocampal connectivity patterns are indicated by *dash lines*. The hippocampus shows greater connectivity with subcortical regions; in contrast, the PHG shows greater connectivity with widespread unimodal and polymodal association areas. The hippocampus shows a strongly heterogeneous pattern of connectivity along its anterior–posterior axis: the posterior hippocampus shows stronger connectivity with widespread cortical and subcortical regions including the ventral medial prefrontal cortex (VMPFC), striatum, thalamus, precuneus and the midbrain while the anterior hippocampus shows stronger connectivity with the anterior temporal lobe and the temporal pole. Unlike the hippocampus, the PHG shows more modest differences in connectivity along its anterior–posterior axis, except for the posterior PHC which shows stronger connectivity with the DMN regions including precuneus and VMPFC, and the PRC which shows stronger connectivity with the temporal pole. *aHIP* anterior hippocampus, *mHIP* middle hippocampus, *pHIP* posterior hippocampus, *aPRC* anterior perirhinal cortex, *ERC* entorhinal cortex, *aPHC* anterior parahippocampal cortex, *pPHC* posterior parahippocampal cortex

Grace 2005; Luo et al. 2011). This circuit is thought to play an important role in reward-based learning and memory in both animals and humans (Schott et al. 2004; Lisman and Grace 2005; Schott et al. 2006; Shohamy and Wagner 2008; Luo et al. 2011; Qin et al. 2012; Wolosin et al. 2012). Furthermore, the hippocampus also showed stronger connectivity with the amygdala, again consistent with known reciprocal anatomical connections between the amygdala

complex and the hippocampus reported in both animal studies (Pitkanen et al. 2000; Richter-Levin and Akirav 2000; Kishi et al. 2006) and human fMRI studies of emotional memory (Kensinger and Corkin 2004; Phelps 2004; Richardson et al. 2004; Dolcos et al. 2005; LaBar and Cabeza 2006).

In contrast, the PHG showed significantly preferential connectivity with multiple widely distributed cortical areas. These areas span several brain systems, including superior and middle temporal gyrus involved in auditory perception, inferior temporal cortex involved in visual object perception (Bancaud et al. 1994; Penfield and Perot 1963; Wheeler et al. 2000), lateral parietal regions involved in attention, episodic retrieval and spatial navigation (Vincent et al. 2006; Wagner et al. 2005; Cabeza et al. 2008; Rosenberg-Lee et al. 2011) as well as motor regions important for retrieval of action-associated events (Nyberg et al. 2001). The PHG also showed greater connectivity with several core posteromedial cortical nodes of the DMN, including posterior cingulate cortex and retrosplenial cortex. These regions have been implicated in various aspects of self-related processing and autobiographical memory (Maddock et al. 2001; Cooper et al. 2001; Maguire 2001; Cabeza and St Jacques 2007; Buckner and Carroll 2007). In line with previous findings from histological tract-tracing studies on rodents and nonhuman primates (Seltzer and Pandya 1976; Van Hoesen and Pandya 1975; Suzuki and Amaral 1994a, b), our findings suggest that the human PHG is a key convergence zone of cortical signals interacting with multiple unimodal and polymodal associations areas to bind sensory and motor representations separated in space and time (Davachi 2006; Squire and Zola-Morgan 1991; Bar 2004; Eichenbaum et al. 2007; Simons and Spiers 2003; Litman et al. 2009; Fernandez and Tendolkar 2006; Qin et al. 2007, 2009).

Although the left and right hippocampus showed very similar connectivity patterns with the rest of the brain, the left hippocampus showed stronger connectivity within the left MTL regions and with the bilateral NAcc. Similarly, we also observed stronger left lateralized PHG connectivity within the left MTL regions, the left amygdala and the left anterior temporal lobe as well as the bilateral VTA and cerebellum. To our knowledge, such a pattern of stronger left hippocampus and left PHG intrinsic functional connectivity has not been reported before in human MTL studies. Task-based functional neuroimaging studies have reported lateralized hippocampal involvement in memory, with greater left hippocampus activity for verbal memory processing (Golby et al. 2001; Toga and Thompson 2003) and greater right hippocampus activity for visuo-spatial information (Iglói et al. 2010). Interestingly, hemispheric asymmetry at the CA3–CA1 pyramidal neuron synapse has recently been demonstrated in mice, with different spine morphology, glutamate receptor content and synaptic plasticity (Kawakami et al. 2003; Shinohara et al. 2008). Critically, optogenetic silencing of CA3 pyramidal neurons in the left rather than right dorsal hippocampus impairs the formation of long-term memories in mice, suggesting a more crucial role for the left MTL in memory processing (Shipton et al. 2014). This pattern is consistent with our finding of stronger left MTL connectivity in our study. Further research is required to investigate how asymmetries in intrinsic functional connectivity contribute to lateralized hippocampal and PHG activation patterns observed in verbal and spatial tasks. Taken together, our findings provide important evidence to suggest that differential functional circuits linking the human hippocampus and the PHG might be critical for integration of disparate aspects of information representations distributed across cortical and subcortical networks involving domain-general and domain-specific perceptual information, reward, novelty and emotional saliency (Di Martino et al. 2008; Gallagher and Chiba 1996; Hua et al. 1998; Wise 2004).

