Introduction to Computational Medicine

Project 1 – Part 2 Writeup

Group 2: Eric Chiang, Jack Wright, Jinrui Liu, Luchao Qi, and Yiyuan Zhang

Justification of Choice

For part 2 of our project, we choose to investigate hippocampus, thalamus, and posterior cingulate cortex (PCC). The justifications are as follow:

Hippocampus:

In an experiment conducted by Wang et al., 13 patients with mild AD and 13 age-matched controls are examined by resting state functional MRI. The functional connectivity of hippocampus is subsequently measured. And they found that the functional connectivity of right hippocampus to several brain regions (medial prefrontal cortex, left cuneus, posterior cingulate cortex, etc.) are disrupted in AD patients. For this reason, we decide to investigate the volume change in hippocampus.

Reference:
Wang, L., Zang, Y., He, Y., Liang, M., Zhang, X., Tian, L., . . . Li, K. (2006).
Changes in hippocampal connectivity in the early stages of Alzheimer's disease: Evidence from resting state fMRI. *NeuroImage*,
31(2), 496–504. https://doi.org/10.1016/j.neuroimage.2005.12.033

Thalamus:

We elected to choose the thalamus as one of our brain structures, due to its involvement in neural pathways, including some pertaining to memory. As such, it is reasonable to assume that this region of the brain would be detrimentally affected by dementias, like Alzheimer's disease. In recent years, the link between the thalamus and Alzheimer's has been more thoroughly investigated, with the literature indicating that the thalamus may actually be one of the earliest regions affected. For example,

Ryan, N. S., Keihaninejad, S., Shakespeare, T. J., Lehmann, M., Crutch, S. J., Malone, I. B., … Fox, N. C. (2013). Magnetic resonance imaging evidence for presymptomatic change in thalamus and caudate in familial Alzheimer’s disease. Brain, 136(5), 1399–1414.

used MRI imaging to investigate if there were any volume or diffusivity changes in the thalamus during both the presymptomatic and symptomatic stages of familial Alzheimer’s disease. At both stages, changes were found.

PCC:

We choose the posterior cingulate cortex (PCC) as our focus since PCC is widely reported to be involved in cognitive study and was proved to have connections with

Alzheimer's disease. A paper was found to be useful for us to initiate our study of the links between PCC and Alzheimer's disease. In *"Regional Rates of Neocortical Atrophy from Normal Aging to Early Alzheimer Disease."* of *McDonald, C. R., et al.* conducted study using MRI techniques on the elders either healthy or suffering from Alzheimer's disease, of which the results showed that PCC is one of the structures contributing to Alzheimer's disease. People with Alzheimer's disease suffer from brain atrophy which includes the depletion of PCC.

Background Research:

Hippocampus:

Describe the anatomy of this structure (Where is it located in the brain? What does it look like? How are its boundaries defined? How can it be found on an MRI?) and show a visualization (3D surface as well as image) from MRICloud screenshots.

The hippocampus is located under the cerebral cortex (allocortical)and in primates in the medial temporal lobe.

The hippocampus, including the dentate gyrus, looks like a curved tube, which has been compared to a seahorse, and a ram's horn (Cornu Ammonis). The hippocampus can be seen as a ridge of gray matter tissue, elevating from the floor of each lateral ventricle in the region of the inferior or temporal horn. Using the above features, hippocampus can be localized in MRI.

There is no consensus as to what hippocampal parts are included so it's hard to define the exact boundaries of hippocampus. Sometimes the hippocampus is said to include the dentate gyrus and the subiculum. Some references include the dentate gyrus and the subiculum in the hippocampal formation, [1] and others also include the presubiculum, parasubiculum, and entorhinal cortex. [2]

MRI Cloud Images:

