Anatomy and White Matter Connections of the Parahippocampal Gyrus

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BACKGROUND: **The parahippocampal gyrus is understood to have a role in high cognitive functions including memory encoding and retrieval and visuospatial processing. A detailed understanding of the exact location and nature of associated white tracts could significantly improve postoperative morbidity related to declining capacity. Through diffusion tensor imaging—based fiber tracking validated by gross anatomic dissection as ground truth, we have characterized these connections based on relationships to other well-known structures.**

METHODS: **Diffusion imaging from the Human Connectome Project for 10 healthy adult controls was used for tractography analysis. We evaluated the parahippocampal gyrus as a whole based on connectivity with other regions. All parahippocampal gyrus tracts were mapped in both hemispheres, and a lateralization index was calculated with resultant tract volumes.**

RESULTS: **We identified 2 connections of the parahippocampal gyrus: inferior longitudinal fasciculus and cingulum. Lateralization of the cingulum was detected ($P < 0.05$).**

CONCLUSIONS: **The parahippocampal gyrus is an important center for memory processing. Subtle differences in executive functioning following surgery for limbic tumors may be better understood in the context of the fiber-bundle anatomy highlighted by this study.**

Key words
- Anatomy
- DTI
- Parahippocampal gyrus
- Tractography
- White matter

Abbreviations and Acronyms
GQI: Q-sampling imaging
ILF: Inferior longitudinal fasciculus
PHG: Parahippocampal gyrus
ROI: Region of interest

INTRODUCTION

Mapping the intricate networks of the human brain with constantly evolving precision and resolution has expanded avenues to study its structure and function while inevitably amplifying the potential for debate regarding the subdivisions of the cortical mantle.[1] Catalyzed by technologic advancements in noninvasive neuroimaging and powerful network modeling tools, comprehending the dynamics of complex systems is now achievable by mapping anatomic regions and their associated interconnecting pathways at high resolution. Interest in the anatomic structure and function of the parahippocampal gyrus (PHG) was fueled from its association to the hippocampus, with consequent research leading to increasing appreciation of its function in memory encoding and retrieval and reinforcing its role in visuospatial processing.[2]

Being a higher order cortical region, the PHG integrates with several other regions to perform complex memory and visuospatial tasks, and thus its association fibers have been of high interest. Previous literature has helped characterize the involvement of the cingulum in connecting the PHG to other cortical regions[3] while the role of the splenium, anterior commissure, and inferior longitudinal fasciculus (ILF) remains open to question.[4-9] These individual bundles and the PHG are well understood independently and are known to be involved in normal cognitive processes. However, the connections of the PHG to other anatomic cortical regions of the brain through white matter tracts are still yet to be conclusive, with previously conducted studies recommending larger longitudinal studies at higher resolutions to enable subregional analysis.[10]

In this study we discuss the relationship between the PHG and the underlying major white matter bundles to examine its role in

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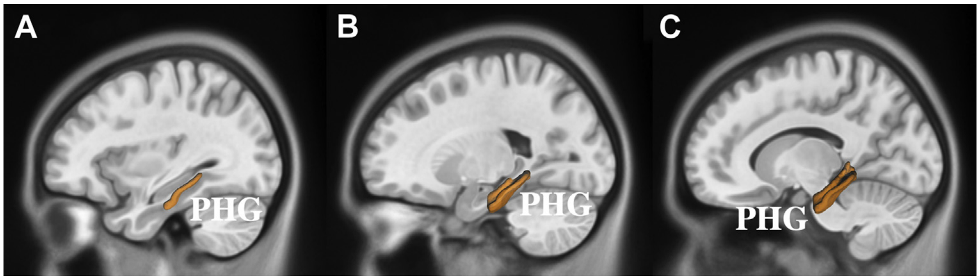

Figure 1. The definition of region of interest of parahippocampal gyrus (PHG), from lateral to medial (**A**–**C**).

episodic memory and visuospatial processing in order to derive clinically applicable knowledge. Using diffusion tractography, the 2-ROI approach was successfully applied to identify the tractographies between 2 cortical regions in previous papers.[11-13] Followed by that, we characterized the macroscopic anatomy of the white matter connections between the PHG and its associated cortical areas. We aim to provide a template for neurosurgeons of the white matter connections between the PHG and neighboring areas and allow the preservation of neural networks dependent on connections in this region of the brain.

