Cortex

Research Report

Extensive cortical functional connectivity of the human hippocampal memory system

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ABSTRACT

The cortical connections of the human hippocampal memory system are fundamental to understanding its operation in health and disease, especially in the context of the great development of the human cortex. The functional connectivity of the human hippocampal system was analyzed in 172 participants imaged at 7T in the Human Connectome Project. The human hippocampus has high functional connectivity not only with the entorhinal cortex, but also with areas that are more distant in the ventral 'what' stream including the perirhinal cortex and temporal cortical visual areas. Parahippocampal gyrus TF in humans has connectivity with this ventral 'what' subsystem. Correspondingly for the dorsal stream, the hippocampus has high functional connectivity not only with the presubiculum, but also with areas more distant, the medial parahippocampal cortex TH which includes the parahippocampal place or scene area, the posterior cingulate including retrosplenial cortex, and the parietal cortex. Further, there is considerable cross connectivity between the ventral and dorsal streams with the hippocampus. The findings are supported by anatomical connections, which together provide an unprecedented and quantitative overview of the extensive cortical connectivity of the human hippocampal system that goes beyond hierarchically organised and segregated pathways connecting the hippocampus and neocortex, and

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'What' vs 'where'
Semantic memory
Dual stream hippocampal model

leads to new concepts on the operation of the hippocampal memory system in humans.

1. Introduction

The human hippocampus is essential for memory function, with major disorders in at least forming new episodic and semantic memory produced by damage to it (Clark et al., 2019; Corkin, 2002; Maguire, Intraub, & Mullally, 2016). In addition, it has been shown that a history of high blood pressure is associated with reduced hippocampal functional connectivity and impaired prospective memory (Feng, Rolls, Cheng, & Feng, 2020), so how the hippocampal system operates in the general population is relevant for neuropsychology and clinical practice. To understand how the hippocampus is involved in memory, and its disorders, we need to know its connections to other brain areas, and especially with the neocortex (Aggleton, 2012; Rolls, 2018, 2021a). The connections of the hippocampus provide major constraints on how this memory system operates computationally. If there are dual hierarchically organised segregated sets of connections to the hippocampus for ventral stream 'what' information via the perirhinal cortex and the lateral entorhinal cortex; and from dorsal, parietal stream areas via the parahippocampal gyrus and medial entorhinal cortex (Burwell, 2000; Burwell, Witter, & Amaral, 1995; Doan, Lagartos-Donate, Nilssen, Ohara, & Witter, 2019; Knierim, Neunuebel, & Deshmukh, 2014; Suzuki & Amaral, 1994; Van Hoesen, 1982), then the hippocampus can be viewed as linking the 'what' and 'where' streams for particular events so that we can associate together for example who was present ('what'), and where they were. This would make the hierarchically organised pathways to and from the hippocampus largely devoted at each stage to passing information to the hippocampus for storage and back to the neocortex for recall, with the appropriate convergence forwards towards the hippocampus and divergence backwards at each stage from the hippocampus (Treves & Rolls, 1994; Kesner & Rolls, 2015; Rolls, 2018, 2021a). A different possibility is that the human hippocampal memory system is less hierarchically organised and the streams are less segregated, which would enable specialization of different cortical regions for different types of computation.

Most of the evidence on hippocampal system connections comes from investigations in animals, and some of the main findings are summarized below and elsewhere (Huang, Rolls, Hsu, Feng, & Lin, 2021). However, to understand the hippocampal memory system in humans, it is important to understand the connections in humans, especially as there has been such great development in humans of ventral visual stream processing to the temporal lobe for invariant object recognition with a plethora of early visual cortical areas, a massively developed parietal lobe dorsal visual stream involved in spatial processing associated with foveal vision and eye movements, a greatly developed orbitofrontal cortex reward/emotional system, and a posterior cingulate cortex not known to be present in rodents (Rolls, 2021a). A recent study (Huang,

Rolls, Hsu, et al., 2021) has utilized diffusion tractography in 172 participants imaged at 7T in the Human Connectome Project (HCP) dataset (Glasser, Smith, et al., 2016), using the HCP atlas to delineate with multimodal analysis 360 cortical areas (Glasser, Coalson, et al., 2016), many with known functions. The diffusion tractography in humans provided evidence for connections between the hippocampus and neocortex that are not entirely hierarchical, and are not entirely segregated between the ventral and dorsal streams (Huang, Rolls, Hsu, et al., 2021). However, the tractography left a number of points unanswered, which we address here with functional connectivity measurements in the same HCP participants with resting state fMRI at 7T. First, with diffusion tractography, it is possible that some connections might be followed incorrectly where fiber bundles (streamlines) cross, or where the streamlines stop and cannot be followed into gray matter, so that the exact brain area of the connection needs to be established. One key aim of the present investigation was to use functional connectivity (FC) with fMRI to further address whether areas shown with connections with diffusion tractography are functionally connected. (Functional connectivity measures the correlations between the BOLD signals in different brain areas, and high correlations reflect interactions between brain areas (which provides information about how areas are interacting through their connectivity, though not necessarily mediated through direct connections, and possibly reflecting common input).) For example, direct connections between the hippocampus that bypass the entorhinal, perirhinal and parahippocampal cortex to reach the anterior temporal lobe 'what/semantic' systems, and the parietal and posterior cingulate cortex 'where' systems were described, with hippocampal connections with early sensory cortical areas for vision, touch and olfaction; and with many cross-connections between the 'what' and 'where' streams in the connectivity before the hippocampus (Huang, Rolls, Hsu, et al., 2021). One aim of the present investigation was thus to investigate whether functional connectivity provides support for functional interactions between the different brain areas identified with connections with the hippocampal system using diffusion tractography (Huang, Rolls, Hsu, et al., 2021). (It is useful to check that none of the results with the diffusion tractography arose because streamlines had been incorrectly followed where they cross.) A second key aim of the present study was to measure the strength of the connections between different parts of the system as they relate to function, for the anatomical measure of the number of streamlines between brain areas may not necessarily reflect the strength of their interaction, as the synaptic strength and where the pathways terminate on neurons are likely to be important. A third aim was to investigate the contralateral connectivity of the hippocampal system in humans, for diffusion tractography does not follow connections well across the midline. The use of functional

connectivity complements anatomical connection measurements, by enabling investigation of more than direct anatomical connectivity, by measuring the strength of the connectivity, and by not relying on tract tracing with diffusion tractography which might be susceptible to limitations in following connections accurately when pathways cross. The overall aim of this investigation was to investigate how the hippocampus and the areas that connect it with the neocortex have connectivity with different cortical areas to provide a connectional basis for better understanding how the hippocampus operates as a system that interacts with known cortical areas many of which have known functions. We did not restrict the cortical regions to be investigated by postulating prior hypotheses relating to particular hypotheses about hippocampal function.

We aim to be very clear in this paper about anatomical connections versus functional connectivity. When we refer to 'connections', we refer to anatomical evidence, from for example tract tracing studies in macaques (summarized below), and from for example diffusion tractography in humans (Huang, Rolls, Hsu, et al., 2021). When we refer to functional connectivity or 'connectivity', we refer to physiological investigations in which the correlation in the BOLD signal between different brain areas is measured, as described above. As explained above, the evidence described by these different approaches is complementary in important ways.

A highlight of the present investigation is the use of the Human Connectome Project atlas (Glasser, Coalson, et al., 2016), which we extended for the present study by including a definition of the subiculum, and by enabling it to be used with standard neuroimaging software such as SPM (Huang, Rolls, Feng, & Lin, 2021; Huang, Rolls, Hsu, et al., 2021). This atlas provides unparalleled subdivisions of the human cortex using multimodal methods, with many of the areas having identified functions (Glasser, Coalson, et al., 2016). The multimodal methods used to generate this HCP-MMP v1.0 parcellation included resting state functional connectivity, cortical myelin content and thickness, and task-related fMRI. By combining all these measures to distinguish different cortical areas, and the use of a large number (420) of participants, 360 cortical regions could be identified across the two hemispheres. This approach provides better categorization of cortical areas than does for example functional connectivity alone (Power et al., 2011). All 8 regions in the HCP-MMP atlas that are thought to provide pathways between the hippocampus and neocortex (based on the anatomical studies described below) were chosen as regions of interest (ROIs). They are the hippocampus, presubiculum, entorhinal cortex, perirhinal cortex, and parahippocampal gyrus areas TF, and TH represented by PHA1-3. As described in the Methods, we went beyond this, and for this particular investigation separated the hippocampal region of HCP-MMP into hippocampus and subiculum, thus providing 9 regions of interest. However, we did not attempt in the present investigation to separate dentate, CA3, CA1 and CA4 subfields of the human hippocampus, as it is difficult to obtain robust and reliable separation of these with resting state fMRI (Yassa et al., 2010), and a recent study using resting state fMRI was able to clearly distinguish primarily anterior from posterior hippocampal regions, and to relate each to mainly

just one set of cortical regions (Ezama, Hernandez-Cabrera, Seoane, Pereda, & Janssen, 2021). Another highlight of the present investigation is the use of the same 172 HCP participants for the functional connectivity described here as for the diffusion tractography (Huang, Rolls, Hsu, et al., 2021), to facilitate direct comparison.