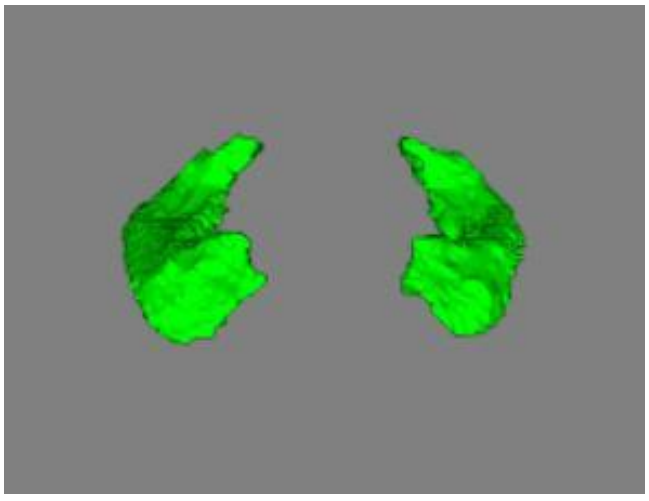


Figure 1 3D view of hippocampus - front

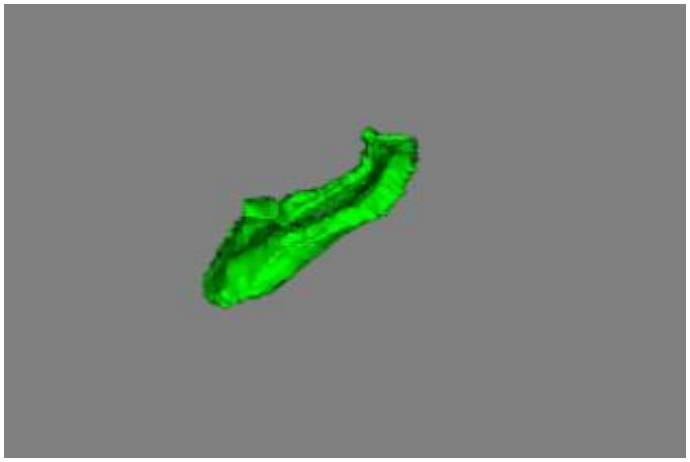


Figure 2 3D view of hippocampus - left

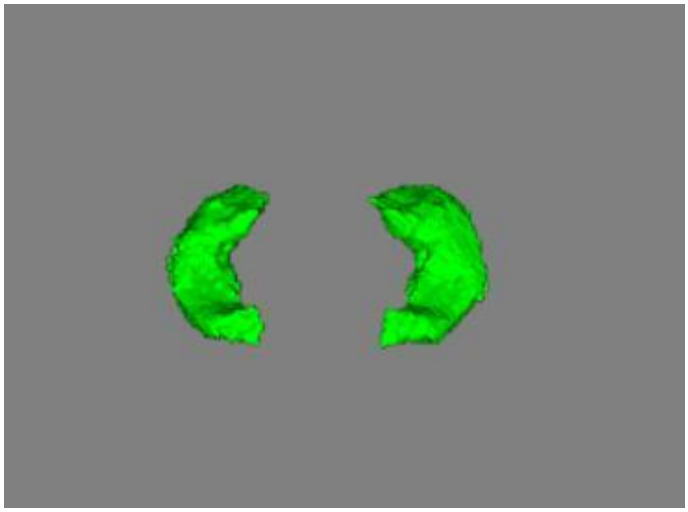


Figure 3 3D view of hippocampus - top

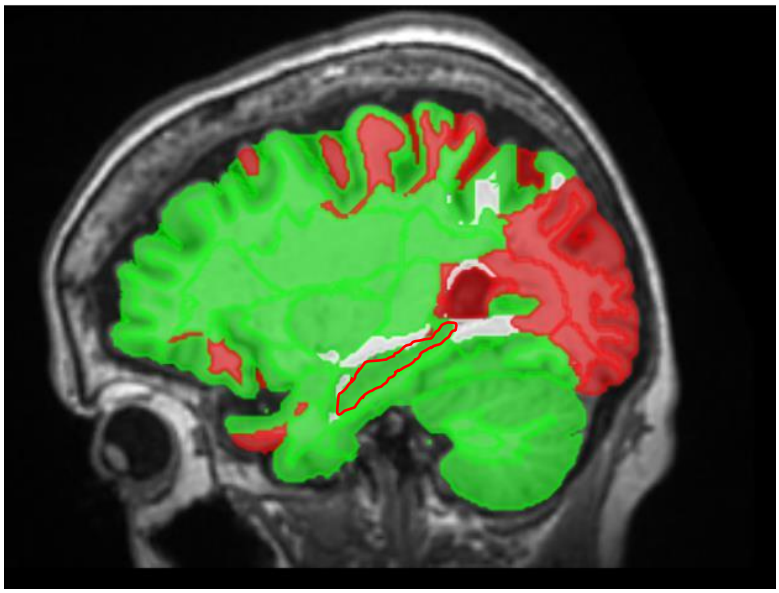


Figure 4 Sagittal view of Hippocampus (outlined in red)

Reference:
[1] Martin, JH (2003). "Lymbic system and cerebral circuits for emotions, learning, and memory". Neuroanatomy: text and atlas (third ed.). McGraw-Hill Companies. p. 382. ISBN 978-0-07-121237-3.
[2] Amaral D, Lavenex P (2007). "Hippocampal neuroanatomy". In Anderson P, Morris R, Amaral, Bliss T, O'Keefe J. The hippocampus book (first ed.). New York: Oxford University Press. p. 37. ISBN 978-0-19-510027-3.