METHODS

Definition of Region of Interest

The study, as shown in Figure 1, comprises gyrus-based descriptions to define regions of connectivity. The inferior surface of the temporal lobe is formed by 3 major gyri, of which the PHG marks the medial point. To help define our ROI, the lateral border is formed by the collateral sulcus, with the ambient cistern defining the region medially. The anterior, rhinal cortex of the PHG is composed of medial and lateral components, namely the entorhinal and perirhinal cortices.[14] The intersection between the inferior demarcation of the PHG and the inferior surface of the collateral sulcus provides the border between the perirhinal and entorhinal cortices. The superior surface of the collateral sulcus highlights the lateral margin of the perirhinal cortex. Finally, the parahippocampal cortex draws the posterior component of the PHG. The subiculum acts as a transitional cortex bridging the PHG and Ammon horn of the hippocampus, which supports studies that directly postulate the symbiotic connection between the 2.[14-16]

Table 1. Demographic Characteristics of 10 Selected Subjects and Their Lateralization Index of White Matter Tracts for the Parahippocampal Gyrus

			Inferior Longitudinal Fasciculus		Cingulum		Corpus Callosum
Subject ID	**Gender**	**Age**	**L**	**R**	**L**	**R**	**/**
MGH_1001	Female	40–44	1.39	0.15	10.94	14.9	26
MGH_1002	Female	35–39	10.23	18.5	8.78	0	39.75
MGH_1017	Female	25–29	0.13	8.65	13.15	28.38	0
MGH_1018	Male	30–34	8.78	19.21	1.722	0	0
MGH_1019	Female	25–29	0.119	0.5	2.56	6.63	0
MGH_1021	Female	20–24	1.04	2.89	0.2	14.7	0
MGH_1022	Male	30–34	7.39	0.12	9.28	13.75	0
MGH_1023	Female	25–29	12.13	23.43	6.52	41	0
MGH_1024	Female	45–59	21.87	20.47	2.78	12.78	0
MGH_1025	Male	45–59	8.03	7.21	2.34	15.72	0
Mean	/	/	7.1109	10.113	5.8272	14.786	6.58
P value	/	/	0.16		0.039		/

L, left; R, right.

