Hippocampal subfields associations with prediabetes and type 2 diabetes: The Maastricht Study

J. Monereo-Sanchez[1, 2, 3], J.F.A. Jansen[1, 3], M.P.J. van Boxtel[4], W.H. Backes[1, 3, 5], S. Köhler[1, 6], C. Stehouwer[5, 7], A.A. Kroon[2, 5, 7, 8], D.E.J. Linden[1, 2], M.T. Schram[1, 5, 7, 8]

1 School for Mental Health & Neuroscience, Maastricht University

2 Faculty of Health, Medicine and Life Sciences, Maastricht University

3 Department of Radiology & Nuclear Medicine, Maastricht University Medical Center

4 Alzheimer Centrum Limburg, Department of Psychiatry and Neuropsychology, School for Mental Health and Neuroscience, Maastricht University

5 School for Cardiovascular Diseases, Maastricht University

6 Department of Psychiatry and Neuropsychology (A.F.J.G., S.K., M.T.S.), Maastricht University Medical Center

7 Department of Internal Medicine, Maastricht University Medical Center

8 The Netherlands Heart and Vascular Centre, Maastricht University Medical Center

Keywords: T2DM, hippocampus

Background: Lower hippocampal volumes are commonly detected in individuals with T2DM. Yet, whether this volume reduction already occurs in prediabetes, and which specific hippocampal subfields are affected is still unclear. Therefore, we investigated whether both T2DM and prediabetes are associated with specific hippocampal subfields atrophy.

Methods: We used data from 4724 participants (58.7±8.5 years, 51.5% women) of The Maastricht Study (Schram et al., 2014). Glucose metabolism status was determined with an oral glucose tolerance test and defined according to the World Health Organization 2006 criteria (World Health Organization, 2006). Participants were classified in three groups: T2DM (n=869), prediabetes (n=671), or normal glucose metabolism (NGM, n=3184). Brain imaging was acquired with a 3T Siemens MRI scan. Images were segmented using FreeSurfer v.6.0 (Fischl, 2012; Iglesias et al., 2015), and quality control was performed following guidelines (Monereo-Sánchez et al., 2021). Total hippocampal volume (THV), as well as the volume of 12 hippocampal subfields per hemisphere were obtained. Left and right hemisphere volumes were averaged. Multiple linear regression was used to assess the associations of T2DM and prediabetes with THV and hippocampal subfields volumes. NGM was used as reference group. Analyses were corrected for MRI lag time, total intracranial volume, age, sex, and cardiovascular risk factors. Given 12 subfields were analyzed and to maintain a type I error rate of 5%, Matrix Spectral Decomposition (Nyholt, 2004) was used to determine the effective number of independent variables (n=7), therefore, alpha threshold for significance was set at 0.05/7= 0.0071.

Results: T2DM was associated with smaller THV (β=-.15, p<.001). Smaller volumes were found in those subfields integrating the hippocampal formation, i.e. CA1 to CA4 (β<-.11, p<.005), (pre)subiculum (β<-.12, p<.004), and dentate gyrus (β=-.14, p<.001). In addition to fimbria (β=-.19, p<.001) and hippocampal tail (β=-.16, p<.001). Prediabetes showed no significant associations with THV or any subfield.

Conclusion: There is a generalized hippocampal atrophy associated with T2DM, which is independent of demographics, cardiovascular and lifestyle risk factors. This atrophy is not yet observable in our analysis for prediabetes stages, which could give a window of action in this stage for the early prevention of brain disease.

References:

Fischl, B. (2012). FreeSurfer. NeuroImage, 62(2), 774-781.

Iglesias, J. E., Augustinack, J. C., Nguyen, K., Player, C. M., Player, A., Wright, M., . . . Wald, L. L. (2015). A computational atlas of the hippocampal formation using ex vivo, ultra-high resolution MRI: application to adaptive segmentation of in vivo MRI. NeuroImage, 115, 117-137.

Monereo-Sánchez, J., de Jong, J. J., Drenthen, G. S., Beran, M., Backes, W. H., Stehouwer, C. D., . . . Jansen, J. F. (2021). Quality control strategies for brain MRI segmentation and parcellation: Practical approaches and recommendations-insights from the Maastricht study. NeuroImage, 237, 118174.

Nyholt, D. R. (2004). A simple correction for multiple testing for single-nucleotide polymorphisms in linkage disequilibrium with each other. The American Journal of Human Genetics, 74(4), 765-769.

Schram, M. T., Sep, S. J., van der Kallen, C. J., Dagnelie, P. C., Koster, A., Schaper, N., . . . Stehouwer, C. D. (2014). The Maastricht Study: an extensive phenotyping study on determinants of type 2 diabetes, its complications and its comorbidities. European journal of epidemiology, 29(6), 439-451.

World Health Organization. (2006). Definition and diagnosis of diabetes mellitus and intermediate hyperglycaemia: report of a WHO/IDF consultation.