Describe the function of this structure.

It is well established that hippocampus plays a critical role in memory. However, it's anatomical connections with other brain structures also make it important for some other cognitive and physiological functions such as spatial navigation and regulation of hypothalamic function [1].

The role of hippocampus in memory is supported by the famous brain lesion patient, H.M. H.M had part of his anterior hippocampus removed and experienced anterograde amnesia (unable to form new memory) and some retrograde amnesia (unable to retrieve old memory) [2]. Thus, the case of H.M and other similar cases have confirmed that hippocampus plays a central role in new memory formation and old memory retrieval. However, interestingly, hippocampus damage does not affect implicit memory (learned knowledge or motor skills like playing piano) [1].

There are also numerous studies confirm that hippocampus play a vital role in spatial information representation and navigation [3]. The key component in hippocampus that is required for this function is place cell. Place cell fire when a person is at a certain location that this very cell represents.

Hippocampus also involves in emotional behavior because its reciprocal connection with amygdala, which is the main emotion regulating structure [1]. Hippocampus also have a role in regulation of adrenocorticotropic hormones release due to its projection to hypothalamus [1]. In addition, research shows that hippocampus is sensitive to conflict and may play a role in decision making under uncertain conditions [4].

Reference:
[1] Dhikav, V., & Anand, K. (2012). Hippocampus in health and disease: An overview. *Annals of Indian Academy of Neurology, 15(4)*, 239. https://doi.org/10.4103/0972-2327.104323
[2] Neylan, T. C. (2000). Memory and the Medial Temporal Lobe. *The Journal of Neuropsychiatry and Clinical Neurosciences, 12(1)*, 103. https://doi.org/10.1176/jnp.12.1.103
[3] Moser, E. I., Kropff, E., & Moser, M. (2008). Place Cells, Grid Cells, and the Brain's Spatial Representation System. *Annual Review of Neuroscience, 31(1)*, 69–89. https://doi.org/10.1146/annurev.neuro.31.061307.090723
[4] O'Neil, E. B., Newsome, R. N., Li, I. H. N., Thavabalasingam, S., Ito, R., & Lee, A. C. H. (2015). Examining the Role of the Human Hippocampus in Approach-Avoidance Decision Making Using a Novel Conflict Paradigm and Multivariate

Functional *Magnetic Resonance Imaging. Journal of Neuroscience, 35(45)*, 15039–15049. https://doi.org/10.1523/jneurosci.1915-15.2015

Describe how this structure may be affected by Alzheimer's or other dementias. Is there loss of volume? Loss of cortical thickness? Disruption in connectivity?

In Alzheimer's disease patients, hippocampus deformation is commonly observed. Both volumetric loss and disruption in connectivity are observed in multiple studies. However, cortical thickness is never investigated for hippocampus because it's not a cortical structure.

In term of volume loss, Vijayakumar and Vijayakumar in 2013 examined the hippocampal volume in 11 Alzheimer's patient, 3 mixed dementia patients, 10 vascular dementia patients, 2 normal pressure hydrocephalus patients, and 15 healthy controls. They found that the hippocampal volume, by ratio, is decreased by 25% in AD patients, 21% in mixed dementia, 11% in vascular dementia and 5% in NPH patients comparing to the controls. And the severer the disease, the more volume loss [1]. Lindberg et al. (2012) found that sever atrophy in left hippocampus is observed for patients suffering from semantic dementia. Frontotemporal dementia patients suffer from atrophy in on the left hippocampal head area whereas Ad patients show most atrophy on the body of the left hippocampus [2]. These studies confirm that the hippocampal volume loss in common in AD and other forms of dementia.

As for disruption in connectivity, Wang et al. (2006) showed in their fMRI study that the functional connectivity of right hippocampus to several brain regions are disrupted. These brain regions include medial prefrontal cortex, right superior and middle temporal gyrus, and posterior cingulate cortex. In addition, they also found the decreased connectivity between hippocampus and visual cortices [3]. In 2017, Park et al. investigated the change in functional connectivity of hippocampus to other brain regions in early-onset AD (EOAD) patients and late-onset AD (LOAD) patients. They found that LOAD, comparing to EOAD, showed greater extent in hippocampal functional connectivity to cortical regions, such as orbitofrontal cortex. This result may indicate that symptoms observed in EOAD, such as memory loss, may be caused by disruption in functional connectivity to other brain regions [4]. In conclusion, it's evident that the hippocampal functional connectivity is disrupted in AD and other dementia patients.