Differential functional connectivity along the long axis of the hippocampus

The differential pattern of connectivity between anterior and posterior hippocampus observed here is consistent with animal models, which have pointed toward distinct neuroanatomical profiles for dorsal and ventral hippocampus subdivisions (Moser and Moser 1998; Fanselow and Dong 2010). These studies have delineated distinct afferent and efferent pathways of the hippocampus, and have linked dorsal/posterior hippocampus pathways with visuo-spatial processing systems and the ventral/anterior hippocampus pathways with emotion-related circuitry (Fanselow and Dong 2010). For example, *dorsal CA1* and the subiculum within the posterior hippocampus contain the greatest density of place cells and head direction cells with massive projections to retrosplenial cortex and cingulate cortex that together form functional circuits important for spatial navigation and episodic memory (Frankland et al. 2004; Fanselow and Dong 2010; Teixeira et al. 2006; Harker and Whishaw 2004; Spiers and Maguire 2006). Unlike the study by Kahl and Shohamy, which reported strongest connectivity of the body (middle portion) of hippocampus with NAcc and VTA (Kahn and Shohamy 2013), we observed stronger connectivity of these core reward circuits with a more posterior hippocampus region. Our findings are more consistent with animal anatomical studies, which have reported that more dense projections from the posterior hippocampus to mammillary and anterior thalamic nuclei via the fornix (Kishi et al. 2000) are critical for habit formation and that the projections of the posterior hippocampus to NAcc and *VTA* are involved in linking

reward and motivated behaviors (Luo et al. 2011; Lisman and Grace 2005; Poppenk et al. 2013).

Neuropsychological and functional neuroimaging studies on humans have provided evidence for a dissociation between functions of the posterior and anterior hippocampus. Several studies have demonstrated the specific role of posterior hippocampal regions in successful encoding and retrieval of information related to spatial scenes, navigation and spatial context (Ryan et al. 2010; Doeller et al. 2008; Maguire et al. 1997; Fernandez et al. 1998; Moser et al. 1993). The posterior hippocampus has also been associated with expertise in complex spatial knowledge, as in the case of London taxi drivers (Maguire et al. 2000), and with accurate recollection of spatial memory (Poppenk and Moscovitch 2011). In contrast, the differential connectivity of the anterior hippocampus with the anterior medial temporal lobe including the amygdala, may reflect strong reciprocal connections between these two regions as identified using histological tract-tracing studies on animals (Pitkanen et al. 2000; Richter-Levin and Akirav 2000; Kishi et al. 2006). Our findings are also consistent with co-activations of the anterior hippocampus and amygdala during encoding and retrieval of emotional memories (Dolcos et al. 2005; Kensinger and Corkin 2004; Richardson et al. 2004; Phelps 2004). The temporal pole is considered part of an extended limbic system given its abundant connections with limbic and paralimbic regions (Olson et al. 2007; Chabardes et al. 2002), suggesting that this region contributes to emotional and social processes via its interaction with the anterior hippocampus and amygdala (Olson et al. 2007; Glosser et al. 2003; Gorno-Tempini et al. 1998; Gorno-Tempini and Price 2001). Extending these observations, our findings suggest that functional dissociations of the hippocampus across multiple cognitive domains mirror the organization of its intrinsic large-scale functional circuits.

Functional connectivity gradients along the long axis of the PHG

The four PHG subdivisions examined in our study—PRC, ERC, aPHC and pPHC—largely showed a similar pattern of connectivity along the anterior–posterior axis of the MTL, with unimodal and polymodal association areas in the temporal, parietal and occipital lobes. The only exception to this was the posterior PHG, which showed significantly greater connectivity with posteromedial cortex, ventromedial prefrontal cortex and bilateral angular gyri, regions that form core nodes of the DMN (Greicius et al. 2003; Raichle et al. 2001).

Our findings of differential connectivity of the posterior PHC with the retrosplenial cortex and adjacent posterior cingulate cortex are in line with anatomical models derived from monkey studies, demonstrating that the majority of projections to the posterior PHC arise from the posteromedial cortex (Goldman-Rakic et al. 1984; Suzuki and Amaral 1994a). Consistent with our findings, task-based fMRI studies have shown that the retrosplenial cortex and posterior PHC are important for spatial navigation and episodic memory for locations and scenes (Maguire et al. 2000; Epstein 2008; Engelien et al. 2000; Schon et al. 2004), while the anterior PHC is more important for recollective and associative memory for non-spatial contextual information (Aminoff et al. 2007; Bar et al. 2008a; Ranganath et al. 2004). Specifically, the recruitment of posterior cingulate cortex and medial prefrontal cortex in retrieval of autobiographical and prospective memories has been widely reported in human fMRI studies (Andrews-Hanna et al. 2010; Buckner and Carroll 2007; Cabeza and St Jacques 2007). The coactivation of these regions likely arises from the dense anatomical connections of the PHC with the retrosplenial cortex as well as the cingulate cortex via the cingulum bundle (Suzuki and Amaral 1994a; Supekar et al. 2010; Greicius et al. 2009).