A summary of some of the anatomical connections of the hippocampal system in macaques follows, and this provides support for many of the anatomical connections (Huang, Rolls, Hsu, et al., 2021), and functional pathways described here, for humans. In addition to the well-known connections involving the perirhinal, entorhinal, and parahippocampal cortex connections in macaques (Lavenex & Amaral, 2000; Lavenex, Suzuki, & Amaral, 2002; Nilssen, Doan, Nigro, Ohara, & Witter, 2019; Suzuki & Amaral, 1994; Van Hoesen, 1982; Witter & Amaral, 2021), further connections include the following. In macaques the hippocampal CA1 region has some direct connections to the cortex in the anterior part of the superior temporal sulcus (Zhong, Yukie, & Rockland, 2005) and to the orbitofrontal and anterior cingulate cortex (Cavada, Company, Tejedor, Cruz-Rizzolo, & Reinoso-Suarez, 2000; Morecraft et al., 2012; Zhong, Yukie, & Rockland, 2006). It has further been reported in macaques that CA1 neurons have direct connections to a number of temporal cortical areas, including the posterior parahippocampal cortex (areas TF and TH), perirhinal (areas 35 and 36) (Insausti & Munoz, 2001), and ventral inferotemporal areas (areas TEav and TEpv) (Yukie, 2000), with connections from CA1 also to the temporal pole (TG) and subiculum (Blatt & Rosene, 1998), to the pregenual anterior cingulate cortex (Insausti & Munoz, 2001), and to anteroventral TE (Ichinohe & Rockland, 2005; Zhong & Rockland, 2004) and the orbitofrontal cortex (Zhong et al., 2006). Moreover, direct projections to CA1 in macaques have been reported from areas 7a and 7b, area TF, and a region in the occipitotemporal sulcus (Ding, Van Hoesen, & Rockland, 2000; Rockland & Van Hoesen, 1999), and from cortex in the superior temporal sulcus, the rostral and retrosplenial portions of the cingulate cortex, the agranular insular cortex, and the caudal orbitofrontal cortex (Suzuki & Amaral, 1990); and also from anteroventral TE (Zhong & Rockland, 2004). The macaque presubiculum has connections to the cortex in the superior temporal sulcus, the lateral orbitofrontal cortex, and the temporal pole (Insausti & Munoz, 2001).

2. Methods

2.1. Participants and data acquisition

Multiband 7T resting state functional magnetic resonance images (rs-fMRI) of 184 individuals were obtained from the publicly available S1200 release (last updated: April 2018) of the Human Connectome Project (HCP) (Van Essen et al., 2013). Individual written informed content was obtained from each participant, and the scanning protocol was approved by the Institutional Review Board of Washington University in St. Louis, MO, USA (IRB #201204036).

Multimodal imaging was performed in a Siemens Magetom 7T housed at the Center for Magnetic Resonance (CMRR) at the University of Minnesota in Minneapolis. For each participant,

a total of four sessions of rs-fMRI were acquired, with oblique axial acquisitions alternated between phase encoding in a posterior-to-anterior (PA) direction in sessions 1 and 3, and an anterior-to-posterior (AP) phase encoding direction in sessions 2 and 4. Specifically, each rs-fMRI session was acquired using a multiband gradient-echo EPI imaging sequence. The following parameters were used: TR = 1000 ms, TE = 22.2 ms, flip angle = 45°, field of view = 208 × 208, matrix = 130 × 130, 85 slices, voxel size = 1.6 × 1.6 × 1.6 mm³, multiband factor = 5. The scanning time for the rs-fMRI protocol was approximately 16 min with 900 volumes. Further details of the 7T rs-fMRI acquisition protocols are given in the HCP reference manual.

(https://humanconnectome.org/storage/app/media/documentation/s1200/HCP_S1200_Release_Reference_Manual.pdf).

The current investigation was designed to complement an investigation with diffusion tractography (Huang, Rolls, Hsu, et al., 2021), and to ensure that the participants were very similar in both investigations, eight rs-fMRI participants were excluded: six with no diffusion scans and two with incomplete rs-fMRI sessions. Then, in order to allow a comparison of the 7T data described here with results obtained at the 3T rs-fMRI dataset, five subjects were excluded: 3 with no 3T fMRI scans and two with incomplete rs-fMRI sessions. That provided 172 participants for the analyses described here (age 22—36 years, 66 males). The functional connectivity shown here was for the first of the 4 sessions of 7T rs-fMRI, to allow future compatibility with effective connectivity for which results from a single session can be used. However the results on the other 3 sessions were checked, and were similar, and the voxel-level results shown in Figs. 2 and S2-S8 were from all 4 time series. The number of participants was the maximum available subject to the above, as fMRI analyses benefit from as much statistical power as possible (Gong et al., 2018).

2.2. Data preprocessing and measurement of functional connectivity

The preprocessing was performed by the HCP as described in Glasser et al. (2013), based on the updated 7T data pipeline (v3.21.0, https://github.com/Washington-University/HCPpipelines), including gradient distortion correction, head motion correction, image distortion correction, spatial transformation to the Montreal Neurological Institute space using one step spline resampling from the original functional images followed by intensity normalization. In addition, the HCP took an approach using ICA (FSL's MELODIC) combined with a more automated component classifier referred to as FIX (FMRIB's ICA-based X-noisifier) to remove non-neural spatiotemporal artefact (Griffanti et al., 2014; Salimi-Khorshidi et al., 2014; Smith et al., 2013). This step also used 24 confound timeseries derived from the motion estimation (6 rigid-body parameter timeseries, their backwards-looking temporal derivatives, plus all 12 resulting regressors squared (Satterthwaite et al., 2013) to minimise noise in the data. (The mean framewise displacement was .083 ± .032 std.) The timeseries were detrended, and temporally filtered with a second order Butterworth filter set to .008−.08 Hz, and then the functional connectivities were measured as the Pearson correlations between the 900 point time series for each pair of brain regions.

As is evident from the above, the HCP was extremely careful in its preparation of the timeseries, to minimize any unwanted noise from headmotion etc. To address this further, we performed a further analysis with the same 172 participants at 3T which has a 1200 point time series with TR = .72. In this set of data, it was possible to regress out the framewise displacement, and it was found that this made little difference, in that the functional connectivities with and without regression of frame-wise displacement were correlated .987. (Frame-wise displacement measures the movement of the head from one volume to the next, and is calculated as the sum of the absolute values of the six realignment estimates (three translation and three rotation parameters) at every timepoint (Power, Barnes, Snyder, Schlaggar, & Petersen, 2012).) We also performed cross-validation, and showed that the functional connectivities described here for 172 participants at 7T were correlated .944 with those in 845 different HCP participants at 3T. These precautions and cross-validation thus show that the functional connectivity measurements described here are robust. It is also noted that although signal dropout can be a complication of fMRI in the medial temporal lobe, this is unlikely to differentially influence the 9 regions of interest analyzed here, as they are all close together in the brain (Fig. 1). Further, in places where this might be relevant, such as the less extensive functional connectivity of the entorhinal cortex than the hippocampus reported here, the temporal signal-to-noise ratio (tSNR) was checked and was not low, and the functional connectivity is consistent with the less extensive anatomical connections of the entorhinal cortex than the hippocampus found with the diffusion tractography (Huang, Rolls, Hsu, et al., 2021).

2.3. Brain atlas and hippocampal system region of interest selection

To construct the functional connectome for the regions of interest in this investigation with other parts of the human brain, we prepared the following atlas: (1) HCP's multi-modal parcellation (v1.0), including 179 cortical regions per hemisphere except for the hippocampus (Glasser, Coalson, et al., 2016). The modified atlas (HCPex) that we used was defined in the asymmetric MNI space of ICBM152 2009c (Fonov et al., 2011), and is described in detail elsewhere (Huang, Rolls, Feng, et al., 2021). We checked with individual participants that the atlas fitted their T1 structural images in native space including in the medial temporal lobe. To distinguish the subiculum from the hippocampus, we used the subiculum mask provided in the CoBrALab atlas (Winterburn et al., 2013). Thus, the final modified HCP atlas contained 362 parcels which cover the cerebral cortex including separate definitions of the hippocampus and subiculum. A list of these regions is provided in Table S1, with coronal slices showing the location of each of these brain regions provided elsewhere (Huang, Rolls, Feng, et al., 2021; Huang, Rolls, Hsu, et al., 2021).

In this investigation, the same nine regions of interest (ROIs) were chosen as in the complementary diffusion tractography investigation (Huang, Rolls, Hsu, et al., 2021) to investigate their whole-brain functional connectivities. They were the Hippocampus (Hipp), Subiculum (Subic), Entorhinal Cortex (EC), Perirhinal Cortex (PeEc), the presubiculum (PreS)
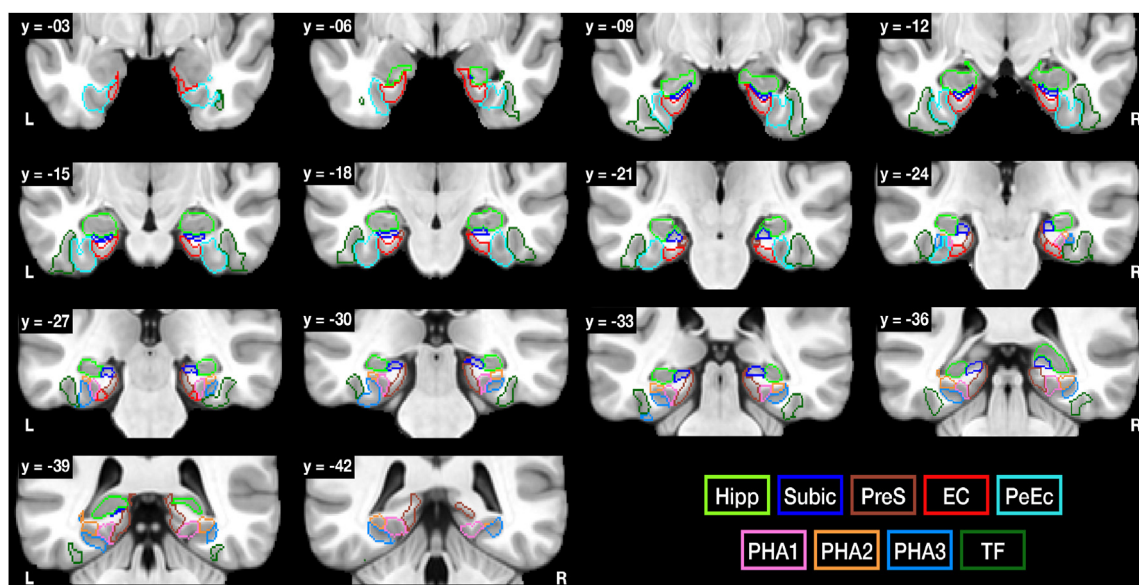
Fig. 1 — The hippocampal, parahippocampal and related regions of interest (ROIs) as defined in the HCP atlas (Glasser, Coalson, et al., 2016) that were used for the functional connectivity. EC - entorhinal cortex; Hipp — hippocampus; PeEc: perirhinal cortex; PHA1-3 - parahippocampal gyrus areas 1—3; TF- parahippocampal area TF; PreS — presubiculum; Subic — subiculum. For the hippocampus and subiculum, the templates were from Winterburn et al. (2013). The y values of these coronal slices are in MNI coordinates. R indicates Right hemisphere.

and parahippocampal gyrus (area TF; area TH in terms of 3 subregions PHA1-3), as shown in Fig. 1. Of the four para-hippocampal areas, PHA1-3 correspond to area TH (which is medial to and extends posterior to area TF), where within TH, PHA1 is medial, PHA2 is dorsolateral, and PHA3 is ventrolateral (see Fig. 1). The hippocampus defined in this investigation was slightly larger than in the original HCP atlas, and was separated from the subiculum, as described in more detail by Huang, Rolls, Hsu et al. (2021).

