Hippocampal metabolic subregions in healthy older and their profiles in neurodegeneration

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Introduction: Hippocampus dysfunction is the hallmark of Alzheimer's pathology and is frequently investigated with FDG-PET metabolism measurements. However, while metabolic changes are a key aspect of Alzheimer's disease (AD), different hippocampus' subregions with their specific metabolic covariance (MC) networks haven't been identified in healthy populations. It is also unclear to what extent these are affected by AD pathophysiology. As the hippocampus portrays cytoarchitectural, connectional and functional heterogeneity, heterogenous patterns of MC could be expected, leading to hippocampal subregions being differentially affected by AD pathology.

Methods: We investigated MC as correlations in metabolism between hippocampus and brain voxels in a large cohort of healthy older participants (n=362). To identify how the pattern of brain MC changes spatially within the hippocampus, we used a data-driven approach to cluster hippocampal voxels based on their whole brain co-metabolism profile (Eickhoff, Yeo, & Genon, 2018). The stability of different parcellation levels was measured using split-half cross-validation. We then examined the whole brain co-metabolism profile of each subregion using the general linear model. To examine whether the local metabolism between the metabolically-identified subregions in healthy older is influenced by AD pathology, we also performed a two-way ANOVA in the healthy older and in a cohort of ADNI patients (n=581) with the mean glucose uptake value as a dependent variable and both the subregions and diagnostic groups as factors. The ANOVA was followed by post-hoc analyses to identify which particular group differences are statistically significant while correcting for multiple comparisons. The results were compared with results of the same analysis using the structurally-defined and widely used FreeSurfer's subfields.

Results: A stable 5-clusters parcellation could be identified which included an Anterior-subiculum(Red), an Anterior-CA(Yellow), an Intermediate-subregion(Pink), a Posterior-subiculum(Blue) and a Posterior-CA(Green) subregions (Fig. 1-A). As illustrated in Fig. 1-C, the Anterior-subiculum(Red) subregion mainly relates to orbito-frontal and temporal regions

while the Intermediate-subregion (Pink) is a transitional subregion towards the Posterior-subiculum(Blue) subregion which has a wide pattern of cortical MC. The Anterior-CA(Yellow) subregion mainly relates to the amygdala while the Posterior-CA(Green) subregion mainly relates to other subcortical structures (Fig. 1-C)**.** For both hippocampal parcellations, the two-way ANOVA revealed both significant main and interaction effects. Nevertheless, overall, the differentiation between CA subregions as provided by FreeSurfer did not exhibit specific group differences while the anterior-vs-posterior distinction offered by our parcellation revealed specific group differences, in particular in the early stages (Table 1).

Conclusions:

Overall, our results suggest a MC based differentiation within the hippocampus that follows the CAs vs Subiculum differentiation known from local microstructure mapping (Fig. 1B) and anatomical connectivity (Fig. 1D). The MC patterns of the identified subregions suggested three main networks relating the anterior subregions to orbitofrontal and anterior temporal regions, the Posterior-CA(Green) subregion to subcortical structures around the ventricles, and the Posterior-subiculum(Blue) subregion to an extended cortical pattern (Fig. 1C). These MC patterns converge with the patterns of structural covariance previously shown in healthy aging (Plachti et al., 2020)(Fig. 1E), as well as the different factors of brain atrophy reported in AD (Zhang et al., 2016)(Fig. 1F) reinforcing the relevance of the derived differentiation in pathological aging. Finally, our parcellation allows the identification of specific diagnostic group differences in regional hippocampus metabolism.

Keywords: hippocampus, metabolic covariance, metabolic networks, parcellation, elderly, dementia, Alzheimer's disease, univariate analysis.

References

Archer, D. B., Moore, E. E., Shashikumar, N., Dumitrescu, L., Pechman, K. R., Landman, B. A., . . . Hohman, T. J. (2020). Free-water metrics in medial temporal lobe white matter tract projections relate to longitudinal cognitive decline. *Neurobiology of Aging*, In press. doi:10.1016/j.neurobiolaging.2020.05.001

Brown, C. A., Johnson, N. F., Anderson-Mooney, A. J., Jicha, G. A., Shaw, L. M., Trojanowski, J. Q., . . . Gold, B. T. (2017). Development, validation and application of a new fornix template for studies of aging and preclinical Alzheimer's disease. *Neuroimage Clin, 13*, 106-115. doi:10.1016/j.nicl.2016.11.024

Eickhoff, S. B., Yeo, B. T. T., & Genon, S. (2018). Imaging-based parcellations of the human brain. *Nat Rev Neurosci, 19*(11), 672-686. doi:10.1038/s41583-018-0071-7

Plachti, A., Kharabian, S., Eickhoff, S. B., Maleki Balajoo, S., Hoffstaedter, F., Varikuti, D. P., . . . Genon, S. (2020). Hippocampus co-atrophy pattern in dementia deviates from covariance patterns across the lifespan. *Brain*. doi:10.1093/brain/awaa222

Zhang, X., Mormino, E. C., Sun, N., Sperling, R. A., Sabuncu, M. R., Yeo, B. T., & Alzheimer's Disease Neuroimaging, I. (2016). Bayesian model reveals latent atrophy factors with dissociable cognitive trajectories in Alzheimer's disease. *Proc Natl Acad Sci U S A, 113*(42), E6535-E6544. doi:10.1073/pnas.1611073113

