Structural Changes in Hippocampal Subfields in Major Depressive Disorder: A High-Field Magnetic Resonance Imaging Study

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Background: Magnetic resonance imaging (MRI) has shown lower hippocampal volume in major depressive disorder (MDD). Preclinical and postmortem studies show that chronic stress and MDD may affect hippocampal subfields differently, but MRI spatial resolution has previously been insufficient to measure subfield volumes.

Methods: Twenty MDD participants (9 unmedicated and 11 medicated, both >6 months) and 27 healthy control subjects were studied. We used T2-weighted two-dimensional fast spin echo and T1-weighted three-dimensional magnetization prepared rapid acquisition gradient-echo sequences at 4.7 T to compare hippocampal subfield volumes at .09 μL voxel volume.

Results: Unmedicated MDD participants had a lower dentate gyrus volume than control subjects or medicated MDD participants and a lower cornu ammonis (CA1–3) volume in the hippocampal body subregion than control subjects.

Conclusions: Hippocampal volumes in unmedicated MDD showed evidence of localization to specific subfields and subregions, findings that appear, on the surface, consistent with preclinical evidence for localized mechanisms of hippocampal neuroplasticity. Strengths include in vivo measurement of entire hippocampal subfields and separation between unmedicated and medicated MDD. Limitations include power to control for multiple comparisons and that MRI landmarks approximate the subfields defined by cellular microstructure.

Key Words: Antidepressant treatment, cornu ammonis, dentate gyrus, hippocampus, major depressive disorder, subiculum

One of the best replicated findings in biological psychiatry is that hippocampal volume is decreased in major depressive disorder (MDD), as confirmed in a recent meta-analysis of 32 magnetic resonance imaging (MRI) studies (1). Predictors of lower hippocampal volume in MDD have included more extensive episode duration and recurrence (1,2) and a history of childhood maltreatment (3–5).

The major subfields across the hippocampal transverse axis are the cornu ammonis (CA1–3), dentate gyrus (DG), and subiculum (6). Stress and glucocorticoid overexposure affect hippocampal neuroplasticity via mechanisms that at least in part localized to specific hippocampal subfields (7–9). Adult neurogenesis is specific to the DG. The neurogenic hypothesis of MDD proposed that a reduced rate of DG neurogenesis might play a role in low hippocampal volume and that successful antidepressant treatment requires an enhanced rate of neurogenesis (10,11). In preclinical studies, stress- and glucocorticoid-induced suppression of DG neurogenesis can be prevented or reversed by antidepressant treatments, which also have direct neurogenic effects (9,12–14). Interference with the neurogenic effects of antidepressants can block their effects on depressive-like behaviors (15). In contrast, the CA, particularly the pyramidal cells of CA3, is most vulnerable to neuronal remodeling and cell loss following chronic stress or glucocorticoid overexposure and antidepressant treatments can also prevent or reverse dendritic remodelling in CA3 (7,8,16–21) and glial loss.

Human postmortem studies have not provided evidence that neuronal apoptosis is a significant factor in the hippocampal volume reduction observed in MDD (22–24). Loss of glia, neuropil loss and suppression of neurogenesis have been suggested as alternative hypotheses (24).

The spatial resolution of MRI in MDD has been insufficient for measurement of hippocampal subfields, although some studies have mapped deformations in hippocampal thickness to make probabilistic estimates of which subfields may be affected (5,25). The improved spatial resolution of high field strength MRI has recently enabled measurements of subfield areas and our group has recently reported the first in vivo measurements of entire hippocampal subfield volumes (26). The main goal of this study was to investigate whether specific hippocampal subfields are affected in MDD.

In addition to the subfields across its transverse axis, the hippocampus has also been suggested to show topographical segregation along its longitudinal axis: ventral to dorsal in rodents and anterior to posterior (head-body-tail) in primates (27,28). Posterior hippocampus, including the hippocampal body and tail, may be particularly susceptible to volume reductions (5,29–32), which may predict a worse acute treatment outcome (33). Furthermore, successful long-term antidepressant treatment may increase posterior hippocampal volume (5,32). A second goal was therefore to investigate whether volume reductions in MDD are specific to more posterior longitudinal subregions (in contrast to transverse subfields), that is, the body and tail.

Despite preclinical evidence that antidepressant treatments affect hippocampal neuroplasticity, there is little published information regarding the possible impact of medication in MRI studies of

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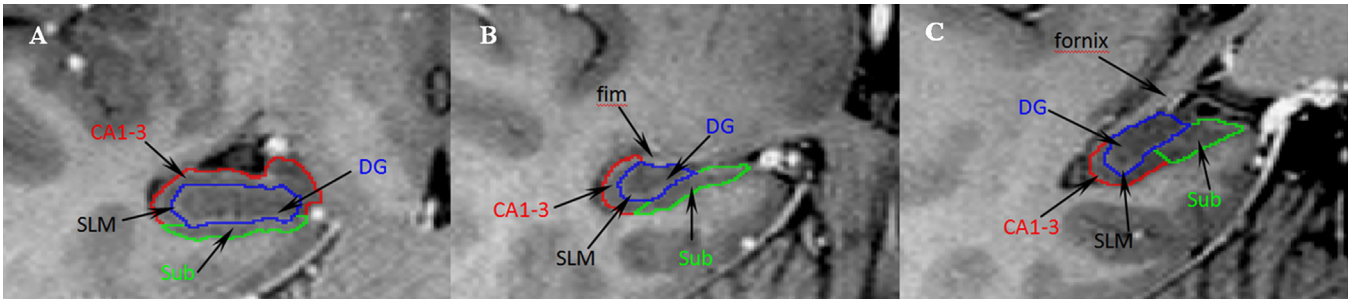