2.4.   Functional connectome

Whole-brain functional connectivity (FC) analysis was performed between the 9 hippocampal system ROIs shown in Fig. 1 and the 362 regions defined above and shown in Table S1. This provided the analyses illustrated in Figs. 3 and 4. This FC was computed for each participant by the Pearson correlations between the average across voxels of the timeseries for each of the hippocampal system ROIs and the average across voxels of the time series of voxels for each of the other brain regions in the HCP atlas. These functional connectivities were then averaged across participants. The temporal filtering used was .008—.08 Hz, to be compatible with future studies of effective connectivity.

In addition, FC analysis was also performed between the 9 hippocampal system ROIs shown in Fig. 1 and every voxel in the brain. This provided the analyses illustrated on coronal slices of the brain in Figs. 2 and S1-S8. For the ROI-with-voxel FC, for each participant, the Pearson correlations between the average across voxels of the time series for a hippocampal system ROI and the timeseries for every other voxel in the brain were computed. These functional connectivities were

then averaged across participants. This analysis utilized the gray matter atlas defined in asymmetric MNI space of ICBM152 2009c (Fonov et al., 2011); download link for this atlas: http://www.bic.mni.mcgill.ca/ServicesAtlases/ ICBM152NLin2009) (see Huang, Rolls, Feng et al. (2021)).

2.5.   Statistics

The functional connectivity of each hippocampal system ROI with other regions in the extended HCP atlas was calculated using the first resting state fMRI session for each HCP participant and then averaged across the 172 participants. An average functional connectivity of less than .39 between any two regions is shown as blank in the connectivity matrices shown in Figs. 3 and 4. This threshold value of $r = .39$ allows for a binary sparseness of the connectivity shown in Figs. 3 and 4 to be .18; that is, all the functional connectivities shown in Figs. 3 and 4 are in the top 18% of all the possible functional connectivities between these 9×181 cortical areas. This threshold allows the different functional connectivity patterns of the 9 hippocampal system areas with other cortical areas to be clearly illustrated (Fig. 3). (For reference in connection with Fig. 3, functional connectivities above a threshold of .51 are in the top 5th percentile, corresponding to a binary sparseness of .05.)

Part of the reason for using this threshold of $r = .39$ for Figs. 3 and 4 is that it produces a sparseness of the connectivity matrix that is very similar to that found for the diffusion tractography connection matrix found in the same 172 HCP participants for these 9 hippocampal system x 181 cortical areas (Huang, Rolls, Hsu, et al., 2021). For the connection matrix shown in Figs. 5 and S11 of Huang et al. (2021), the
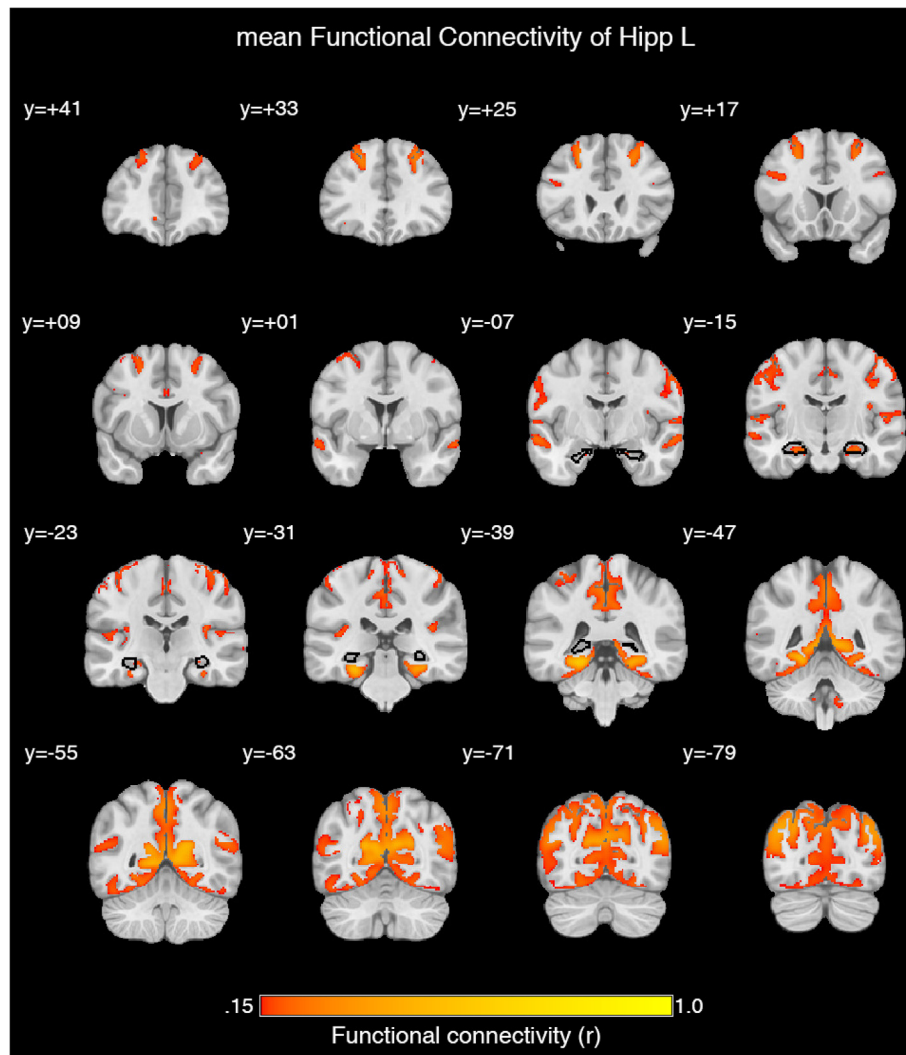
Fig. 2 – The voxel-level functional connectivity of the left hippocampus. The Region of interest, the Hippocampus, is outlined in black. The mean functional connectivity averaged across the 172 participants is shown. The threshold was selected at .15 to reveal the selectivity of the connectivity. The y value is in MNI coordinates.

connections shown are in the top 20.6%, so the sparseness of the functional connectivity matrix shown here in Figs. 3 and 4 is similar to that of the connection matrix. That facilitates comparison between the functional connectivity matrix and the anatomical connection matrix.

In a further analysis, Fig. S9 shows the mean and the standard error of the mean of the functional connectivity of the hippocampus region with the 181 cortical areas calculated over the 172 participants. This shows that the standard errors are low, and that the differences between the functional connectivities of the hippocampus with cortical areas are very significant (indicated by whether the standard errors overlap). Indeed, a one way ANOVA for the hippocampus region showed that it had highly significantly different functional connectivity with the 181 different cortical areas (F [180, 30,591] = 66.1, $p = 0$). Fig. S9 also shows the threshold of r = .39 used for Figs. 3 and 4, and shows that the functional connectivities selected in Figs. 3 and 4 for analysis here are different

from most of the generally much lower functional connectivities of the hippocampus with other cortical areas.

For the ROI to voxel functional connectivity shown in Figs. 2 and S1-S8, a threshold of .15 was used, as the voxel-level r values are lower. These Figures are designed to show the exact brain areas at the voxel level with the functional connectivity described here.

To test whether the patterns of functional connectivities of each of the 9 hippocampal system ROIs with the 181 areas in the left hemisphere of the modified HCP atlas were significantly different, the interaction term was calculated for each pair of the 9 hippocampal system ROIs in two-way ANOVAs (each 2 × 181) across the 172 participants, and Bonferroni correction for multiple comparisons was applied.