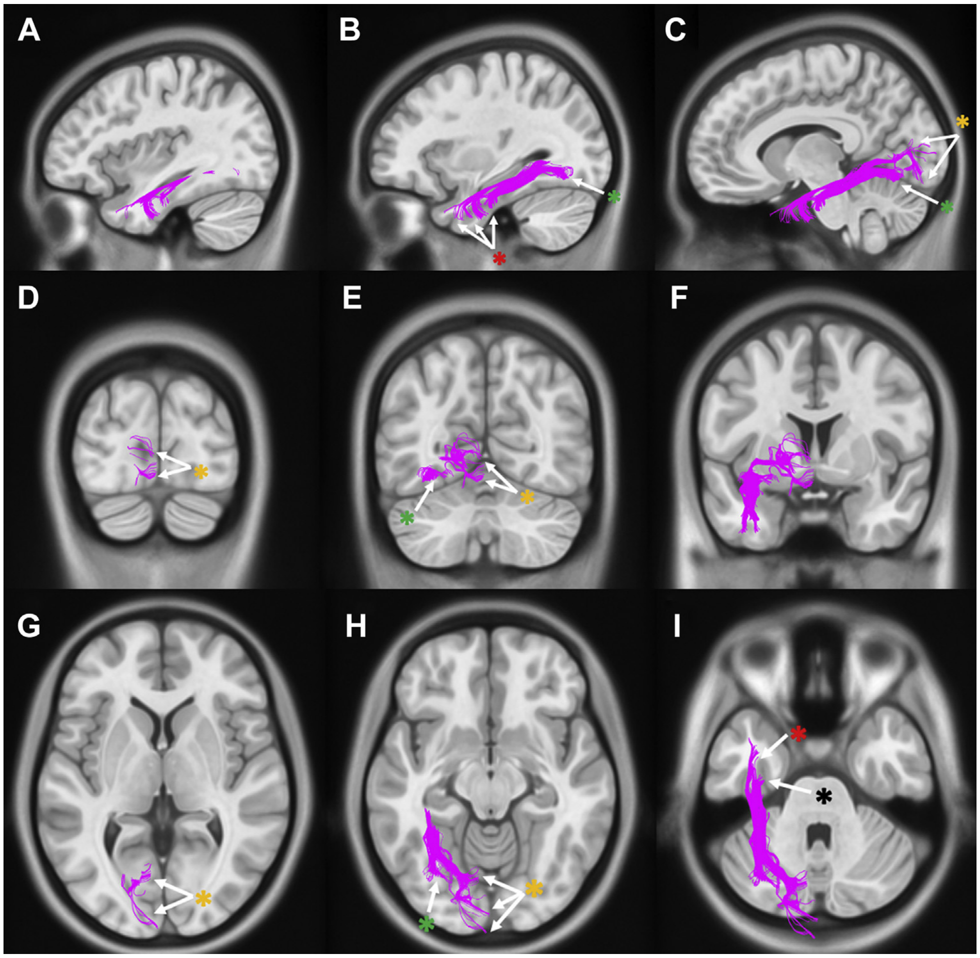

Figure 2. Tractography of association fibers that connect the parahippocampal gyrus to other cortical areas. (**A–C**) Axial sections, from lateral to medial. (**D–F**) Coronal sections form the posterior to anterior. (**G–I**) Axial sections from superior to inferior. ILF, inferior longitudinal fasciculus.

Tractography

Publicly available imaging data from the Human Connectome Project[17] were obtained for this study (http://human-connectome.org, release Q3). Imaging was analyzed from 10 randomly selected adult subjects (HCP subject IDs: MGH_1001, MGH_1002, MGH_1017, MGH_1018, MGH_1019, MGH_1021, MGH_1022, MGH_1023, MGH_1024, MGH_1025). A multishell diffusion scheme was used, with *b*-values of 1000, 3000, and 5000, and 10,000 s/mm^2. Each *b*-value was sampled in 64, 64, 128, 256 directions, respectively. The in-plane resolution was 1.5 mm. The slice thickness was 1.5 mm. The diffusion data were reconstructed using generalized q-sampling imaging (GQI)[18] with a diffusion sampling length ratio of 1.25.

Following registration to Montreal Neurological Institute space, tractography with GQI[18] was performed in DSI studio (http://dsi-studio.labsolver.org) using a region of interest (ROI) approach to initiate the fiber tracking from a user-defined seed region.[19] A 2-ROI-approach was used to isolate tracts, and all were tested for reproducibility.