Reference:

[1] Vijayakumar, A., & Vijayakumar, A. (2013). Comparison of Hippocampal Volume in Dementia Subtypes. *ISRN Radiology*, 2013, 1–5. https://doi.org/10.5402/2013/174524

[2] Lindberg, O., Walterfang, M., Looi, J. C., Malykhin, N., Östberg, P., Zandbelt, B., . . . Wahlund, L. (2012). Hippocampal Shape Analysis in Alzheimer's Disease and Frontotemporal Lobar Degeneration Subtypes. *Journal of Alzheimer's Disease, 30(2),* 355–365. https://doi.org/10.3233/JAD-2012-112210

[3] Wang, L., Zang, Y., He, Y., Liang, M., Zhang, X., Tian, L., . . . Li, K. (2006). Changes in hippocampal connectivity in the early stages of Alzheimer's disease: Evidence from

resting state fMRI.
NeuroImage, 31(2), 496–504. https://doi.org/10.1016/j.neuroimage.2005.12.033
[4] Park, K. H., Noh, Y., Choi, E., Kim, H., Chun, S., & Son, Y. (2017a). Functional Connectivity of the Hippocampus in Early- and vs. Late-Onset Alzheimer's Disease. *Journal of Clinical Neurology, 13(4)*, 387. https://doi.org/10.3988/jcn.2017.13.4.387

Thalamus:

Anatomy and Function

The thalamus is formed by a pair of ovoid grey matter structures (one per hemisphere) that make up part of the diencephalon. The thalamus lies near the center of the brain, with its medial surface forming the upper lateral wall of the third ventricle. A flattened band of tissue known as the Massa Intermedia, or the interthalamic adhesion, connects the two halves of the thalamus. The thalamus can be further subdivided into anterior, lateral and medial regions. These subdivisions are separated by a Y shaped bundle of nerve fibers known as the internal medullary lamina. Similarly, the external medullary lamina separates the thalamus from the subthalamus and the thalamic reticular nucleus. The three subdivisions of the thalamus are composed of smaller regions known as thalamic nuclei, which have three basic types: relay nuclei, association nuclei, and nonspecific nuclei. These nuclei are closely tied with the overall functions of the thalamus.

The thalamus is primarily a relay station that transmits information between subcortical areas and the cerebral cortex via nerve fibers projecting out into the cortex in all directions. In particular, the thalamus is known for its role as a sensory relay for the visual, auditory, somatosensory, and gustatory systems. However, the thalamus also plays an important role in wakefulness, emotion, arousal, motor control, and other cognitive functions.

The relay nuclei, as their name suggests, are involved in relaying received motor and sensory information to the associated cortical area. Relay nuclei have two major subtypes, motor nuclei, which include the ventral anterior (VA) nucleus and ventral lateral (VL) nucleus, and somatosensory nuclei, which include the ventral posterior medial (VPM) nucleus, and ventral posterior lateral (VPL) nucleus. Smaller bodies, known as the LGN, MGN, and VPPC relay auditory, visual, and gustatory information. The VA nucleus receives input from the basal ganglia, and outputs signals to the premotor cortex, the primary motor cortex, and the supplementary motor area, aiding in the initiation and control of voluntary movements. The VL nucleus also outputs to cortical motor areas, since it is involved in fine motor control and balance. It, however, receives input from the cerebellum primarily. The VPM nucleus is involved in somatosensation of the head. As such it relays information from the trigeminal nerve to the primary somatosensory cortex. Similarly, the VPL nucleus is involved in somatosensation of the rest of the body, instead receiving input from pathways of the spinal cord. Adjacent to the VPM is the VPPC, or ventral posterior parvocellular part, which conveys taste sensory input from the solitary tract to the corresponding sensory cortical area. Lastly, the MGN and LGN (or medial/lateral geniculate nuclei) relay auditory and visual signals, respectively. The MGN relays from the inferior colliculus

to the auditory cortex, whereas the LGN relays from the optic nerve to the primary visual cortex.