We have reported how we determined the sample size, all data exclusions, all data inclusion/exclusion criteria, that inclusion/exclusion criteria were established prior to data analysis, all manipulations, and all measures in this study.
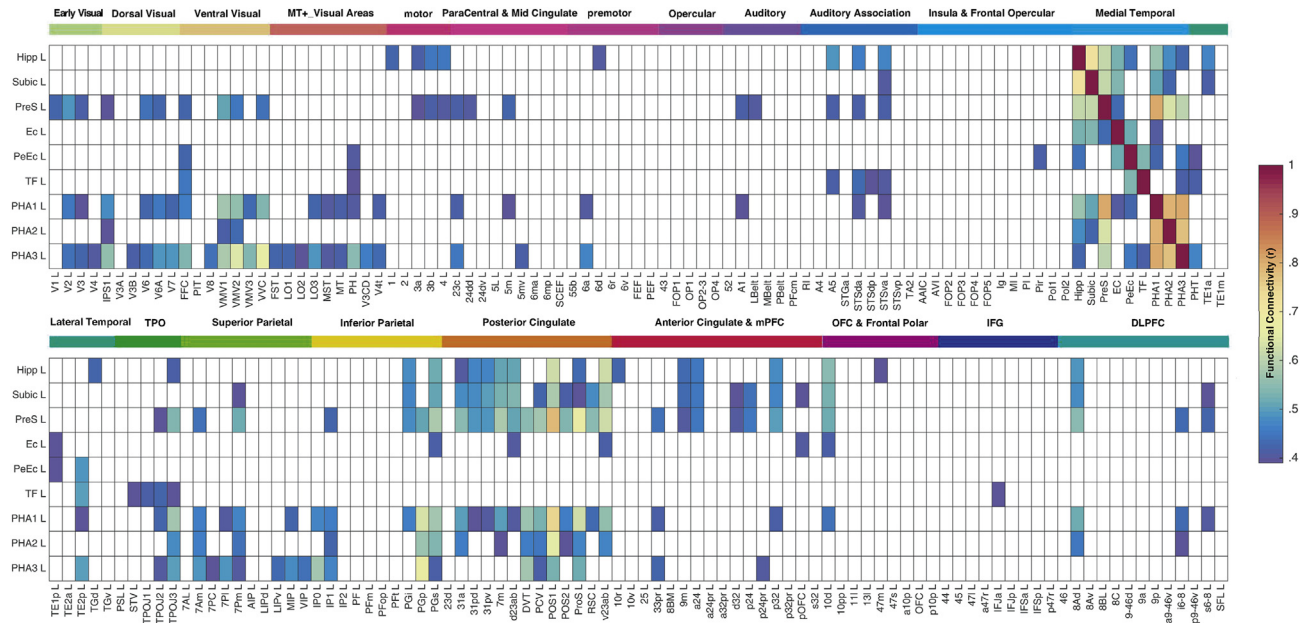
Fig. 3 — Mean functional connectivity across the 172 participants of hippocampal formation regions for the left hemisphere. The rows show the hippocampal system regions of interest and the columns the 181 regions in the modified HCP atlas, ordered and with the abbreviations shown in Table S1. The threshold was set at r = .39 and the data were from 7T. This threshold allows the top 18% of the functional connectivities between all these areas to be shown. (The data at 3T were qualitatively similar, with the r values a little lower.) Hipp - hippocampus; Subic - subiculum; PreS — Presubiculum; EC — entorhinal cortex; PeEc — perirhinal cortex; TF — parahippocampal gyrus region TF; PHA1-3 — parahippocampal gyrus region TH subregions 1—3. IFG — inferior frontal gyrus; DLPFC — dorsolateral prefrontal cortex.

3. Results

The 9 hippocampal system regions of interest (ROIs) investigated are shown in Fig. 1 (see Methods). The functional connectivity of these human hippocampal system ROIs measured in 172 HCP participants at 7T with all other voxels in the brain, and with all 362 areas in the modified HCP atlas, are described next.
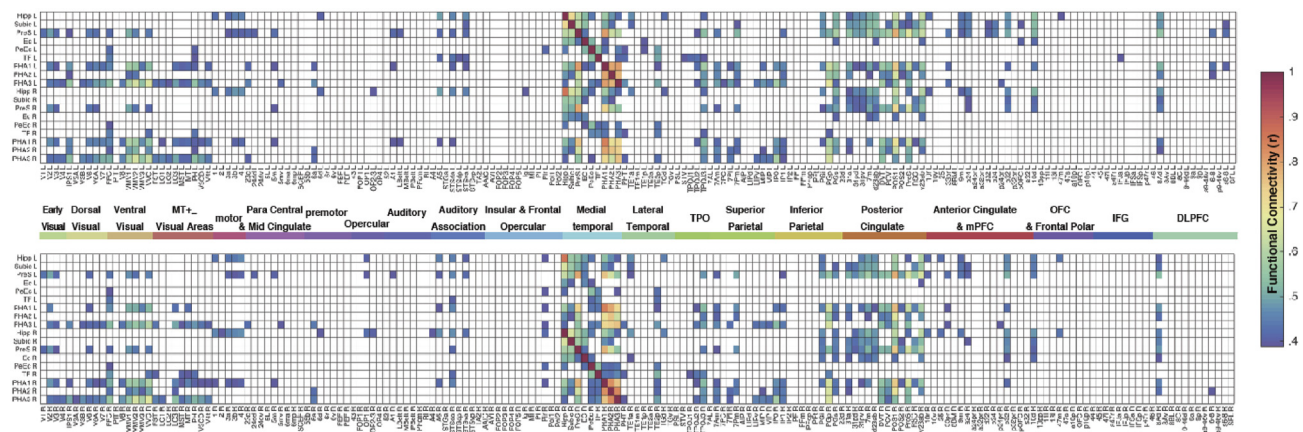

Fig. 4 — The full functional connectivity matrix for each of the left and right hippocampal regions of interest (the rows) with all HCP atlas cortical areas. The top matrix shows the connections of the ROIs with the left hemisphere, and the bottom matrix connections of the ROIs with the right hemisphere. The strength of functional connectivity between the HCP regions is shown in this Figure, in order to allow assessment of the absolute magnitude of the connectivity between each pair of HCP regions. The threshold was set at r = .39. Hipp - hippocampus; Subic — subiculum; PreS — presubiculum; EC — entorhinal cortex; PeEc — perirhinal cortex; TF — parahippocampal gyrus region TF; PHA1-3 — parahippocampal gyrus regions comprising TH. IFG — inferior frontal gyrus; DLPFC — dorsolateral prefrontal cortex. L indicates the left hemisphere, and R the right hemisphere.
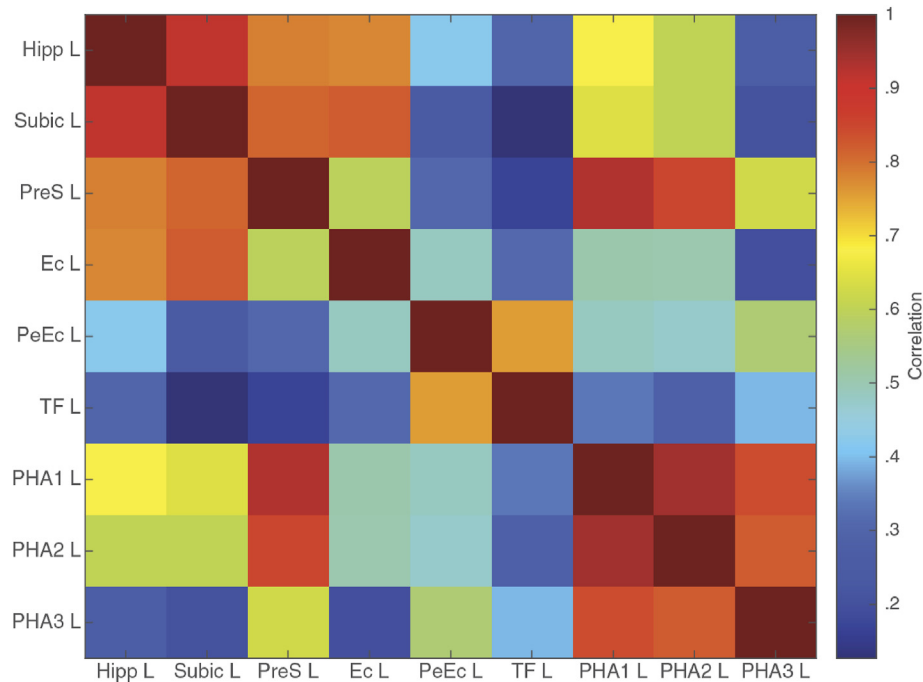
Fig. 5 − Similarities and differences between the functional connectivities of the nine hippocampal system ROI areas. The correlation matrix shows the correlations between all nine hippocampal ROIs based on their functional connectivity vectors with each of the 181 left cortical areas in the modified HCP atlas across 172 participants. Abbreviations as in Fig. 3.

3.1.   Hippocampal ROI-with-voxel functional connectivity of the human hippocampal system

The functional connectivity of the human hippocampus with all other voxels in the brain is shown in coronal slices in Fig. 2. The ROI region (in this case the Hippocampus) is outlined in black. Corresponding results for the other 8 hippocampal system ROIs are shown in Figs. S1-S8, as it is helpful to see the data at this level of detail. Reference should be made to these Figures in the remainder of the Results.

3.2.   Hippocampal ROI-with-HCP-cortical region functional connectivity of the human hippocampal system

The functional connectivity of the human hippocampal system with all 181 cortical regions in the left hemisphere of the modified HCP brain atlas is shown in Fig. 3. This is useful as it shows quantitatively the connectivity with what are in many cases cortical regions with identified functions. The full names in the modified HCP atlas are shown in Table S1, and are shown labelled in coronal slices elsewhere (Huang, Rolls, Feng, et al., 2021; Huang, Rolls, Hsu, et al., 2021). The patterns of functional connectivities of each of the 9 hippocampal system ROIs with the 181 areas in the modified HCP atlas were all significantly different from each other (the interaction term in a 2-way ANOVA across the 172 participants was $p < 10^{-100}$ for the comparisons between every pair of the 9 ROIs after Bonferroni correction for multiple comparisons).

Fig. 4 extends this analysis to both hemispheres, so that contralateral functional connectivities can be shown, and to enable analysis of possible left-right asymmetries. The connectivities are thresholded at r = .39 at 7T in both Figs. 3 and 4,

as this facilitates comparison of the functional connectivities of these nine regions with each other, but also with the direct connections shown with diffusion tractography of the same 9 regions with the same HCP areas in the same participants (Huang, Rolls, Hsu, et al., 2021).

In the remainder of the results, the functional connectivity of each of the 9 hippocampal system ROIs is considered, referring throughout to the data shown in Figs. 2−4 and S1-S8. Some reference to known functions of the areas considered is provided, for this helps to illuminate the significance and relevance of the functional connectivities described for each region.

3.3.   Hippocampus

A key point evident in Figs. 3, 4 and S3 is that the hippocampus has higher functional connectivity with many cortical areas than does the entorhinal cortex (F [1,63,920] = 3.72 × 10³, $p < 10^{-20}$). This is consistent with the evidence from tractography that in humans some of the communication between the hippocampus and cortical areas may bypass the entorhinal cortex.

As expected, the hippocampus does have at least moderate functional connectivity (FC) with nearby areas such as the entorhinal cortex, subiculum, and presubiculum (Fig. 3). But it also has high connectivity with areas such as TH (PHA1-2) medially in the parahippocampal gyrus; with parietal cortex areas (including PG and medial parietal 7m); and with posterior cingulate cortex areas (including 31 and 23 and the retrosplenial cortex) (Figs. 3 and 2).