[20] The 2-ROI approach used the PHG as the primary gyrus or first ROI, and a secondary gyrus was used as the second ROI. The secondary gyri were other gyri from the same hemisphere with suspected white matter connections to the PHG. Tractography was conducted sequentially between the 2 respective ROIs until we identified and localized substantial white matter connections, displayed in our respective data set. Preset gyri were used initially, but they were visually modified as the study progressed to produce the most accurate results.

Dissecting in Montreal Neurological Institute space allowed for ready assessment of variability among subjects. Voxels within each ROI were automatically traced with a maximum angular threshold of 45 degrees. When a voxel was approached with no tract direction or a direction >45 degrees, the tract was halted. Tractography was stopped after reaching the length of 800 mm. In

Table 2. Major Connectivity of the Parahippocampal Gyrus

Target		Connecting Pathway
Frontal lobe	Caudal anterior cingulate cortex	Cingulum
	Rostral anterior cingulate cortex	Cingulum
Parietal lobe	Pericalcarine cortex	ILF
	Isthmus cingulate of cingulate gyrus	Cingulum
Occipital lobe	Lingual gyrus	Cingulum, ILF
	Cuneus	ILF
	Lateral occipital cortex	ILF
Temporal lobe	Fusiform gyrus	ILF
	Inferior temporal gyrus	ILF
	Superior temporal gyrus	ILF
Limbic lobe	Hippocampus	ILF

ILF, inferior longitudinal fasciculus.

some instances, exclusion ROIs were placed to exclude spurious tracts or tracts not involved in the network of interest.