The association nuclei include the anterior and lateral nuclear groups, as well as the medial dorsal nucleus. The anterior nuclear group plays a role in alertness and memory and is comprised of the anteromedial, anteroventral, and anterodorsal nuclei. These nuclei receive input from hippocampal subiculum, the anterior and posterior cingulates, the retrosplenium, and the inferior parietal lobule. In general, their inputs are sent back to the cortex, specifically to association areas. The anteromedial nucleus is thought to serve a role in prefrontal processing, whereas the anteroventral nucleus, on the other hand, is thought to aid in memory formation, and the anterodorsal nucleus is believed to be involved in spatial navigation and manipulation. The lateral nuclear group consists of the lateral dorsal (LDN) and posterior (LPN) nuclei, in addition to the pulvinar. The pulvinar is the most important of these, since it has as role in multisensory integration, behavior and attention, though it is not yet fully understood. It has connections to the parietal association cortex, as well as the prefrontal cortex, cingulate cortex, insula, and amygdala. The LDN aids the anterior nuclei. Likewise, the LPN aids the pulvinar. Finally, the medial dorsal (MD) nucleus receives input from the amygdala and olfactory cortex, conveying them to the prefrontal cortex and limbic system. The MD projects to many other regions of the brain as well, and it plays a role in emotional processing, attention, abstract thinking, and memory.

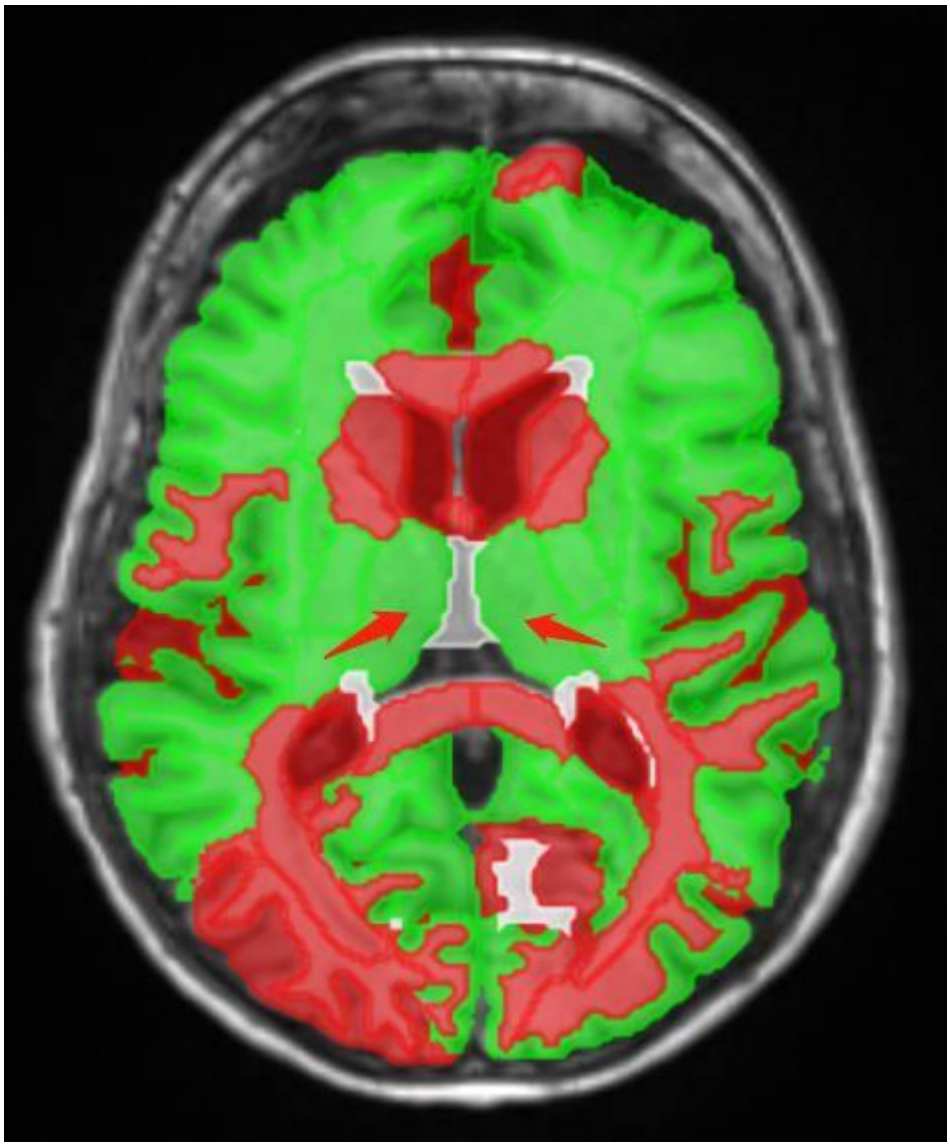
The nonspecific nuclei include the midline nuclear group, the intralaminar nuclei and the reticular nucleus. The midline group is made up of the paratenial, paraventricular, and rhomboidal nuclei and the nucleus reuniens. This group has broad connections to other thalamic nuclei, the limbic system, and cortical areas. It is hypothesized to play a role in functions such as stress, fear, reward and possibly alertness. The intralaminar nuclei, as their name implies, are found within the internal medullary lamina. It is believed they are involved in pain, arousal, and awareness. The thalamic reticular nucleus is unique in that it laterally encapsulates the nucleus. It gets input from the cerebral cortex, basal ganglia, and from thalamic fibers passing through it. The reticular nucleus contains inhibitory cells and its primary function is to modulate signals passing through the thalamus.