The hippocampus also has some FC with some ventral visual stream areas, including the anterior inferior temporal cortex area TE1 and the temporal pole TG.

Interestingly, the hippocampus has some FC with the anterior cingulate cortex (p32), the frontal pole (10d), the dorsolateral prefrontal cortex (8Ad, which is probably the frontal eye field region involved in the short-term memory for spatial location for eye movements (Funahashi, Bruce, & Goldman-Rakic, 1989)), and the lateral orbitofrontal cortex (area 47) (Fig. 3). Given the orbitofrontal cortex functional connectivity with the hippocampus, we checked the amygdala, and found that the amygdala has functional connectivity with the hippocampus (r = .52) (and with the perirhinal cortex, r = .43). Some functional connectivities are also found with somatosensory/motor areas 1, 3a, 3b and 4; and with auditory and related areas in the superior temporal sulcus (A5, STSda, STSva) (Fig. 3). At a slightly lower threshold of r = .36, functional connectivity of the hippocampus was also found with the pyriform (olfactory) cortex, with the subgenual anterior cingulate cortex (area 25), and with the posterior orbitofrontal cortex (pOFC).

The hippocampal functional connectivity with both ventral and dorsal stream areas probably relates to the ability of primate hippocampal neurons to respond to learned associations of objects and spatial views (Rolls, Xiang, & Franco, 2005), which are typically involved in episodic memory (Kesner & Rolls, 2015; Rolls, 2018).

3.4. Subiculum

The subiculum (Subic) has FC with fewer cortical regions than the hippocampus (Figs. 3 and S1). The subiculum does have strong FC with the hippocampus, and moderate connectivity with the presubiculum (PreS), entorhinal cortex (EC), parahippocampal area TH, posterior cingulate areas including 31, 23 and retrosplenial cingulate cortex, and lateral parietal areas (PG). The subiculum is thus connected with dorsal stream areas rather than ventral stream areas. The subiculum contains whole body motion cells sensitive to vestibular signals and optic flow (O'Mara, Rolls, Berthoz, & Kesner, 1994), which probably reflect the connectivity with the parietal cortex (Rolls, 2021c).

3.5. Presubiculum

The presubiculum has functional connectivity with many different brain areas (Figs. 3 and S2). It has high FC with the hippocampus and subiculum, and also with TH, parietal cortex (7, PG), and posterior cingulate cortex including the retrosplenial cingulate cortex. It is thus strongly connected with dorsal stream 'where' areas in humans; and correspondingly has moderate connectivity with dorsolateral parts of the prefrontal cortex (8Ad). The primate presubiculum contains head direction cells (Robertson, Rolls, Georges-François, & Panzeri, 1999), which probably relate to its parietal cortex connectivity. The human presubiculum also has functional connectivity with early visual cortical areas (V1−V3 and POS1); with VMV1 and VMV2 which together with TH (PHA1-3) form the parietal place or scene area (Sulpizio, Galati, Fattori, Galletti, & Pitzalis, 2020); somatosensory cortex (3a,b);

auditory cortex (A1,LBelt, A5); anterior cingulate cortex (32); frontal pole (10); and prefrontal cortex (8Ad).

3.6. Entorhinal cortex (EC)

As expected, the entorhinal cortex does have moderate FC with the hippocampus, subiculum, perirhinal cortex, and presubiculum (Figs. 3 and S3). It also has some FC with the inferior temporal cortex, parietal cortex, posterior cingulate cortex, posterior orbitofrontal cortex, and frontal pole (10) (Fig. 3).

3.7. Perirhinal cortex

The perirhinal cortex (PeEc) also has functional connectivity with many fewer cortical areas than the hippocampus (Figs. 2, 3 and S4). As expected, the perirhinal cortex does have moderate FC with the hippocampus and entorhinal cortex. Interestingly, the perirhinal cortex has FC with TF which is lateral parahippocampal cortex, and TF has FC with the temporal lobe visual cortical areas such as TE2 (Fig. 3). Consistently, the perirhinal cortex has FC with ventral stream temporal cortical visual areas TE2 and TE2 and the fusiform face cortex (FFC).

3.8. Parahippocampal cortex TF

Parahippocampal area TF (which is isocortex) is lateral to and extends more anteriorly than parahippocampal area TH (which is proisocortex) (Fig. S1 of Huang et al. (2021)).

Parahippocampal area TF has FC with ventral stream visual areas including the perirhinal cortex, and parts of the inferior temporal visual cortex TE, and FFC (Figs. 3 and S5). At slightly lower thresholds, TF has functional connectivity with more parts of TE and TG, and with the inferior frontal areas (more than IFja) involved in 'what' short-term memory (Figs. 3 and S5). TF does not have marked FC with dorsal stream/parietal areas. Thus in humans, this lateral and more anterior part of the parahippocampal gyrus, TF, is related to ventral stream rather than dorsal stream areas.

3.9. Parahippocampal cortex TH (areas PHA1-3)

The Parahippocampal TH areas PHA1-3 are medial and extend posteriorly in the parahippocampal gyrus (Fig. 1). PHA1-3 have strong functional connectivity with each other (Fig. 3 and S6-S8). They also have moderate functional connectivity with the hippocampus and with dorsal stream/parietal areas including area 7 and PG. TH also has moderate FC with posterior cingulate areas including the retrosplenial cingulate cortex (RSC). TH also has moderate FC with i6-8 and 8Ad, a relatively dorsal part of the frontal cortex in the superior frontal sulcus, linking TH to spatial, 'where', prefrontal cortex short-term memory systems. TH also has moderate connectivity with early visual cortical areas (including the ventromedial visual areas VMV1-3 (see Fig. S1 of Huang, Rolls, Hsu et al. (2021)) that together form the parahippocampal place (or scene) area (PPA) (Sulpizio et al., 2020). This is consistent with the discovery of spatial view cells in the primate parahippocampal gyrus as

well as hippocampus (Georges-François, Rolls, & Robertson, 1999; Rolls, 2021c; Rolls, Robertson, & Georges-François, 1997).

3.10. Right versus left hippocampal system connectivity

The full functional connectivity matrix for each of the left and right hippocampal system regions of interest (the rows) with all HCP cortical atlas areas (the columns) is shown in Fig. 4. The top matrix shows the functional connectivity of all the ROIs with the 181 left hemisphere HCP atlas areas, and the bottom matrix the connections of the ROIs with the right hemisphere 181 HCP atlas areas. The functional connectivity is again averaged over the 172 participants. What is especially evident in Fig. 4 is that most of the hippocampal formation connections are almost bilaterally symmetrical. This is quite different to the direct connections as revealed with diffusion tractography, which is less able to show interhemispheric connections, and which shows connections across the midline mainly for the hippocampus, presubiculum and TH (Huang, Rolls, Hsu, et al., 2021).

Fig. 4 also shows that the connections of the right and left hippocampus are overall similar. However, statistical comparison with Bonferroni correction $p < .01$ showed that some of the functional connectivities of areas PHA1-3 were greater in the right hemisphere (especially with the parietal and posterior cingulate cortex, and early visual cortical areas), consistent with a specialization of the right hemisphere for spatial function including that implemented in the parahippocampal place area. Further, the functional connectivities of all 9 hippocampal system areas with the prefrontal cortex (with most of the areas IFsa through s6-9 shown in Table S1) was greater in the left hemisphere, consistent with specialization of the left hippocampus for functions implemented with the left prefrontal cortex, which may be related to short-term memory, and planning for the future. Perhaps related to this, the functional connectivity of left TF with Broca's area (45 and 44) and the adjoining 47l were also greater in the left hemisphere, implicating language in these computations (Rolls, 2021a).

3.11. Comparison between the functional connectivities of the nine different hippocampal system ROIs

Fig. 5 shows the matrix of correlations between all nine ROIs based on their functional connectivity vectors with each of the 181 areas in the left hemisphere of the modified HCP atlas. Many features stand out. First, the 3 areas that comprise parahippocampal region TH (PHA1-3) are quite correlated with each other, as they have similar functional connectivity to each other, and different connectivities from the other parahippocampal region, TF. Second, TH has a high correlation of its functional connectivities (FC) with the presubiculum, and low correlations with the connectivities of TF and the perirhinal and entorhinal cortex. In contrast, TF has moderate correlations with the connectivities of the perirhinal cortex, but not with TH areas. The implication is that TF is related to ventral stream areas via the perirhinal cortex, whereas TH is related to other brain regions (which as shown in Fig. 3 include parietal cortex dorsal stream areas). Third, the presubiculum and subiculum have highly correlated vectors of functional connectivity, which are also highly correlated

with the vector of hippocampal connectivity. The presubiculum and subiculum also have moderate similarity to the connectivity of the entorhinal cortex, and to the more medial and dorsal parts of TH (PHA1 and PHA2). Fourth, the hippocampus has moderately similar functional connectivity not only with the subiculum and presubiculum, but also with the entorhinal cortex, and some similarity with the medial and dorsal parts of TH (PHA1 and PHA2). The correlations reflect the similarity of the row vectors shown in Fig. 3, which does provide more detailed information on the functional connectivities of the nine hippocampal ROIs with the 181 cortical regions in the modified HCP atlas. As noted above, all pairs of the nine hippocampal system ROIs had different patterns of functional connectivity with the 181 brain areas in the modified HCP atlas (all $p < 10^{-100}$).

Fig. 6 provides a summary diagram of the strengths of the functional connectivities between the different parts of the hippocampal system and other brain areas, all thresholded at .4, with those connections considered next. In a ventral visual stream (shown in blue) connecting with the hippocampus, early visual cortical areas have connectivity with the temporal cortical visual areas, which in turn have connectivity with the perirhinal cortex, which in turn has connectivity with the entorhinal cortex, which in turn has connectivity with the hippocampus. Interestingly, parahippocampal gyrus area TF (which is lateral in the parahippocampal gyrus) is part of this ventral visual stream in humans, in that it has connectivity with the temporal cortical visual areas and the perirhinal cortex. In a dorsal visual stream (shown in red) with connectivity with the hippocampus, early visual cortical areas have connectivity with the parietal cortex and parahippocampal area TH, both of which have connectivity with the presubiculum, which in turn has connectivity with the hippocampus. The posterior cingulate cortex is linked with this dorsal system, in that it has connectivity with the parietal cortex; and then onward connectivity via the presubiculum with the hippocampus.