RESULTS

Tractography

Tractography including the tract volume and number of tracts was analyzed from 10 randomly selected healthy subjects for both right and left hemispheres (Table 1). The ILF was observed in all subjects for both hemispheres, with the cingulum noted in all of the subjects' left hemispheres and 8 of the subjects' right hemispheres. The laterality indexes of white matter tracts were also summarized in Table 1, which shows lateralization of the cingulum ($P < 0.05$).

Major Connections

The ILF and cingulum were found to be the major connecting fibers of the PHG (Figure 2). The cingulum had terminations in the anterior cingulate cortex of the frontal lobe and isthmus cingulate of the cingulate gyrus. The ILF was found to terminate in the pericalcarine cortex of the parietal lobe; lingual gyrus, cuneus, and lateral occipital cortex of the occipital lobe; fusiform, inferior, and superior temporal gyri of the temporal lobe; and the hippocampus of the limbic lobe. These results are summarized in Table 2.

The anterior branches of ILF from the PHG course through the PH of the limbic lobe. In continuation of the anterior branches, the ILF curves laterally and inferiorly to connect the superior and inferior temporal gyri of the temporal lobe. The ILF travels posteriorly, and the branching fibers terminate in the fusiform gyrus of the temporal lobe, lingual gyrus, cuneus, and lateral occipital cortex of the occipital lobe. The tractography of the ILF is summarized in Figure 3.

The tractography of the cingulum is shown in Figure 4. The cingulum originates from the anteromedial surfaces of the PHG, which travels posterior-medially and converges laterally to give off terminating branches along its course to the lingual gyrus in the occipital lobe. It then bends anteriorly at the level of splenium of corpus callosum and gives off branches to the isthmus of the cingulate gyrus. The cingulum passages superiorly to the corpus callosum and terminates at the rostral and caudal cingulate gyri of the frontal lobe.

DISCUSSION

The PHG is critically involved in surgical planning due to its proximal location to the hippocampus. For example, it is well understood that the hippocampus is strongly associated with long-term epilepsy-associated tumors,[21-23] which require hippocampectomies to control the epilepsy due to the presence of tumor infiltration and dual pathology.[22,24] The structural connectivity of the PHG has, however, received little attention due to greater focus on large-scale whole-brain methodologies. This has limited the surgical applications where detailed PHG anatomy and associated cortico-cortical connections are important to avoid damage to these tracts during surgery in this region. In this paper, we attempt to bridge the gap by offering a detailed anatomic approach to discuss how the PHG is, which would provide important implications to surgical techniques.

Key Association Fibers That Connect PHG to Other Cortical Areas

On the basis of dissections of the PHG, the entorhinal cortex was found to be the major source of connection to the hippocampus. The entorhinal cortex in turn receives its projections from the adjoining perirhinal and posterior hippocampal cortices, which are fed by projections arising from the frontal, temporal, and parietal lobes.[25,26] Through tractography, we observed that the cingulum and ILF are the major association fibers that connect the PHG to other cortical areas. On the contrary, the splenium and anterior commissure fibers in this study were found to be insignificantly involved in connecting the parahippocampal gyrus to cortical areas. However, our results are not definitive and further research would be needed to completely rule out any involvement of the 2 tracts. Moreover, the splenium's main role is thought to be connecting the occipital lobes and enabling visual cue processing,[27] while the anterior commissure fibers have multiple interhemispheric connections. These include the temporal pole, inferior temporal, superior temporal, fusiform gyri, amygdala, orbitofrontal cortex, olfactory bulb, and parahippocampal gyrus[28]; the latter was not supported in this study and requires further research.