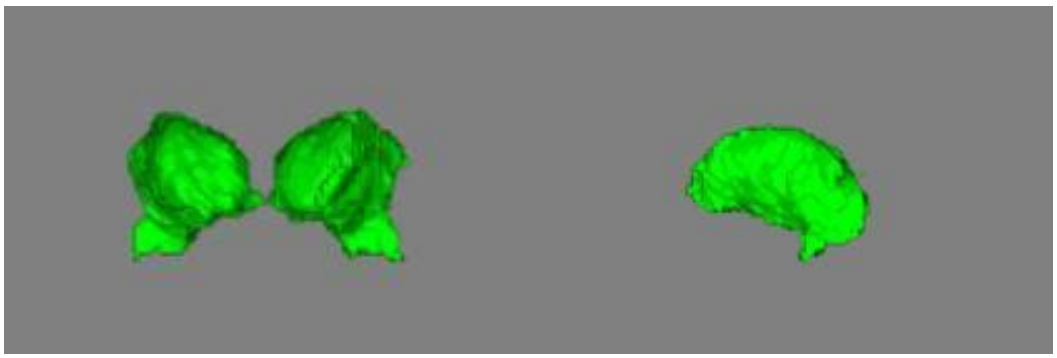
Effect of Alzheimer's

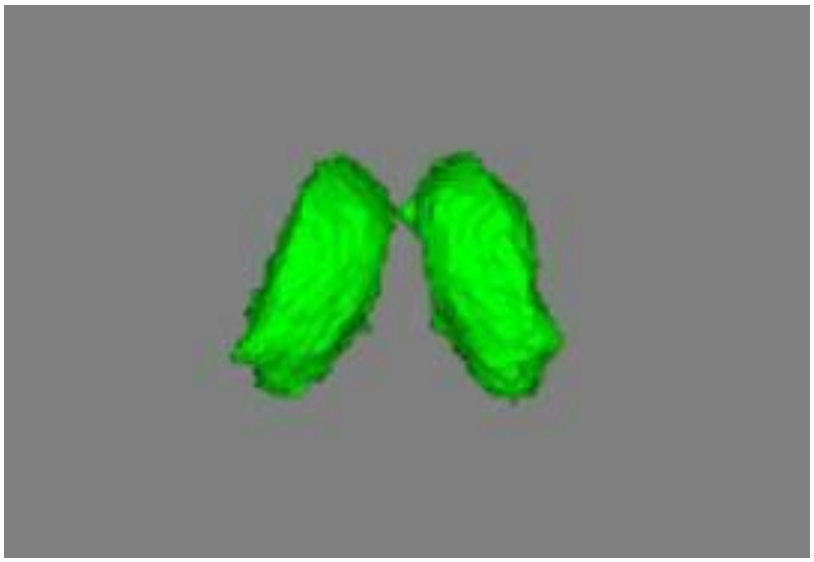
Dementias, such as Alzheimer's, can negatively impact the thalamus. The adverse effects of Alzheimer's on the thalamus haven't been fully studied, as traditionally the thalamus hadn't been associated with Alzheimer's. Nevertheless, recent studies have shown the thalamus to be affected in the early stages of Alzheimer's disease. Amyloid plaque deposits and intraneuronal neurofibrillary changes, both hallmarks of Alzheimer's, have been observed in thalamus, particularly the anterior and dorsal nuclei. These regions have lots of connection to the hippocampus, an area traditionally linked with Alzheimer's. Similarly, measured volume loss and increase in fractional anisotropy further support the notion of thalamic involvement in early Alzheimer's disease. These factors indicate a loss of neurons as well as a disruption of white matter pathways, leading to a degeneration of brain networks involved in memory.

MRI Identification and Visualization

On an MRI, the thalamus can be relatively easily identified as a pair of grey, egg shaped structures near the center of the brain, below the corpus callosum, above the brainstem, and adjacent to the ventricles. The following images from MRIcloud serve as an example.