In addition to these differences associated with the posterior PHG, the PRC, within the anterior portion of the PHG, showed the strongest connectivity with the anterior temporal lobe (Heil et al. 1996; Odagaki et al. 1999; Kahn et al. 2008; Libby et al. 2012). This finding is consistent with the view that the anterior temporal lobe contributes to modality-independent semantic categorization and memory by integrating multiple perceptual inputs from dorsal auditory, ventral visual and medial olfactory streams, which converge on the PRC (Courtney et al. 1998; Henson et al. 2000; Ranganath et al. 2000; Young et al. 2013). These findings point further to differences in intrinsic functional connectivity along the anterior–posterior axis of the PHG and suggest that their distinct roles in memory and cognition may arise from differential connectivity with fronto-temporal association areas and posteromedial cortices.

Functional gradients of network organization along the long axis of the hippocampus and the PHG

Graph theoretical analysis revealed functional gradients in network organization along the long axis of the hippocampus and PHG. The most posterior nodes in the bilateral PHG as well as in the right hippocampus showed high node degree and centrality, reflecting more highly connected hubs (Bullmore and Sporns 2009, 2012) and a posterior-dominant pattern of connections with other nodes in MTL-based target networks. The posterior right hippocampus showed higher node centrality than the middle and anterior hippocampus, but no significant differences in node degree. This profile suggests that the large-scale connectivity of the

hippocampus is characterized by continuous gradients (Strange et al. 2014) rather than dichotomous patterns along its anterior–posterior axis (Fanselow and Dong 2010; Moser and Moser 1998; Poppenk and Moscovitch 2011; Poppenk et al. 2008, 2013). Crucially, the observed pattern of significantly greater node centrality in the posterior hippocampus provides new quantitative data reflecting the relatively dense projections to and from the posterior hippocampus (Fanselow and Dong 2010; Moser and Moser 1998; Strange et al. 2014). Notably, greater node centrality in the posterior hippocampus, compared to the anterior and middle hippocampus, suggests that, relative to the other hippocampal subdivisions, a larger proportion of posterior hippocampus projections participate in integration of information within the MTL network.

Furthermore, we observed an even more robust increase in both node centrality as well as node degree along the anterior-to-posterior long axis of the bilateral PHG, with the posterior PHC and the anterior PRC demonstrating the highest and lowest values, respectively. This pattern of network organization complements our findings from whole-brain connectivity analysis and further suggests that the posterior PHC is a highly integrative hub. This finding is consistent with previous qualitative reports of converging information streams from sensory and perceptual systems into the MTL through the PHG (Davachi 2006; Squire and Zola-Morgan 1991; Bar 2004; Eichenbaum et al. 2007; Simons and Spiers 2003; Litman et al. 2009; Fernandez and Tendolkar 2006; Qin et al. 2007, 2009). Conversely, the PRC showed the lowest node degree and centrality—a pattern consistent with findings of more domain- and stimulus-specific mnemonic processing in both animals and humans (Daunizeau et al. 2009; Staresina et al. 2011; Mayes et al. 2007).

Taken together, these findings provide novel quantitative evidence from a large-scale brain network and graph-theoretic perspective, adding to our current understanding of gradients in intrinsic functional organization and network architecture of individual human MTL subdivisions.

Conclusions

Our study demonstrates that the intrinsic large-scale organization of the human MTL is characterized by distinct patterns of hippocampus and PHG connectivity. Compared to the PHG, the hippocampus showed stronger connectivity with multiple subcortical regions, whereas the PHG showed significantly greater connectivity with multiple unimodal and polymodal association areas. The left and right hippocampal and PHG connectivity patterns were remarkably similar, except that left hemisphere connectivity was relatively stronger than right hemisphere connectivity in both the hippocampus and PHG regions. Whole-brain connectivity and graph-theoretical analyses revealed functional gradients in hippocampus and PHG connectivity, node degree and centrality along the anterior–posterior axes, highlighting previously unknown aspects of their functional heterogeneity in the context of large-scale brain networks. Our findings extend current models of MTL circuitry and network organization and have important implications for a more principled understanding of MTL pathways that support memory and cognition.

Acknowledgments This work was supported by the National Institutes of Health (HD047520, HD059205 and K99MH105601), the Netherlands Organization for Scientific Research (NWO 446.10.010), the Child Health Research Institute (CHRI) at Stanford University and Lucile Packard Foundation for Children's Health and the Stanford CTAS (UL1RR025744), and the Natural Science Foundation of China (61035006 and 61125304). We declare that there are no conflicts of interest.

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