Cingulum Connectivity. The cingulum is a tract that follows the cingulate gyrus from the subcallosal gyrus of the frontal lobe to the parahippocampal gyrus,[29] bending parallel to the splenium and passing inferocranially into the temporal lobe.[30] The cingulum comprises fibers of different lengths, the longest fibers extending among the PHG, amygdala, uncus, and subgenual areas of the frontal lobe.[31] In par with existing research, we found imperative connections between the PHG and cingulate cortex of the frontal lobe, the isthmus of the cingulate gyrus in the parietal lobe, and the lingual gyrus of the occipital lobe.[6,7,25,26]

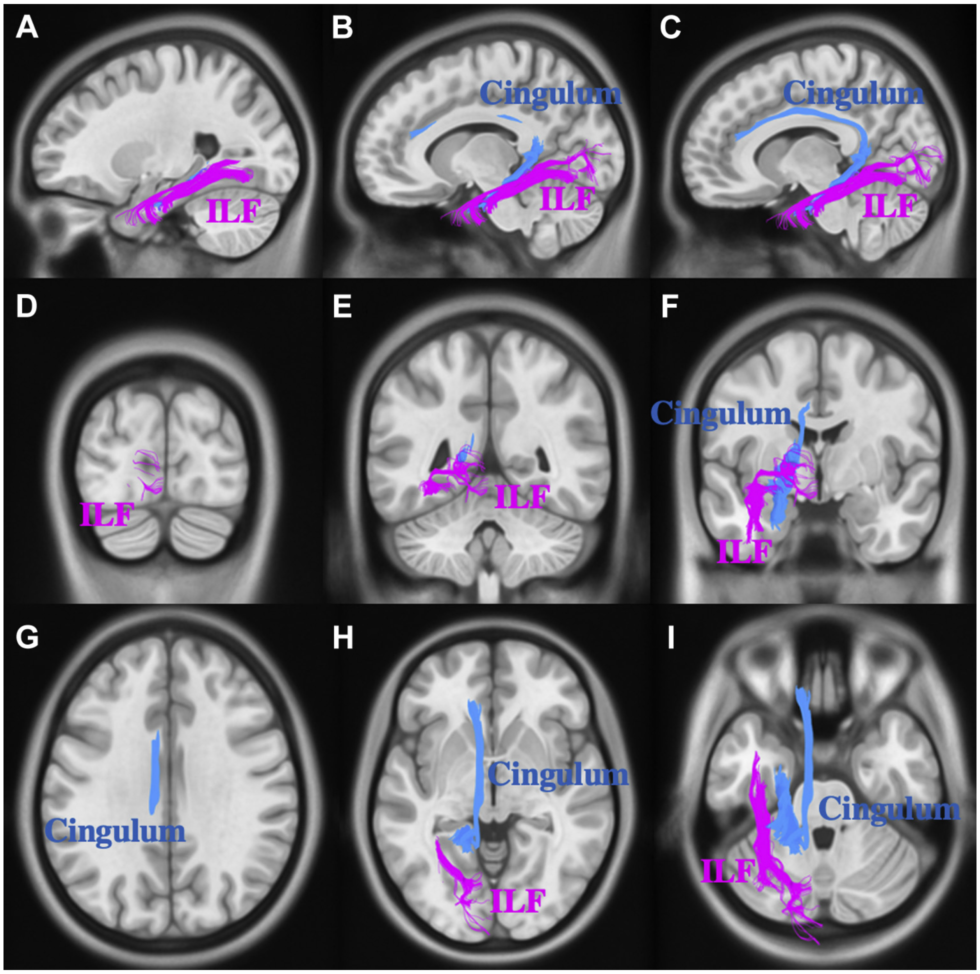

Figure 3. Tractography of inferior longitudinal fasciculus (ILF) that originates from the parahippocampal gyrus. (**A–C**) Sagittal sections from lateral to medial demonstrating the extent of ILF, which projects between the temporal and occipital lobes. (**D–F**) Coronal sections from the posterior to anterior highlighting the termination of ILF at the inguinal gyrus and lateral occipital cortex of the occipital lobe and the fusiform gyrus of the temporal lobe. (**G–I**) Axial sections from superior to inferior demonstrating the posterior terminations of ILF including the fusiform gyrus, inguinal gyrus, and lateral occipital cortex. The ILF connects the hippocampus and superior and inferior temporal gyri, while descending inferiorly and anteriorly toward the parahippocampal gyrus. *Green star,* association fibers that connect the parahippocampal gyrus and the fusiform gyrus; *orange star,* association fibers that connect the parahippocampal gyrus, inguinal gyrus, and lateral occipital cortex; *red star,* association fibers that connect the parahippocampal gyrus and superior and inferior temporal gyrus, *black star,* association fibers that connect the parahippocampal gyrus and the hippocampus. ILF, inferior longitudinal fasciculus.

The cingulum bundle is a part of the "Papez circuit," which is known for its vital role in normal cognition[32,33] and emotional control.[34] Functional imaging studies demonstrate a critical role of the cingulum in executive control, emotion, pain, and episodic memory.[6] Clinically, deficits in the cingulum may result in a wide range of neurologic and psychiatric conditions including schizophrenia,[35-37] autism spectrum disorder,[38,39] depression, post-traumatic stress disorder,[40,41] obsessive compulsive disorder,[42] mild cognitive impairment, and Alzheimer disease.[43-45] Specifically, patients with cingulum deficits have been found to have memory recall impairments, with the presence of significant white and gray matter loss in the parahippocampal and hippocampal regions.[6,43] Furthermore, the role of the cingulum in memory is reinforced by the correlation between memory deterioration in Alzheimer disease and alterations in cingulum microstructure and disease.[6,46-50]

Inferior Longitudinal Fasciculus Connectivity. The ILF connects the anterior temporal regions of the brain to the temporal-occipital and occipital regions and is thought to be crucial in major brain

