

Study of hippocampal size and age

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Abstract

Objective (or background): The hippocampus is a thoroughly studied structure of the temporal lobe. In contrast to our current knowledge of hippocampal anatomy, neurophysiology and pathophysiology, scientific literature on the relationship between the hippocampal size and age is limited. Our study aims to further the understanding of this relationship. **Methods:** 16 hippocampi were anatomized, photographed, measured and analyzed in comparison to age and gender using Pearson and bootstrap analyses with IBM SPSS®. **Results:** The results for all three independent variables of size, age and gender were not statistically significant. **Conclusions:** We were unable to show a statistically significant result on the correlation between the size of the hippocampus and age due to small sample size.

Keywords

Hippocampus, hippocampal atrophy, aging.

Abbreviations list: cornu ammonis (CA), dentate gyrus (DG)

Introduction

The hippocampus is a thoroughly studied structure of the temporal cerebral lobe¹ due to its key role in the systems involved in learning, memory, emotional behavior, motor and homeostatic control.² It inferiorly borders the temporal horn of the lateral ventricle,³ resembling a seahorse, and is composed of a head with hippocampal digitations, a body and a tail, both with fimbriae. It is anatomically connected medially, ventrally and posteriorly to the fornix, and inferolaterally connected to the parahippocampal gyrus through the subiculum. It contains a bilaminar internal structure comprised of the cornu ammonis (CA) and dentate gyrus (DG). Cornu ammonis can be subdivided into four structures according to its display of pyramidal neurons, namely from CA1, which is continuous with the subiculum, to CA4, which is the nearest region to the DG.²

The hippocampus is susceptible to different means of damage and, among them, epilepsy, hypoxia, ischemia, and encephalitis are associated with amnesic effects.¹

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Cardiovascular disease, vascular risk factors, diabetes, obesity, obstructive sleep apnea, and psychiatric disorders, among others, are factors associated with hippocampal atrophy with increasing age.^{4,7} Moreover, pathologies of the brain related to a loss of hippocampal function, such as Alzheimer's disease and dementia, are also associated with atrophy of the hippocampus and its internal structures.^{4,5,6} The rate of hippocampal atrophy in cognitively normal individuals increases with age, which substantially increases onwards from midlife.⁹

In contrast to our current knowledge of hippocampal anatomy, neurophysiology and pathophysiology, scientific literature on the relationship between the hippocampal size and age is limited.⁵ Our study aims to further the understanding of this relationship.

Methods

The available and relevant clinical information about the cadaveric specimens, sex and age, were collected from the national network of services of death verification in Brazil.

Anatomization: We dissected 8 brains that were set in formaldehyde for 2 days from individuals of variable age and sex. We isolated each hippocampus from the adjacent cortical structures by starting with an incision with a scalpel on the ipsilateral superior temporal sulcus, between the superior and middle temporal gyri, reaching the temporal horn of the lateral ventricle. Then, we extended the cut anteriorly and posteriorly, following the ventricle and avoiding damage to the hippocampus. We resected the middle and inferior temporal gyri up to a few centimeters anteriorly to the preoccipital notch, followed by the partial resection of the fusiform gyrus. After removing the choroid plexus in the temporal horn (Figure 1), we identified the borders of the hippocampus for its resection: the hippocampal fimbriae as a medial boundary for both the body and the tail, and the collateral eminence as the lateral boundary. Then, we separated the hippocampus and parahippocampal gyrus from the superior temporal gyrus anteriorly, the fornix posteriorly, and from the remaining fusiform gyrus at the collateral sulcus. The parahippocampal gyrus was digitally removed from the image of the hippocampi during the image processing step, which is explained as follow.

Photography: A camera with 12 megapixels was set up to take a picture of the resected hippocampi individually from a distance of 20cm perpendicular from its superior surface. Each image was processed with a computer in order to trace each hippocampus and substitute the background of the image with a millimeter grid (Figure 2).

Measurement: The millimeter grid was used in order to measure the hippocampal size (mm²), subtracting the area not covered by the hippocampus from the total area of the background grid.

