Icahn School of Medicine at Mount Sinai

Translational and Molecular Imaging Institute

Hippocampus Subfield Segmentation at 7T MRI in Patients with Major Depressive Disorder: First Results

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Introduction: Major depressive disorder (MDD) is a disabling illness of very high prevalence worldwide [1], affecting 6.9% of the U.S. population annually [NIMH]. There is a pressing need to better understand the underlying pathophysiology and etiology of MDD for enhanced treatment design and efficiency. Previous studies have shown an association between the volumes of hippocampus subregions and MDD, making subregion volumes potential biomarkers for the disease [2-4]. Using the ultrahigh field 7 Tesla MRI scanner to acquire the data for volumetric analysis can allow for more accurate volumetric measurements due to higher contrast and resolution compared to lower field strength. The aim of this study is to demonstrate the feasibility of hippocampal subfield segmentation for MDD patients at 7T using high-resolution anatomical T_2 weighted MRI. We also perform a preliminary analysis to evaluate differences in subfield volumes between healthy subjects and MDD patients in a pilot dataset as a starting point for a larger clinical study.

Methods & Results: Five MDD patients (ages 40-55 years) and five healthy controls (ages 34-46 years) were enrolled in this IRB-approved prospective study and underwent an MRI scan at 7T (Magnetom, Siemens). The MR imaging protocol consisted of: A) 3 sequences acquired at a coronal oblique orientation: MP-RAGE (TR 3500 ms, TI 1050 ms , TE 1.95 ms, voxel 0.7x0.7x0.7 mm^3), MP2RAGE (TR 6000 ms, TI1 1050 ms , TI2 3000 ms, TE 5.06 ms, voxel 0.8x0.8x0.8 mm^3), and T_2 TSE (TR 9000 ms, TE 69 ms, voxel 0.45x0.45x2 mm^3); B) 2 sequences acquired at an axial orientation: Susceptibility weighted imaging (SWI) (TR 23 ms, TE 14 ms, voxel 0.2x0.2x1.5 mm^3) and Diffusion weighted imaging (DWI) (TR 5500 ms, TE 65.2 ms, voxel 1.1x1.1x2.1 mm^3); and C) GRE 4echo QSM (TR 39 ms, TE1 6.17 ms, TE2 13.78 ms, TE3 22.25 ms, TE4 30.72 ms, voxel 0.9x0.9x1.1 mm^3). Manual segmentation was performed in OsiriX (Pixmeo, Switzerland), using high-resolution 7T T_2 TSE (0.45x0.45x2 mm^3) images by the same trained image analyst. The subfields delineated were CA1, CA2 3, CA4 DG, choroid plexus, inferior lateral ventricle, presubiculum, and subiculum. A sample segmentation of the hippocampus subfields on a TSE image is displayed in **Figure 1**. The tracing method was guided by a neuroradiologist and the subregion boundaries were patterned after those in a previous study [5]. We computed the volumes of the five MDD subjects and five healthy controls for each of the subfields and the total hippocampus, adding the right and left region values for each. We then computed the mean volume and standard deviation for each of the subregion volumes and the total hippocampus volumes in both patients and controls. A comparison of the MDD patients to the healthy controls was done in each of the seven subregion mean volumes and total hippocampus mean volumes. P values were calculated to examine the significance of the volumetric differences between the MDD and control subjects. The average volume and standard deviation for each subfield and the total hippocampus in the five MDD subjects and five healthy controls as well as the corresponding p values are reported in **Table 1**. The p value corresponding to the volumetric difference in the inferior lateral ventricle between MDD patients and control subjects indicates significance ($p<.05$). The inferior lateral ventricle is shown to have a greater volume in MDD patients than healthy controls.

Conclusion: We have demonstrated feasibility of hippocampal subfield segmentation and volume analysis for MDD patients at 7T. The increased volume in the inferior lateral ventricle measured in MDD patients when compared to healthy controls is supported by a previous MDD studies with similar findings. [6] This may suggest a link between MDD and inferior lateral ventricle dilation, which would be an interesting question to investigate in future larger scale clinical 7T studies. Significant volumetric differences were not observed in the other hippocampus subfields, which can be attributed to the small sample size for this preliminary study. Based on the standard deviations of our data and previous studies, we calculated that a sample size of 40 is required to obtain sufficient statistical power for this study. Another limitation to the work proposed in this study is the time and expertise needed to manually identify the hippocampus subregions. Therefore, in future studies, we plan to explore creating a semi-automated segmentation method as well as use a larger sample size. Identifying a correlation between MDD and hippocampus subfield volumes can lead to new biomarkers of the disease. Uncovering the role of these potential biomarkers can have serious applications in diagnostics and treatment.