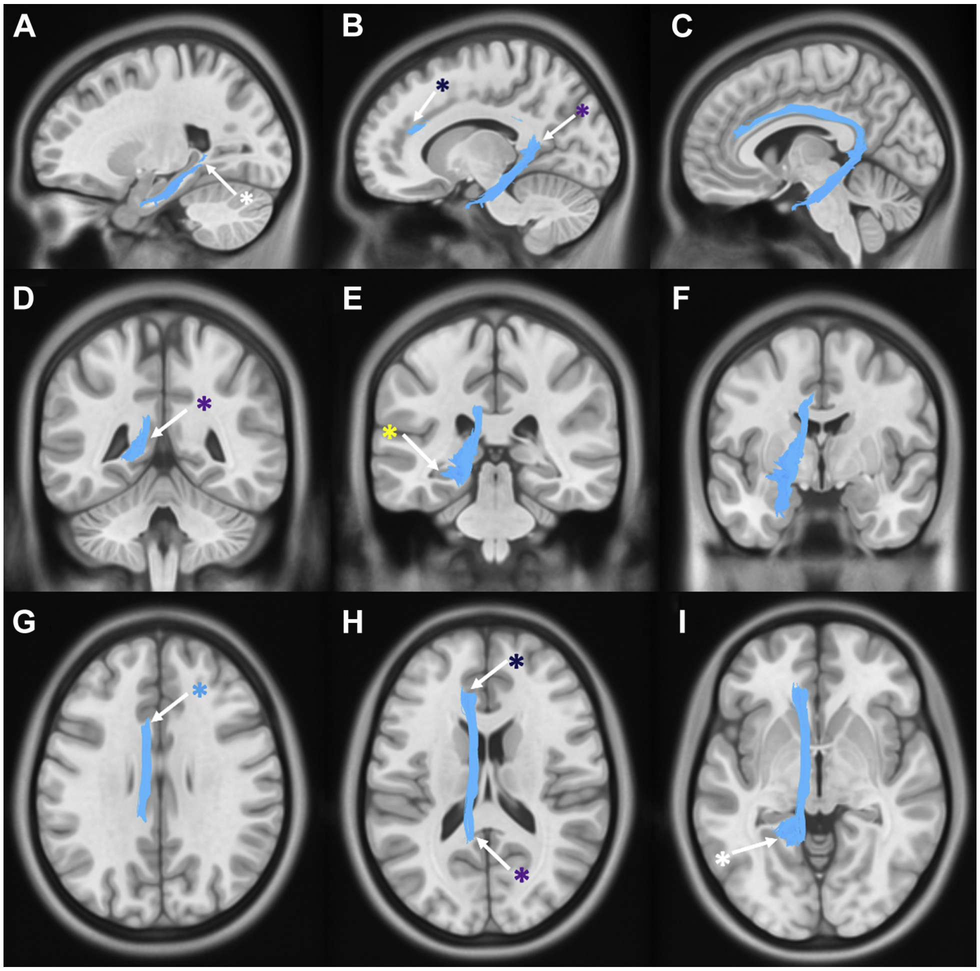

Figure 4. Tractography of cingulum that originates from the parahippocampal gyrus. (**A**–**C**) Sagittal sections from lateral to medial highlighting the cingulum travels from the parahippocampal gyrus to the frontal lobe. The cingulum bends anteriorly at the level of splenium of corpus callosum and connects the isthmus and rostral anterior cingulate gyri. (**D**–**F**) Coronal sections from the posterior to anterior highlighting the terminations of cingulum at the isthmus cingulate and lingual gyri of the parietal and occipital lobes. (**G**–**I**) Axial sections from superior to inferior demonstrating the anterior origins of cingulum including the caudal and rostral anterior cingulate gyri. The cingulum bends inferiorly at the splenium of corpus callosum and connects the isthmus cingulate and lingual gyri to the parahippocampal gyrus. *Light blue star,* association fibers that connect the parahippocampal gyrus and the caudal anterior cingulate gyrus; *Dark blue star,* association fibers that connect the parahippocampal gyrus and rostral anterior cingulate gyrus; *white,* association fibers that connect the parahippocampal gyrus and the lingual gyrus; *purple star,* association fibers that connect the parahippocampal gyrus and the isthmus cingulate gyrus; *yellow star,* association fibers that connect the parahippocampal gyrus and lingual gyrus.

functions.[19,51,52] Our findings corroborate other studies, in which the ILF runs between PHG and the pericalcarine cortex, cuneus, lateral occipital cortex and lingual gyrus, fusiform gyrus, inferior and superior temporal gyri, and hippocampus.[26,52]

The ILF is a direct occipito-temporal pathway, which creates instant feedback by transmitting signals from the visual association areas directly to the PHG while receiving feedback from the amygdala back to the visual association area.[52] Therefore the ILF is closely associated with brain functions including visual modality, semantic lexicon, reading and emotional processing, visual memory, and place, object, and face processing.[5,53] Its implication in memory has been supported by studies where memory deficits including visual amnesia were observed in patients who had compromised ILF due to lesions such as brain tumors.[54-56] In addition, due to its role in facial perception and visual recognition and processing, visual prosopagnosia, visual agnosia, and visual hypoemotionality were grave consequences noted in lesion findings.[5] This is explained by the strong connections of the ILF between the occipital and temporal lobes, the former relaying visual input.[57,58]

Functional Significance of the PHG

Our understanding of PHG comes from lesion study, tumor surgery, and functional magnetic resonance imaging (fMRI). fMRI studies show that the PHG functions concurrently with the other cortical areas to perform higher cognitive tasks including visual spatial processing and episodic memory.