One feature of the connectivity shown in Fig. 6 is that the ventral and dorsal streams in humans can be considered as partly separated pathways that converge in the hippocampus.

A second feature shown in Fig. 6 is that the presubiculum in terms of functional connectivity appears to be an important part of the dorsal visual stream's route with the hippocampus. However, the entorhinal cortex can potentially also provide a route for the dorsal visual stream to connect with the hippocampus, in that the presubiculum and parietal cortex have connectivity with the entorhinal cortex, though it is at the low end of what is considered here.

A third feature of the connectivity shown in Fig. 6 is that the hippocampus has connectivity that can bridge over intermediate areas. For example the hippocampus has functional connectivity with the perirhinal cortex and temporal lobe cortex that is apparent across intervening areas such as the entorhinal cortex. Similarly, in the dorsal visual stream, the hippocampus has functional connectivity with the parahippocampal cortex TH, the posterior cingulate cortex, and the parietal cortex that is apparent over intervening areas such as the entorhinal cortex and presubiculum. This was supported by partial correlation analysis which showed for example that the functional connectivity between the
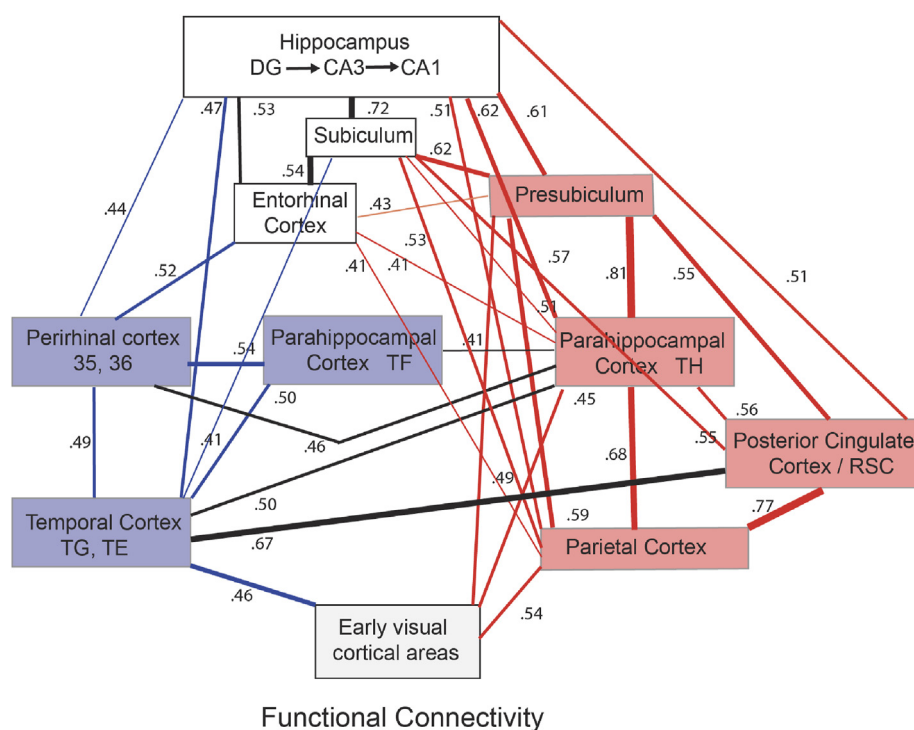
Fig. 6 — Functional connectivities between the parts of the human hippocampal system and other cortical areas. The functional connectivities are shown by their _r_ values, with links shown only where _r_≥0.4. The value of _r_ shown in the case of brain regions such as the parietal and temporal cortex with many subregions is the largest _r_ value with any subregion. The blue regions and functional connectivity edges (lines) are part of the ventral visual system, and the red regions and functional connectivity edges are part of the dorsal visual system. The entorhinal cortex and subiculum have connectivity with both the dorsal and ventral streams, and their connectivity with each other and the hippocampus is shown in neither red nor blue, but in black. The width of the lines or links or edges connecting areas is related to the strength of the functional connectivity shown.

hippocampus and parahippocampal gyrus PHA1 of r = .57 remained substantial (r = .45) when partial correlation was used to remove the effects of correlations with the entorhinal cortex.

Fourth, Fig. 6 makes it clear that there are influences that cross between the two visual streams before the hippocampus, between for example the perirhinal cortex and parahippocampal gyrus TH; and for the temporal cortical visual areas with the posterior cingulate cortex and parahippocampal TH.

Fifth, the entorhinal cortex and subiculum have functional connectivity with both the dorsal visual stream as shown in Fig. 6 in red, and with the ventral visual stream as shown in blue. Accordingly their connectivities with the each other and with the hippocampus are shown in neither red not blue but in black in Fig. 6.

4.   Discussion

In the first part of the discussion, a synthesis is made of what can be learned by the combination of the complementary methods of functional connectivity as described here, and of diffusion tractography (Huang, Rolls, Hsu, et al., 2021), about the connections and connectivity of the human hippocampus. The approach being taken is unprecedented in previous

research, most of which has not been in humans (though the supporting anatomical evidence from macaques described in the Introduction is incorporated into this synthesis); most of which has involved the study of single brain areas with neuroanatomical tract tracing in animals, rather than the quantitative connections (Huang, Rolls, Hsu, et al., 2021) and connectivity of 9 main parts of the hippocampal system in humans with 181 cortical areas in each hemisphere that can be defined anatomically but also to some extent functionally using the HCP atlas (Glasser, Coalson, et al., 2016). This synthesis is facilitated by the fact that the tractography (Huang, Rolls, Hsu, et al., 2021) and the functional connectivity (described here) were performed using the same HCP atlas and with the same HCP participants.

Then in the second part of the Discussion the functional implications of the connectivity of the human hippocampal memory system are considered, in terms of some of the computations that take part in different parts of the human hippocampal system and its connected neocortical areas.

4.1.   Comparison of functional connectivity of the human hippocampal system with connections measured with diffusion tractography

The functional connectivity of the hippocampal system described here and summarized in Fig. 6 is very helpful to

compare with the direct connections of the hippocampal system as revealed by diffusion tractography in the same group of 172 individuals from the Human Connectome Project (Huang, Rolls, Hsu, et al., 2021). The functional connectivity both supports key new findings about the direct connections in humans as described recently (Huang, Rolls, Hsu, et al., 2021), by showing functional connectivity correlates; and also is important by showing the brain regions beyond those with direct hippocampal connections that are influenced by activity in the hippocampal system. A key part of the importance of the functional connectivity described here is that it shows that the pathways of the hippocampal system identified with diffusion tractography (Huang, Rolls, Hsu, et al., 2021) are not false positives, in that all have functional connectivity, which would not be present if the tractography had followed pathways incorrectly. We focus on these comparisons next, with key points based on Figs. 3 and 6 in the present paper compared with Figs. 5 and 6 of Huang, Rolls, Hsu, et al. (2021), the tractography in the same participants.

First, the human hippocampal system has far more extensive direct connections with cortical areas than in even non-human primates, including with the temporal pole, many parietal cortex areas, many posterior including retrosplenial cingulate cortical areas, and even with early sensory areas for vision, olfaction, somatosensation, and a part of what is auditory cortex in the superior temporal sulcus (Fig. 5 of Huang, Rolls, Hsu, et al., 2021). The functional connectivity described here extends that anatomical evidence, by confirming that there is strong functional connectivity between the hippocampus and most of these cortical areas, including the TE and TG temporal areas, many parietal cortex areas, and many posterior cingulate cortex areas (Figs. 2 and 3). The existence of direct connections is consistent with the macaque anatomy (see Introduction), though the connections of the human hippocampus with these areas is more extensive, and they are now much more systematically defined in the human HCP-MMP atlas (Glasser, Coalson, et al., 2016). Of particular interest though to consider is the evidence of direct connections of the hippocampus with early sensory cortical areas suggested by the tractography (Fig. 5 of Huang, Rolls, Hsu, et al., 2021), including somewhat surprisingly (given the evidence in macaques) with somatosensory, olfactory, and even early visual cortical areas. The functional connectivity described here supports this, in that there are functional correlations of the hippocampus with the somatosensory cortical areas (Fig. 3), the early visual cortical areas (in at least some participants, see Fig. 2), and the pyriform (olfactory) cortex has a correlation with the contralateral hippocampus (Fig. 4, and a weaker correlation with the ipsilateral). Thus even if we can not be sure yet that there are direct connections of the hippocampus per se with these early visual cortical areas such as V1–V3, due to some limitations of tractography (Huang, Rolls, Hsu, et al., 2021), the functional connectivity described here shows that the human hippocampus has clear functional interactions with early visual cortical areas including POS1 (Fig. 3) in at least some participants (Fig. 2). The distribution of functional connectivities across participants between the hippocampus and early visual cortical areas was consistent, with some participants having high functional connectivities, though across all the participants the mean

was not high though clear in Fig. 3 for POS1. It would be fascinating if high functional connectivities between the hippocampus and early visual cortical areas in individual people were associated with visual imagery.