References:
Aggleton, J. P., Pralus, A., Nelson, A. J. D., & Hornberger, M. (2016). Thalamic pathology and memory loss in early Alzheimer's disease: moving the focus from the medial temporal lobe to Papez circuit. Brain, 139(7), 1877–1890. http://doi.org/10.1093/brain/aww083

Risacher, S. L., & Saykin, A. J. (2013). Neuroimaging Biomarkers of Neurodegenerative Diseases and Dementia. *Seminars in Neurology*, *33*(4), 386–416. http://doi.org/10.1055/s-0033-1359312

Ryan, N. S., Keihaninejad, S., Shakespeare, T. J., Lehmann, M., Crutch, S. J., Malone, I. B., … Fox, N. C. (2013). Magnetic resonance imaging evidence for presymptomatic change in thalamus and caudate in familial Alzheimer's disease. Brain, 136(5), 1399–1414. http://doi.org/10.1093/brain/awt065

https://www.britannica.com/science/thalamus#ref340575
https://radiopaedia.org/articles/thalamus
https://en.wikipedia.org/wiki/Thalamus

PCC:
Describe the anatomy of this structure (Where is it located in the brain? What does it look like? How are its boundaries defined? How can it be found on an MRI?) Show a visualization (3D surface as well as image) from MRICloud screenshots.
The posterior cingulate cortex (PCC) (Fig.2) is the backmost part of the cingulate cortex (Fig.1), located behind the anterior cingulate cortex (ACC), having a granular cellular structure/look (Fig.3). In Brodmann areas defining the cytoarchitechure of human brain's cerebral cortex, the posterior cingulate cortex is associated with section 23 and 31 (Fig.4). The posterior cingulate cortex is bordered by marginal ramus above, corpus

callosum beneath, parieto-occipital sulcus posteriorly and anterior cingulate cortex in the front. Using the above information, the location of PCC is easily determined in MRI.

Fig.1 The Location of cingulate cortex. Cingulate cortex lies in the midline of the brain.

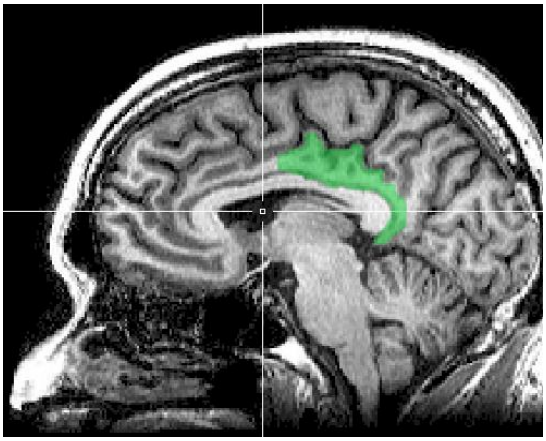


Fig.2 The Location of posterior cingulate cortex (PCC). PCC is the backmost part of cingulate cortex.

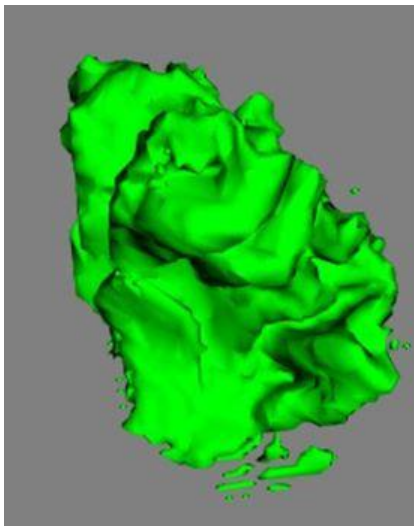


Fig.3 3D surface of posterior cingulate cortex (PCC) from MRICloud

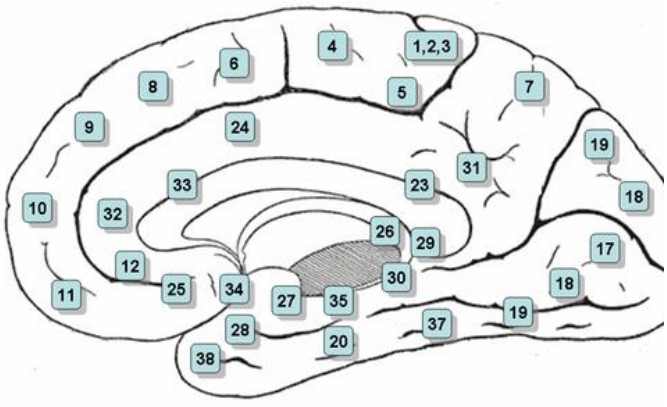


Fig.4 PCC in Brodmann areas 23 and 31

Describe the function of this structure.