Analysis: We analyzed the hippocampal size of 8 individuals, both right and left independently, thus 16 samples in total. We then analyzed these 16 samples in comparison to age and sex, using Pearson analysis and Bootstrap analysis utilizing IBM SPSS®. A constant code was given to each side (1 - right, 2 - left) and sex (1 - male, 2 - female), while the variables were assigned as age (from 26 years to 81 years) and size (from 36mm² to 453mm²).

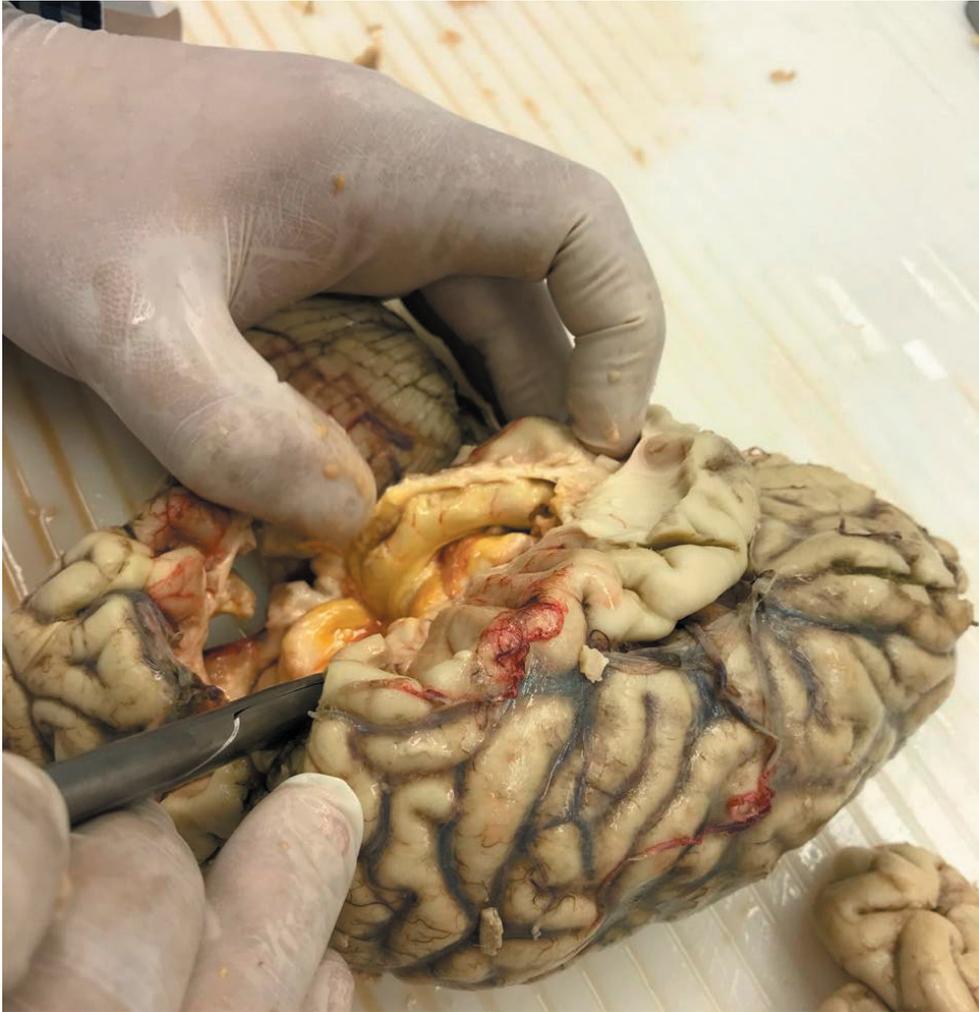


Figure 1. Picture of exposed hippocampus, after dissection of temporal lobe gyri and removal of choroid plexus.

Results

The collected hippocampi and their respective sizes, side (right or left), age and sex are shown on Figure 3.

Two types of analysis were conducted to evaluate the results of the relationship between the hippocampal size, age and sex - Pearson correlation and Bootstrap analysis.

Pearson analysis (Table I) shows the correlation between size and each side of the hippocampus, sex and age (-0.25, 0.064, -0.163 respectively). All three correlations were not significant ($p > 0.05$).



Figure 2. Picture of hippocampi over the millimeter grid background.