Parahippocampal Gyrus and Visual Spatial Processing. Our study showed extensive cortico-cortical connections among the PHG, frontal, parietal, temporal, and occipital lobes via the cingulum and ILF. This may explain the cortical functions of the PHG in receiving visual inputs, mainly from the visuospatial association areas in the dorsal visual stream, and to a lesser extent from the dorsolateral prefrontal and retrosplenial cortices.[59,60] Specifically, the PHG is related to visuospatial processing including scene perception, spatial representation, and navigation.[61] The PHG was found to be activated more by spatial and nonspatial associations as compared with noncontextual items, with the posterior PHG activated by spatial contexts and the anterior PHG activated by nonspatial contexts.[62] This was further dissected, proposing a regional specialization for visuospatial processes within the cortex, with the posterior PHG specializing in the extraction of scene layout information.[63,64] Clinically, patients experiencing landmark agnosia were found to have lesions in the right posterior PHG, together with the lingual and fusiform gyri, which are particularly associated with prosopagnosia.[65]

Parahippocampal Gyrus and Episodic Memory. Our findings demonstrated extensive connections between the PHG and hippocampus via the ILF. This may explain functional neuroimaging findings suggesting that recognition memory depends on the integrity of the medial temporal lobes including the PHG and hippocampus proper.[66-69] Studies reveal 2 elements involved in recognition memory, recollection and familiarity,[70] with the anterior PHG associated with familiarity and the posterior PHG and hippocampus associated with recollection, though whether there is such a clear distinction remains contentious.[71-73] Regardless, based on our findings and previous studies, it is evident that the cortico-cortical connections between the PHG and other cortical areas, including the occipital, temporal, and parietal cortices, underlie the role of the PHG in associative memory, linking several domains to achieve recognition (e.g., attributing a name to a face). Indeed, if the PHG is damaged (e.g., in temporal lobe epilepsy), patients face significant memory impairment.[59,74,75]

Functional Significance of the Parahippocampal Gyrus: Parahippocampal Gyrus and Language

Our results demonstrated that the ILF is the predominant tract connecting the various regions of the basal temporal language area (BLTA), which is situated in the inferior temporal cortex. The BLTA mainly consists of the left parahippocampal, fusiform, and inferior temporal gyri,[76] and research has demonstrated this region's importance in written and spoken language. Injuries or damage to the BLTA produced naming disturbances in English and alexia and agraphia of Japanese kanji in some studies.[77] Additionally, surface stimulation to the PHG results in aphasic reactions, suggesting it has a role in language comprehension and production.[78] Our results have further applications for the surgical treatment of mesial temporal lobe epilepsy, as restricted resection and preservation of the BTLA including the PHG has shown significant reduction in seizures while promoting better postoperative neuropsychologic performance associated with language.[79]

Limitations

Diffusion spectrum imaging (DSI) maps the 3-dimensional probability density function (PDF) of water molecule diffusion at each voxel.[80] Therefore a limitation of using DSI is that during the process of aligning vectors, the algorithm could follow the wrong path, leading to false or missing tracts. Furthermore, with the use of DSI, we notice that there is significant variability among subjects due to the fact that every individual is different. However, in contrast to other tractography frameworks, such as DTI, DSI favors the study of tractography and offers the visualization of detailed white matter anatomy by identifying fiber crossings and highlighting the anatomy of fibers in a 3-dimensional anatomic structure.[81]

CONCLUSIONS

This study highlights the principle white-matter pathways of the PHG and highlights key underlying connections. We present a summary of the relevant clinical anatomy for this region of the cerebrum as part of a larger effort to understand the network in its entirety.

CRediT AUTHORSHIP CONTRIBUTION STATEMENT

Yueh-Hsin Lin: Writing - original draft, Formal analysis. **Vukshitha Dhanaraj:** Methodology, Investigation. **Alana E. Mackenzie:** Writing - review & editing. **Isabella M. Young:** Formal analysis, Investigation. **Onur Tanglay:** Data curation. **Robert G. Briggs:** Writing - original draft. **Arpan R. Chakraborty:** Investigation. **Jorge Hormovas:** Validation. **R. Dineth Fonseka:** Visualization. **Sihyong J. Kim:** Visualization. **Jacky T. Yeung:** Resources, Software. **Charles Teo:** Supervision. **Michael E. Sughrue:** Conceptualization, Supervision.

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