Clinical Relevance: Identifying a correlation between MDD and hippocampus subfield volumes can lead to new biomarkers of the disease. Uncovering the role of these potential biomarkers can have serious applications in diagnostics and treatment.

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Figures and tables

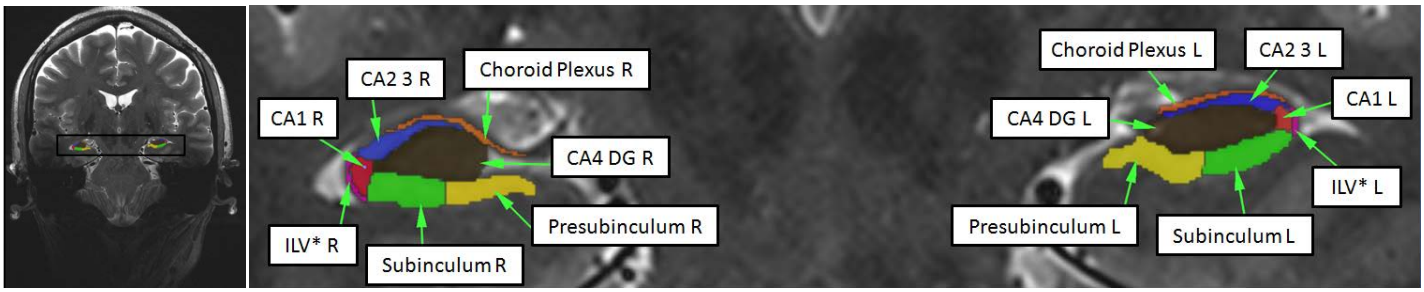

Figure 1: Hippocampus subfield segmentation labeled and color-coded. 'R' denotes right hemisphere regions and 'L' denotes left hemisphere regions. *ILV= inferior lateral ventricle

Mean Volumes ± Standard Deviation and P values for MDD patients and healthy controls

Subfields	MDD	Healthy	P Value
CA1	170 ± 48	171 ± 37	0.52
CA2 3	244 ± 46	278 ± 59	0.26
CA4 DG	980 ± 160	1050 ± 250	0.52
Choroid Plexus	120 ± 35	126 ± 29	0.68
Inferior Lateral Ventricle	70 ± 11	49 ± 17	0.01
Presubiculum	420 ± 80	496 ± 148	0.12
Subiculum	315 ± 56	367 ± 96	0.09
Total Volume	2320 ± 210	2540 ± 560	0.19

Table 1: Subfield volumes of the five MDD subjects and five healthy controls for each subfield and the total hippocampus (right and left regions were added) and p values indicating significance in volumetric differences between the MDD and control subjects. Volumes are given as population average +/- standard deviation.

References

1. Kessler RC, Berglund P, Demler O, et al. for the National Comobordity Survey Replication. The epidemiology of major depressive disorder: results from the National Comorbidity Survey Replication (NCS-R) JAMA (2003) [PubMed]
2. Huang Y, Coupland NJ, Lebel RM, Carter R, Seres P, Wilman AH, Malykhin NV. Structural changes in hippocampal subfields in major depressive disorder: a high-field magnetic resonance imaging study. Biol Psychiatry, 74 (2013) [PubMed]
3. Malykhin NV, Coupland NJ. Hippocampal neuroplasticity in major depressive disorder. Neuroscience (2015) [PubMed]
4. Malykhin NV, Carter R, Seres P, Coupland NJ. Structural changes in the hippocampus in major depressive disorder: contributions of disease and treatment. J. Psychiatry Neurosci. (2010) [PMC]
5. Winterburn J, Pruessner J, Chavez S, Schira M, Lobaugh N, Voineskos A, et al. A novel in vivo atlas of human hippocampal subfields using high-resolution 3 T magnetic resonance imaging. NeuroImage, 74 (2013) [Elsevier]
6. Westeneng HJ, Verstraete E, Walhout R, Schmidt R, Hendrikse J, Veldink JH, et al. Subcortical structures in amyotrophic lateral sclerosis. Neurobiol Aging (2015) [PubMed]