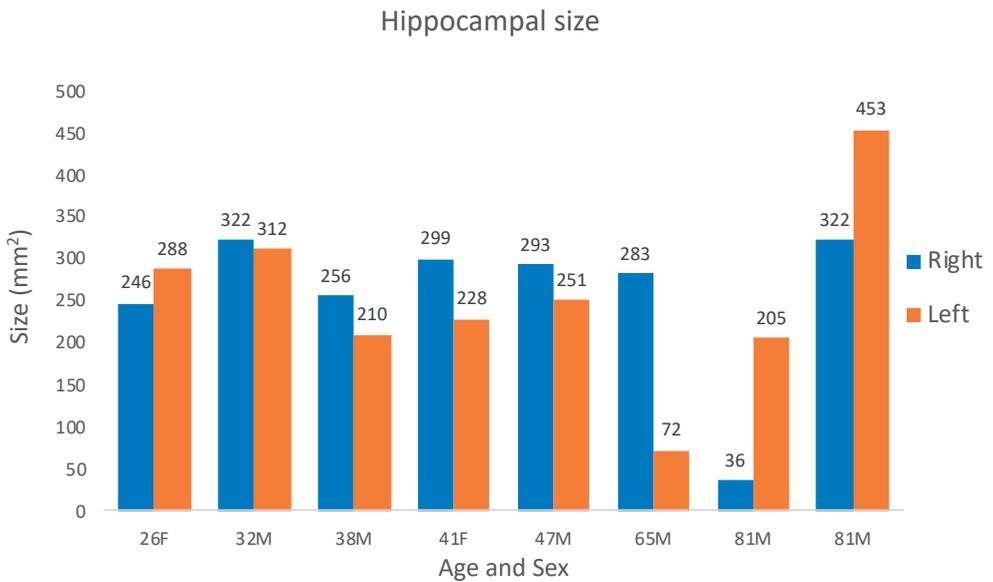


Figure 3. Graph of hippocampal size (mm²) in regard to age, sex and side.

To confront the sample size limitation, we used Bootstrap analysis (Table I). Up to 1,000 data sets were created for comparing two independent samples based on the 16 hippocampal samples. The 16 hippocampal samples comprise of both right and left

Table 1. Pearson Correlation and Bootstrap analysis.

		Side	Sex	Age	
Pearson correlation		-0.025	0.064	-0.163	
Sig. (2-tailed)		0.927	0.814	0.547	
Size	Bias	-0.038	-0.015 ^e	-0.003	
	Standard Error	0.274	0.177 ^e	0.342	
	Bootstrap ^d	Lower	-0.653	-0.332 ^e	-0.806
		Upper	0.437	0.389 ^e	0.548

d. Unless otherwise noted, bootstrap results are based on 1000 bootstrap samples.

e. Based on 991 samples.

sides of the hippocampus of each individual. The results for all three independent variables were similar to the Pearson correlation and no statistically significant result was found.

Discussion

The standardized approaches to dissection and image collection were essential to avoid artifacts in our dataset.

As the hippocampal formation is very complex, it was crucial to have careful attention to its gross anatomy and boundaries during resection. The lateral approach that was used in this study is a useful route to reach the lateral and superior aspects of the hippocampus, which is presented as a C-shaped bulging structure in the temporal horn of the lateral ventricle.^{2,3} To reach the hippocampus without damaging it during anatomization, the initial, careful approach to the temporal horn from the superior temporal sulcus was an essential step. After successfully reaching the temporal horn, the excision of the middle and inferior temporal gyri could be done with proper attention to the ventricle space in order to prevent damaging the structures of interest. The expanded access to the hippocampus with the resection of the gyri permitted the clear view of the borders of interest for the separation of the hippocampus and parahippocampal gyrus from the adjacent structures.

The hippocampus is located superiorly to the parahippocampal gyrus, which is composed of the subiculum posteriorly and the uncus and entorhinal cortex anteriorly.² The subiculum is continuous with the CA1 field,¹⁰ therefore it would be difficult to separate them physically using only the hippocampal sulcus as a landmark for separation.² From a superior view, the subiculum can be seen medial to the hippocampus, hence it was the most evident part of the parahippocampal gyrus to be digitally removed during the background replacement step. Such digital removal of the parahippocampal gyrus, rather than the physical removal, was permitted by the technique of photography, which was taken exactly 20cm from the superior surface of the hippocampus. Hence, structures inferior and lateral to the hippocampus would not interfere with the measurements.