Second, a key finding of the tractography related to the concept of widespread cortical connections of the human hippocampus above is that the human hippocampus has direct connections with the perirhinal cortex, and parahippocampal gyrus areas TF and TH (Huang, Rolls, Hsu, et al., 2021), which can bypass the entorhinal cortex. That suggested that the entorhinal cortex is not in humans the primary, main, gateway to and from the hippocampus. The functional connectivity of these areas described here is consistent with the concept that the entorhinal cortex is not 'the gateway' via a serial hierarchy to and from the hippocampus in humans, for the perirhinal cortex and even TE and TG areas, and the TH and parietal areas, do have strong interactions with the hippocampus (Fig. 3), which could be mediated by direct hippocampal connections with these areas rather than mainly through the entorhinal cortex as in the simplified schematic dual stream model (Fig. 1 of Huang, Rolls, Hsu, et al., 2021). Further, the entorhinal cortex and even the peririhinal cortex have functional connectivity with relatively few cortical areas compared to the hippocampus (Figs. 3, 6 and S3, S4). An implication is that the entorhinal cortex may implement some specialized processing, such as grid cells in the medial entorhinal cortex (Moser, Rowland, & Moser, 2015) including spatial view grid cells in primates (Garcia & Buffalo, 2020; Meister & Buffalo, 2018), and time encoding cells in the lateral entorhinal cortex (Rolls & Mills, 2019; Tsao et al., 2018).

A third key finding of the tractography is that the human parahippocampal gyrus is not mainly for connections with the dorsal visual system/parietal areas, as in the dual stream model (Fig. 1 of Huang, Rolls, Hsu, et al., 2021). Instead, what the functional connectivity described here strongly supports is that, in humans, area TF, which is lateral and extends relatively anterior, is connected with ventral stream 'what' areas (Figs. 3 and 6). In a complementary way, area TH of the parahippocampal gyrus (and proisocortical, and possibly of early evolutionary origin (Pandya, Seltzer, Petrides, & Cipolloni, 2015)), which is more medial and extends more posterior, appears to provide the functional connections between the hippocampus and dorsal stream areas including parietal and posterior cingulate areas including the retrosplenial cingulate cortex. This supports the human tractography (Huang, Rolls, Hsu, et al., 2021). Moreover, the functional connectivity reveals that it is especially area TH and the presubiculum, and to some extent the hippocampus, that has functional connectivity with early sensory areas (Figs. 3 and 6), and that extends the tractography. The functional connectivity certainly supports the concept that in humans, the hippocampal system has connectivity with early sensory cortical areas (Figs. 3 and 4, and S2, S3, S8).

A fourth key finding from the functional connectivity is that this extends bilaterally (Fig. 4), in strong contrast to the tractography, which is able to show connections mainly unilaterally (Huang, Rolls, Hsu, et al., 2021). However, it is noted that it could be an advantage if the human CA3 attractor network is mainly unilateral because this would enable the human hippocampus to operate as two separate attractor

networks, allowing the left human hippocampus to specialise more for language-related functions (Rolls, 2018; 2021a). This effectively doubles the memory capacity of the human hippocampus, as the capacity is determined largely by the number of CA3-CA3 connections onto each CA3 neuron in each separate attractor network (Rolls, 2018; 2021a).

A fifth finding was that in terms of cross-connectivity between the dorsal and ventral stream areas relating to the hippocampus shown in Fig. 6, the entorhinal cortex connects with ventral stream information from the perirhinal cortex, and also with dorsal stream information via its connections with the presubiculum, parietal cortex, TH, and posterior cingulate cortex (Figs. 3 and 6). In addition, there is cross-connectivity between the parahippocampal TH and the perirhinal cortex (Fig. 6), which again is not part of the simplified dual stream model shown in Fig. 1 of Huang et al. (2021). Also of interest in Fig. 6 is the functional connectivity of the temporal cortical areas TE and TG with the posterior cingulate cortex and TH, which may be indirect connectivity because the tractography did not reveal direct connections between these areas (Huang, Rolls, Hsu, et al., 2021).

Sixth, an area with which the human hippocampal system does have functional connectivity, probably implemented by direct connections (Huang, Rolls, Hsu, et al., 2021), is with the human anterior temporal lobe (Figs. 3 and 6). This may be important in relation to language, as the human left anterior temporal lobe is implicated in semantic representations (Bonner & Price, 2013; DeWitt & Rauschecker, 2016; Fairhall & Caramazza, 2013a, 2013b; Rolls, 2021a). Indeed, it must be remembered that the formation of new semantic representations, as well as episodic memory, is impaired by hippocampal damage (Rolls, 2021a), and the connectivity with especially the anterior temporal lobe provides clues about this functionality (Huang, Rolls, Hsu, et al., 2021; Rolls, 2022).

Seventh, there is functional connectivity of the hippocampus with some auditory cortex areas (Fig. 3), and this is likely to be mediated through direct connections of the hippocampus with areas STGa and AAIC, with which the hippocampus does have direct connections (Fig. 5 of Huang, Rolls, Hsu, et al., 2021).

Eighth, there is moderate functional connectivity of the hippocampus with some parietal cortex areas (Fig. 3), and this may be mediated by direct connections, and also by connections via the posterior cingulate cortex and presubiculum (Fig. 5 of Huang, Rolls, Hsu, et al., 2021).

Ninth, it is of interest that most parts of the hippocampal system described here have functional connectivity with prefrontal area 8, especially 8Ad at the junction of the superior and middle temporal gyri. This was not evident in the tractography (Fig. 5 of Huang, Rolls, Hsu, et al., 2021), so this is probably a trans-synaptic connection. This is probably part of the frontal eye fields (FEF) which have extensive connectivity with dorsal visual stream areas (Passingham & Wise, 2012), which are involved in eye movements to remembered targets (Funahashi et al., 1989; Goldman-Rakic, 1996), and which are involved in top-down attention (Germann & Petrides, 2020) which requires short-term memory to hold the object of attention online (Deco & Rolls, 2005; Rolls, 2021a). The hippocampal spatial view representation of scenes by spatial view cells (Rolls, 2021a; Rolls & Wirth, 2018; Rolls & Xiang,

2006) that can be updated by self-motion (Robertson, Rolls, & Georges-François, 1998; Wirth, Baraduc, Plante, Pinede, & Duhamel, 2017) may relate to this brain area when the movements have to be remembered, as they do for idiothetic update (Rolls, 2020; 2021c).

Tenth, there was evidence for functional connectivity of the hippocampus with the lateral (area 47, Fig. 3) and posterior orbitofrontal cortex, and with the anterior cingulate cortex (Fig. 3, area 32), which are areas related to punishment, reward, and emotion (Rolls, 2019; Rolls, Cheng, & Feng, 2020). Remembering where rewards are is an important aspect of hippocampal episodic memory, and this reward connectivity may also be important in the generation of semantic memories using recalled episodic memories (Rolls, 2022). This is supported by evidence from macaques (Cavada et al., 2000).

The diffusion tractography streamlines reflect the magnitude of the number of connections between hippocampal system ROIs and HCP atlas cortical regions, and so reflect potentially the magnitude of what is being communicated between the pair of brain regions (Huang, Rolls, Hsu, et al., 2021). This is the case because it is likely that the number of neurons transmitting information is an important factor in how much information is transmitted (Rolls, 2021a; Rolls & Treves, 2011). With the functional connectivity measures, the r values measure just the correlation between the BOLD signals, and do not reflect the size of the areas nor the number of connections between them and thus necessarily the amount of information that may be transmitted. This must be borne in mind when comparing the diffusion tractography (Huang, Rolls, Hsu, et al., 2021) with the functional connectivity measures described here. However, for many of the connections shown in Figs. 3 and 6, there is a good correspondence with the number of streamlines revealed in the diffusion tractography shown in Figs. 5 and 6 of Huang et al. (2021).

We also analyzed the functional connectivity in approximately 1000 HCP participants imaged at 3T, and found overall very similar results, though the r values are higher at 7T.

4.2. Functional implications of the connectivity of the human hippocampal memory system

The synthesis of the functional connectivity of the hippocampal system shown in Fig. 6 can be related to the functions of the different connected regions as follows, based on evidence in humans and macaques, as the cortical areas that connect to the hippocampus are so much more developed than in rodents (Rolls, 2021a). The approach is to take the types of information represented in the hippocampus, and show how this relates to the connectivity shown, and thus help to build an understanding of the operation of this hippocampal memory system in humans.

First, the hippocampus and parahippocampal gyrus contain spatial view cells that respond to parts of scenes (Rolls et al., 1997; Robertson et al., 1998; Rolls, Treves, Robertson, Georges-François, & Panzeri, 1998; Georges-François et al., 1999; Rolls & Xiang, 2006; Wirth et al., 2017; Rolls & Wirth, 2018; Rolls, 2021a, 2021c) with very similar neurons in humans (Tsitsiklis et al., 2020). Activations in humans to viewed spatial scenes are found in the parahippocampal place

area which is located medially in the parahippocampal gyrus, and extends posteriorly into the ventro-medial visual (VMV) areas (Epstein & Baker, 2019; Sulpizio et al., 2020) that we show here have high functional connectivity with the medial part of the parahippocampal gyrus, area TH, with consistent evidence in macaques (Nasr et al., 2011; Kornblith, Cheng, Ohayon, & Tsao, 2013). Given the high functional connectivity between the hippocampus and area TH reported here (Fig. 3), and the anatomical evidence that these are direct connections in humans (Huang, Rolls, Hsu, et al., 2021) and macaques (Yukie, 2000), the route from VMV via the parahippocampal gyrus TH is likely to be the route through which hippocampal spatial view cells are activated. In addition, the functional connectivity shown in Figs. 3 and 6 indicates high connectivity of both the hippocampus and TH with the presubiculum, which is thereby aligned with this spatial view processing system. Indeed, in humans the presubiculum, subiculum and hippocampus are all activated by spatial scenes (Epstein & Baker, 2019). Part of this system in terms of connectivity is the posterior cingulate cortex and retrosplenial cingulate cortex (Fig. 6), and consistently in humans these cortical areas are also activated in humans by viewed spatial scenes (Epstein & Baker, 2019; Sulpizio et al., 2020). These cortical areas also have high functional connectivity with parts of the parietal cortex including area 7 and PG (Figs. 3 and 6), which relate this whole system to the dorsal visual stream (Ungerleider, 1995), and indeed there is evidence that visual cells that respond in allocentric (world-based) spatial coordinates are found in parietal area 7 (Snyder, Grieve, Brotchie, & Andersen, 1998). These parietal (and similar posterior cingulate (Dean & Platt, 2006)) neurons may convey information about allocentric bearings to landmarks, which with hippocampal spatial view cells may be important and frequently used in human and more generally primate navigation (Rolls, 2020; 2021c).