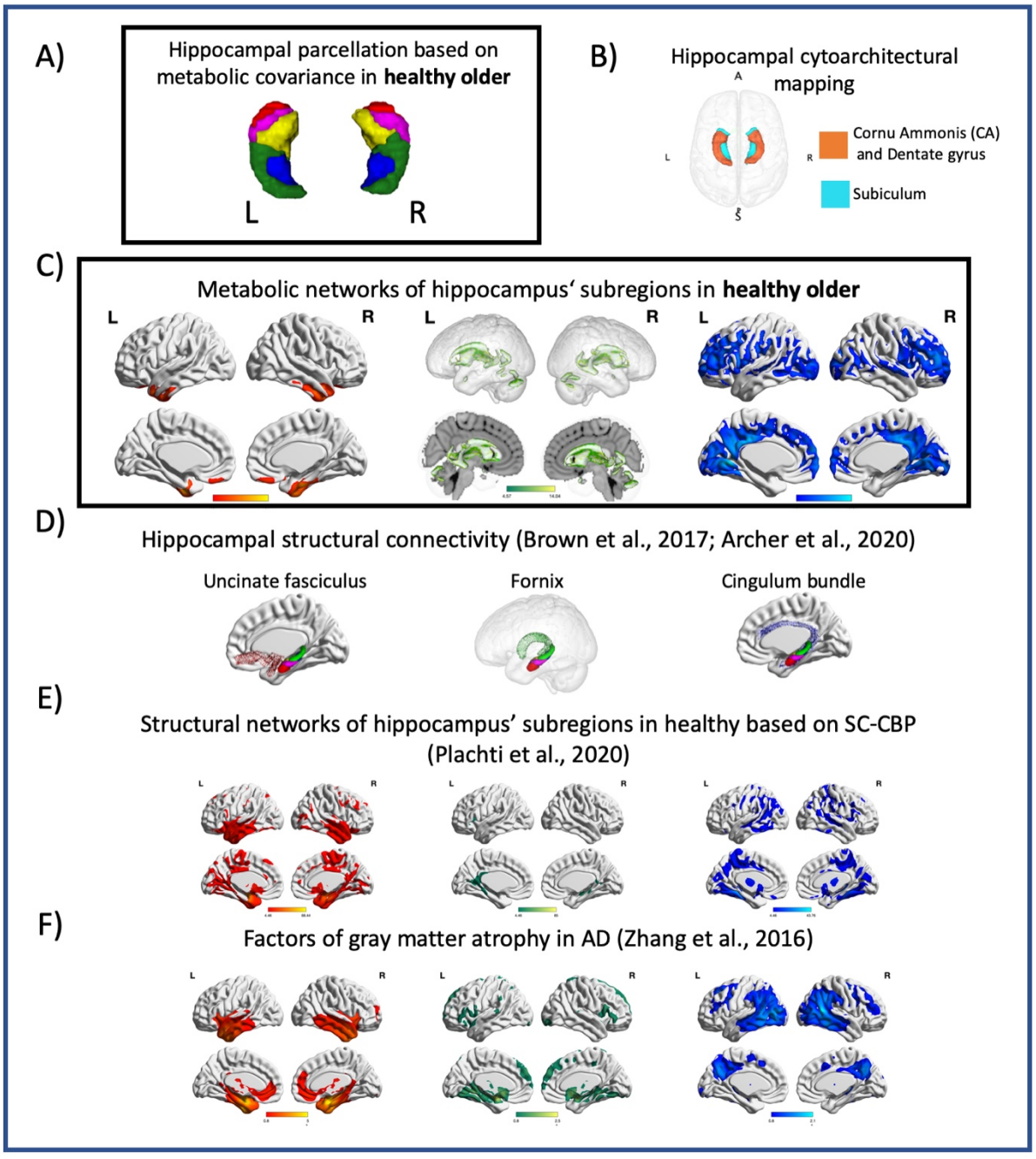

Fig1. Overview of this study's findings in metabolic co-variation pattern of hippocampal subregions in healthy older (corrected for family-wise error (FWE) rate at the significance level of $p < 0.05$) and linking these findings with previous studies in structural connectivity and structural covariance in healthy older and whole brain patterns of atrophy in AD .

Table 1. Group comparsions of mean glucose uptake value across four different dignostic groups in bilateral hippocampal subregions A) Metabolically-defined subregions in healthy older ; B) structurally-defined FreeSurfer's subfields.

		Left Hippocampus									
		Metabolic covariance based Parcellation in healthy older					FreeSurfer Parcellation				
		Anterior-subiculum(Red)	Posterior-subiculum(Blue)	Intermediate-subregion(Pink)	Anterior-CA(Yellow)	Posterior-CA(Green)	Subiculum	CA1	CA3	CA4+DG	HP-tail
Healthy older	Early MCI	×	×	✓	✓	✓	×	✓	✓	✓	✓
	Late MCI	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
	AD	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Early MCI	Late MCI	×	✓	✓	✓	✓	✓	✓	✓	✓	✓
	AD	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Late MCI	AD	✓	✓	✓	✓	✓	✓	✓	✓	✓	×
		Right Hippocampus									
		Metabolic covariance based Parcellation in healthy older					**FreeSurfer Parcellation**				
		Anterior-subiculum(Red)	Posterior-subiculum(Blue)	Intermediate-subregion(Pink)	Anterior-CA(Yellow)	Posterior-CA(Green)	Subiculum	CA1	CA3	CA4+DG	HP-tail
Healthy older	Early MCI	×	×	×	×	✓	×	×	×	×	✓
	Late MCI	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
	AD	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Early MCI	Late MCI	×	✓	✓	✓	✓	✓	✓	✓	✓	✓
	AD	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Late MCI	AD	✓	✓	✓	✓	✓	✓	✓	✓	✓	×

CA : Cornu Ammonis ; HP : Hippocampus; MCI : Mild cognitive impairment; AD : Alzheimer's disease; ✓ : A significant group difference ($P_{FWE} < 0.05$); × : No significant group difference ($P_{FWE} \geq 0.05$) .