Hippocampal atrophy is associated with aging, multiple risk factors and pathologies, making it difficult to distinguish between the causes of atrophy in a given sample. It is also possible that a preclinical stage of pathology leading to the atrophy of the hippocampus are not detected in seemingly healthy patients.⁹ A limitation of the present study is the unavailability of the clinical history of the cadavers. Such information would help distinguish the factors that would cause atrophy in the samples.

The results of the analysis demonstrated no statistical significance between hippocampal size, age and sex, so it is difficult to make any assessment based on these results without further samples. The results do show a trend towards a smaller hippocampal size with increased age, but one out the 8 patients dissected had an unusually large hippocampal size at an older age. Larger hippocampus and decreased atrophy could be explained by other variables, such as education level and physical activity.⁸ Perhaps more samples would improve the significance of the association between age and the decreasing size of the hippocampus.

Conclusion

In our research we were unable to show a correlation between the size of the hippocampus and age due to a small sample size. The insignificance of the results was due to one sample that was unusually large for its older age, and, without it, there appears to be a trend towards a decreased size in hippocampus as age increases. More samples might need to be obtained in order to reach significant results.

References

1. Knierim J.J. (2015) The hippocampus. *Curr Biol.* 25 (23): R1116-R1121. <https://doi.org/10.1016/j.cub.2015.10.049>
2. Duvernoy H.M., Cattin F., Risold P. (2013) *The Human Hippocampus: Functional Anatomy, Vascularization and Serial Sections with MRI.* Springer, New York.
3. Nolte J. (2008) *Human Brain: An Introduction to Its Functional Anatomy.* Mosby, Missouri.
4. Fotuhi M., Do D., Jack C. (2012) Modifiable factors that alter the size of the hippocampus with ageing. *Nat Rev Neurol.* 8 (4): 189-202. <https://doi.org/10.1038/nrneurol.2012.27>
5. Adler D.H., Wisse L.E.M., Ittyerah R., Pluta J.B., Ding S., Xie L., Wang J., Kadirvar S., Robinson J.L., Schuck T., Trojanowski J.Q., Grossman M., Detre J.A., Elliott M.A., Toledo J.B., Liu W., Pickup S., Miller M.I., Das S.R., Wolk D.A., Yushkevich P.A. (2018) Characterizing the human hippocampus in aging and Alzheimer's disease using a computational atlas derived from ex vivo MRI and histology. *Proc Natl Acad Sci U S A.* 115 (16): 4252-4257. <https://doi.org/10.1073/pnas.1801093115>
6. Lebedeva A., Sundström A., Lindgren L., Stomby A., Aarsland D., Westman E., Winblad B., Olsson T., Nyberg L. (2018) Longitudinal relationships among depressive symptoms, cortisol, and brain atrophy in the neocortex and the hippocampus. *Acta Psychiatr Scand.* 137 (6): 491-502. <https://doi.org/10.1111/acps.12860>

7. Santos M.A.O., Bezerra L.S., Carvalho A.R.M.R., Brainer-Lima A.M. (2018) Global hippocampal atrophy in major depressive disorder: A meta-analysis of magnetic resonance imaging studies. *Trends Psychiatry Psychother.* 40 (4): 369-378. <http://dx.doi.org/10.1590/2237-6089-2017-0130>
8. Hashimoto M., Araki Y., Takashima Y., Nogami K., Uchino A., Yuzuriha T., Yao H. (2016) Hippocampal atrophy and memory dysfunction associated with physical inactivity in community-dwelling elderly subjects: The Sefuri study. *Brain Behav.* 7 (2): 1-8. <https://doi.org/10.1002/brb3.620>
9. Fraser M.A., Shaw M.E., Cherbuin N. (2015) A systematic Review and Meta-Analysis of Longitudinal Hippocampal Atrophy in Healthy Human Ageing. *15 (112): 364-374.* <https://doi.org/10.1016/j.neuroimage.2015.03.035>
10. Schultz C., Engelhardt M. (2014) Anatomy of the Hippocampal Formation. *Front Neurol Neurosci.* 34: 6-17. <https://doi.org/10.1159/000360925>