Figure 1. Coronal views of the hippocampal subregions: **(A)** hippocampal head, **(B)** hippocampal body, **(C)** hippocampal tail. CA1–3, cornu ammonis (shown in red); DG, dentate gyrus (shown in blue); Sub, subiculum (shown in green); SLM, stratum lacunosum-moleculare; fim, fimbria. T2-weighted fast spin echo images are shown in inverted contrast.

hippocampal volume in MDD (1). Our cross-sectional study and longitudinal research suggest that long-term antidepressant treatment may be protective against or reverse volume loss (2,5,32). Volume differences may be therefore be more marked in MDD patients who have not recently received antidepressant treatment.

Methods and Materials

Participants

Twenty patients meeting DSM-IV criteria for MDD with moderate or severe episodes were recruited, based on full clinical assessment and the Structured Clinical Interview for Diagnosis for DSM-IV (SCID) (34), together with 27 healthy control subjects. Participants were males or premenopausal females aged 18 to 50 years, and the groups were similar in age, sex, education, and smoking. Of the MDD participants, 11 reported continuous use of antidepressant treatment for more than 6 months (median 30, range 15–130 months; 2 bupropion, 6 selective-serotonin reuptake inhibitor [SSRI], 2 serotonin and norepinephrine reuptake inhibitor, 1 SSRI/bupropion); 4 were antidepressant-naive, and 5 were medication-free for more than 6 months (median 24, range 8–40 months). Exclusion criteria were MDD with only mild episodes, psychotic or atypical features, seasonal affective disorder, lifetime schizophrenia, bipolar disorder, alcohol or substance dependence, anorexia nervosa, predominant personality or anxiety disorder, systemic corticosteroid use, significant medical or neurological disease, pregnancy or lactation, or treatment with mood stabilisers. Healthy control subjects had no lifetime psychiatric disorders or reported psychosis or mood disorders in first-degree relatives. Written informed consent was obtained, and the research was approved by the University of Alberta Health Research Ethics Board. Subjects were recruited via local notices and assessed in the outpatient psychiatry department (N.J.C.).

Symptom severity was assessed using the 17-item Hamilton Depression Rating Scale (HAM-D). Childhood maltreatment was ascertained using Childhood Trauma Questionnaire (CTQ) (35) total scores, or meeting moderate-severe cut-scores on any CTQ subscale. We divided MDD participants into those with less or more than 2 years of episodes, based on a recent meta-analysis that associated smaller hippocampal volume with more than 2 years' duration (1).

MRI Data Acquisition and Analysis

Imaging was performed using a 4.7-T whole-body imaging system (Varian, Palo Alto, California). T2-weighted fast spin echo (FSE) acquisitions used contiguous 1-mm-thick slices, with a 90° excitation followed by four 140° refocusing pulses, an echo time of 39 msec, repetition time of 11000 msec, field of view of 20 × 20 cm and in-plane matrix of 384 × 296, native resolution of .52 × .68 × 1.0 mm^3. Ninety slices were obtained perpendicular to the anterior–posterior commissure line in a total acquisition time of 13.5 min. Images were reconstructed and inspected for motion artifacts with the subject in the scanner, allowing a second FSE data set to be collected if required (26). Images were interpolated in-plane by a factor of 2 to yield a final resolution of .26 × .34 × 1.0 mm^3 and voxel volume of .09 μL. A whole brain T1-weighted three-dimensional magnetization prepared rapid gradient echo sequence (axial, echo time/repetition time/inversion time = 5 msec/1.8 sec/850 msec, 10° flip angle, in-plane resolution .75 × .75 mm^2, whole brain coverage with 256 contiguous .75 mm slices) was used to obtain intracranial volumes (ICV).

The program DISPLAY (Montreal Neurological Institute, Montreal, Quebec, Canada) was used to trace ICVs on the T1-weighted magnetization prepared rapid gradient echo images and hippocampal subfields on the T2-weighted FSE images. Detailed protocols for hippocampal volume, subfield and subregion volumes and ICV have been previously reported (26,36,37). Microscopic delineation between hippocampal subfields is not possible without histological examination, and we therefore defined the three subfields according to internal anatomic landmarks visible on MRI. These corresponded to our best approximations to the CA1-3, DG, and subiculum (Figure 1). When following the results and discussion, it is important to note that DG refers to tissue encompassed by the molecular layer of the DG, which includes both DG proper and a portion of the CA. Neuroanatomists have used varying nomenclature for this region,[1] but the main point is that the measurement includes the molecular layer and the granule, polymorphic and pyramidal cell layers that can be differentiated microscopically but not by MRI.

All measurements were performed by a single rater (Y.H.), trained by the developer of the protocol (N.V.M.). Interrater reliabilities for hippocampal subfield volumes and ICV measures were assessed and intrarater reliability was also assessed at a 1-week interval, in each case based on images from five subjects

[1]DG refers to tissue within the concavity of the dentate gyrus. As noted in our method paper (26), the literature varies as to whether the polymorphic and/or pyramidal cell layers in this region are separately named CA4 (or hilus)/CA3, respectively (38), or are named CA4 collectively (6). Because differentiation between these cell layers is not possible with MRI, the editorial decision for the method paper was to use the term DG. We have therefore adhered to the term DG to avoid adding confusion by changing terminology between papers.