The posterior cingulate cortex is one of the most highly metabolically active regions in the brain, experiencing 40% above average cerebral blood flow. It has been proved to be functional in several brain activities

Hypothesis has been that emotions may contributed to induce/strengthen the posterior cingulate cortex's activity, leading to successful recollection of memories. And it was shown that the posterior cingulate cortex is the only highly active brain structure during

an autobiographical recollection process, which proves that its function involves memory recollection activity. This role of the posterior cingulate cortex is involved with Alzheimer's disease.

Posterior cingulate cortex also serves as the central node in the default mode network (DMN), which is known as one of the intrinsic control networks in the brain. DMN has been proved to be inactive at externally directed tasks such as working memory, while being active at internally directed activities such as daydreaming. A further study showed that posterior cingulate cortex was found deactivated with undistracted, effortless mind wandering and activated during distracted and controlled awareness.

Describe how this structure may be affected by Alzheimer's or other dementias. Is there loss of volume? Loss of cortical thickness? Disruption in connectivity?

Alzheimer Disease normally starts with short-term memory loss, then gradually developing into language problem and disorientation and finally loss of self-care managing.

Reduced metabolism in the default mode network (DMN), in which the posterior cingulate cortex (PCC) serves as the central node, is an early sign of Alzheimer's disease and is frequently present before a clinical diagnosis. In early Alzheimer's disease, the reduced metabolism in DMN/PCC is typically one part in a diffuse pattern of metabolic dysfunction in the brain to metabolic abnormalities, which disrupts the connection between PCC and hippocampus in the brain. As a result, amyloid deposition and brain atrophy happen, with a spatial distribution that resembles the nodes of DMN. Carrie McDonald et. al (*McDonald, C. R., et al. "Regional Rates of Neocortical Atrophy from Normal Aging to Early Alzheimer Disease." Neurology, vol. 73, no. 6, Oct. 2009, pp. 457–465.)* observed increased atrophy in this region with progression of Alzheimer's disease. Participants are grouped by their developments of the Alzheimer's disease and took MRI scans for the brain every month. The percentage of cortical volume loss for each participant was calculated and repeated analyses were conducted for covariance in order to evaluate group differences in atrophy rates across regions as a function of impairment. The result showed that there is loss of volume of not only PCC but also many other structures with in the cortex (Fig.5), which indicates that Alzheimer's disease involved with the whole brain instead of several certain structures. In addition of volume loss, the decline of cortical thickness has also been proved in Alzheimer's disease in the research of Lerch JP et. al.

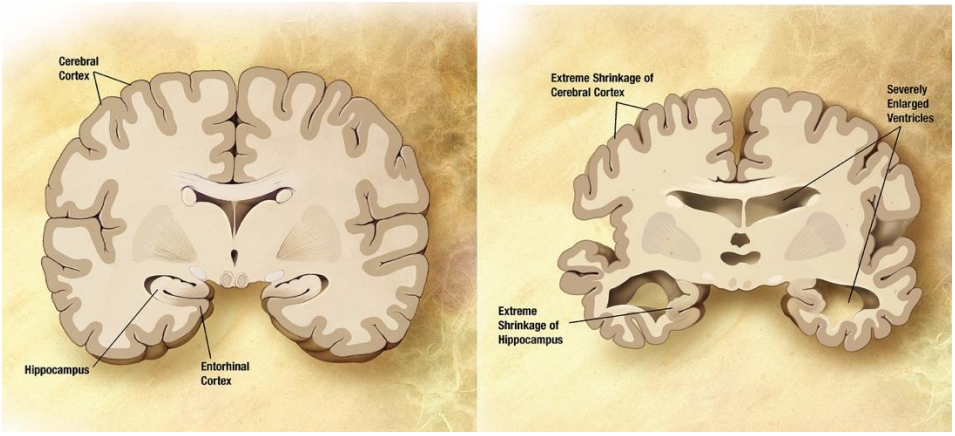


Fig.5 Comparison of a normal aged brain (left) and the brain of a person with Alzheimer's (right).

References:

Mcdonald, C. R., et al. “Regional Rates of Neocortical Atrophy from Normal Aging to Early Alzheimer Disease.” Neurology, vol. 73, no. 6, Oct. 2009, pp. 457–465., doi:10.1212/wnl.0b013e3181b16431.

Lerch, Jason P., et al. “Focal Decline of Cortical Thickness in Alzheimers Disease Identified by Computational Neuroanatomy.” Cerebral Cortex, vol. 15, no. 7, Oct. 2004, pp. 995–1001., doi:10.1093/cercor/bhh200.

https://en.wikipedia.org/wiki/Posterior_cingulate_cortex

https://en.wikipedia.org/wiki/Alzheimer%27s_disease

Volumetric analysis

For the result of volumetric analysis, please see Part2_Volumetric Analysis.pdf.