Second, another type of information is represented in the primate presubiculum, which contains head direction cells (Robertson et al., 1999). Given the connectivity shown in Figs. 3 and 6, similar head direction information could be represented in other parts of the system shown in red in Fig. 6.

Third, information about linear and angular whole body motion is represented in the hippocampus and subiculum by 'whole body motion' cells, and the signals that can drive these neurons can be vestibular or optic flow or both (O'Mara et al., 1994). (What are probably similar cells have been described in the rodent medial entorhinal cortex, but have been termed 'speed cells' (Kropff, Carmichael, Moser, & Moser, 2015).) The hippocampus and subiculum share high functional connectivity with parietal PG areas, and with the posterior cingulate cortex, which are likely to be part of the same system. Consistent with this, vestibular and optic flow signals are found in the parietal cortex of primates in area 7a (Avila, Lakshminarasimhan, DeAngelis, & Angelaki, 2019; Bremmer, Duhamel, Ben Hamed, & Graf, 2000; Cullen, 2019; Wurtz & Duffy, 1992), and activations in humans to optic flow are found in early visual cortical areas such as 6A (Sherrill et al., 2015), which may be sources of input to the hippocampus and subiculum that drive the whole body motion neurons.

Fourth, the functional connectivity of the other main (i.e., ventral) cortical system that connects with the human

hippocampus is shown in blue in Fig. 6. The temporal cortical areas have functional connectivity with the perirhinal cortex, which in turn has connectivity with the perirhinal cortex, which in turn has connectivity with the hippocampus. One feature of especial interest is that the connectivity of both the temporal cortical visual areas and the perirhinal cortex with the hippocampus is high, which is consistent with the direct anatomical connections revealed by tractography between these regions that bypass the entorhinal cortex in humans (Huang, Rolls, Hsu, et al., 2021). The temporal lobe cortical areas have neurons that respond to faces, and have invariance for where the objects or faces are, so provide 'what' but not 'where' information (Tovee, Rolls, & Azzopardi, 1994; Rolls, Aggelopoulos, & Zheng, 2003; Rolls, 2012, 2021a, 2021b). The ventral stream pathways thus provide a route for 'what' information, about objects and faces, to reach the hippocampus, and that information may reach the hippocampal system directly as well as via the entorhinal cortex. Some hippocampal spatial view neurons respond to combinations of objects and spatial views (Rolls et al., 2005) and the recall of each from the other (Rolls & Xiang, 2006), and this is how it is proposed that episodic memory in primates including humans is implemented, for it prototypically involves remembering and later recalling where people or objects have been seen in the spatial environment (Rolls, 2010, 2013a, 2013b, 2016, 2018, 2021a; Kesner & Rolls, 2015). The functional connectivity shown in Fig. 6 showing how human visual 'what' (in blue) and 'where' (in red) pathways connect with the hippocampus, where convergence can occur and is evident in these memory-related neuronal responses, thus can be related to this key memory computation performed by the primate including human hippocampus.

It is interesting that TF is in humans part of this ventral 'what' system in terms of its functional connectivity shown in Figs. 3 and 6. The hippocampo-cortical system is very different in rodents, with its much less developed visual pathways, and emphasis on representations of the place where the rodent is located (McNaughton et al., 1996; O'Keefe, Burgess, Donnett, Jeffery, & Maguire, 1998; Hartley, Lever, Burgess, & O'Keefe, 2014). Another difference from rodents is the high functional (and direct (Huang, Rolls, Hsu, et al., 2021)) connectivity of the hippocampus with the anterior temporal lobe TG (Fig. 3), for this area is implicated in semantic representations (Bonner & Price, 2013; DeWitt & Rauschecker, 2016; Fairhall & Caramazza, 2013a, 2013b; Rolls, 2021a), which may need to be incorporated into human episodic memory, in addition to the hippocampal episodic memory system contributing to semantic memory by recalling past episodes (Rolls, 2022).

With respect to the functional connectivity of the human hippocampal system with some early sensory cortical areas (Fig. 3), it is suggested that part of the functional significance of this is that for especially the early sensory cortical areas, this may provide a direct route for the some low-level sensory details to be incorporated into episodic memory, making them vivid and potentially more useful as all the low-level sensory details may not be represented higher in the hierarchy (Rolls, 2021a). These connections may include afferents to the hippocampus from some of these parietal and temporal areas, and, based in research in macaques, some of

these are direct to hippocampal CA1 (Blatt & Rosene, 1998; Ding et al., 2000; Ichinohe & Rockland, 2005; Rockland & Van Hoesen, 1999; Yukie, 2000; Zhong & Rockland, 2004), rather than through the trisynaptic circuit from the dentate gyrus and CA3 to CA1. That raises the important concept that in humans (and to some extent in non-human primates), direct inputs to CA1 may be combined with memories recalled using completion in the CA3 recurrent collateral attractor system to enable detailed cortical information to be combined in CA1 with what is recalled via the CA3 route to CA1 (Rolls, 2018). Another interesting possibility not generally considered is that connections reaching CA1 might re-enter the hippocampal circuitry via the entorhinal cortex, and via that route reach the dentate and CA3. It is further noted that some of this hippocampal system connectivity may be back to the early sensory cortical areas, and this could be important in imagery.

4.3. Limitations and future research

Functional connectivity does not measure the direction of interaction, as the measure is a Pearson correlation of the BOLD signals between a pair of brain regions. It would be interesting to extend this with effective connectivity, which measures the strength of the effects in both directions between each pair of brain regions, and so provides a causal and generative map. Further, given that differences have been reported between the posterior and anterior hippocampus in their connectivity (Ezama et al., 2021) and functions (Brunec et al., 2018; Strange, Witter, Lein, & Moser, 2014), it would be of interest to perform a future investigation of the cortical connectivity of posterior versus anterior parts of the hippocampus with all the 360 cortical regions in the HCP-MMP atlas. Further, although separating out different fields of the hippocampus (e.g., dentate, CA3, CA1 and CA4) is difficult with MRI (Bakker, Kirwan, Miller, & Stark, 2008; Bonnici et al., 2012; Yassa et al., 2010), it would be of interest to investigate the extent to which they may have different connectivity with all the 360 cortical regions in the HCP-MMP atlas. It is further noted that functional connectivity does not provide evidence on whether a connectivity is by a direct connection between brain regions, or by an intermediate region or by common input. That is why part of the strength of this paper is the comparison with the diffusion tractography, which does provide evidence about direct connections. Part of the importance of the functional connectivity measures described here is that they complement the diffusion tractography (Huang, Rolls, Hsu, et al., 2021), by showing that false streamlines where tracts cross did not produce false results, and by providing measures of the physiological strength of the interactions between brain regions.

4.4. Conclusions

The research described here provides an important and new complement to the evidence for the extensive anatomical cortical connectivity of the human hippocampus (Huang, Rolls, Hsu, et al., 2021), by presenting new evidence in the functional domain (compare Fig. 3 in the present paper with Fig. 5 of Huang, Rolls, Hsu et al. (2021)). First, the functional connectivity confirms that the human hippocampus has connectivity with many more cortical areas than does the entorhinal cortex, providing further evidence that the entorhinal cortex is not the sole gateway for human hippocampal connectivity with the rest of the brain. Second, the functional connectivity confirms the close relation of the hippocampus with early visual cortical areas; and with primary auditory, olfactory and somatosensory cortical areas (Fig. 3). This connectivity is suggested to be involved in low-level sensory details being included in episodic memories. Third, the functional connectivity confirms that parahippocampal gyrus TF is closely connected with ventral stream visual cortical areas (including TE and TG areas); whereas parahippocampal gyrus TH is closely connected with dorsal stream visual cortical areas (including parietal area 7, LIP, VIP, MIP and the retrosplenial cingulate cortex). Fourth, a key difference from the anatomical connectivity is that the functional connectivity of the human hippocampal system is shown to be largely bilateral (Fig. 4), which is not revealed by the diffusion tractography (Fig. 6 of Huang, Rolls, Hsu et al. (2021)). Fifth, the functional connectivity described here provides important supporting evidence that the pathways of the hippocampal system identified with diffusion tractography (Huang, Rolls, Hsu, et al., 2021) are not false positives, in that all have functional connectivity, which would not be present if the tractography had followed pathways incorrectly. Taken together, these two papers provide a foundation for an understanding of the human hippocampus that extends far beyond the dual stream 'what' and 'where' model with its primarily hierarchical and segregated processing. A highlight is that we show that important advances can be made, in this case about the connectivity of the human memory system, based on the large investments in studies designed to collect data on the human connectome such as the Human Connectome Project (Glasser, Smith, et al., 2016), and on the atlas provided with the Human Connectome Project (Glasser, Coalson, et al., 2016). Moreover, here we extend the HCP atlas, by providing separate subregions for the hippocampus and for the subiculum, which is helpful as the subiculum is a separate region to the hippocampus, and is important in understanding the connections of the hippocampal system.

Ethical permissions

No data were collected as part of the research described here. The data were from the Human Connectome Project, and the WU-Minn HCP Consortium obtained full informed consent from all participants, and research procedures and ethical guidelines were followed in accordance with the Institutional Review Boards (IRB), with details at the HCP website (http://www.humanconnectome.org/).

Data and code availability

The data are available from the Human Connectome Project (http://www.humanconnectome.org/). Standard functions in Matlab were used for the analysis. No part of the study procedures or analyses was preregistered prior to the research being conducted.

Author contributions

QM performed the voxel-level functional connectivity. ETR designed the investigation, performed the statistical quantitative analyses with the modified HCP atlas, and wrote the paper; C—CH provided the modified HCP atlas; JF and WC provided funding and WC provided advice. All authors approved the paper.

Open practices

The study in this article earned an Open Data — Protected Access badge for transparent practices. Data for this study can be found at: http://www.humanconnectome.org/.

Declaration of competing interest

The authors have no competing interests to declare.

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Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cortex.2021.11.014.

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