Hippocampal Structural MRI Abnormalities in Euthymic Bipolar I Disorder

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Bipolar disorder (BD) is a common, complex psychiatric illness characterised by extremes of mood and disordered thinking. Recent meta-analyses of small, heterogenous study populations have implicated hippocampal volumetric differences between BD patients and controls (1). This study sought to confirm this finding as a potential trait abnormality by investigating hippocampal volume in 60 prospectively confirmed euthymic bipolar I disorder patients compared to 60 individually age and gender matched controls in the largest known MRI region-of-interest study of its type to date.

Method: ***Subjects*****:** MRI data was acquired on 60 euthymic BD type I and 60 individually age (±3 years) and gender matched control subjects. Diagnosis of BD-I was determined by DSM-IV SCID and euthymia confirmed both 1month prior to, and on the day of testing using the Young Mania Rating Scale (YMRS) and Hamilton Rating Scale for Depression (threshold <6). Exclusion criteria for all subjects included neurological or co-morbid psychiatric disorders, learning disability, drug and alcohol abuse within the last year, and loss of consciousness> 5 mins.
Acquisition/processing*:* High-resolution, 3D, T1-weighted Magnetization-prepared rapid gradient echo (MPRAGE) data was collected using a 1.5T MRI scanner (Siemens, Erlangen) : FOV 230mm, TR: 1140ms TE 4.38ms, matrix size 256 x 256, interpolated to 512 x 512, yielding an in-plane pixel resolution of 0.45mm x 0.45mm, slice thickness 0.9mm. Following bias-correction (N3,MNI), the images were re-sampled in standard space to $1mm^3$ using a 6-parameter affine transformation (FLIRT/FSL,FMRIB). The hippocampus was manually segmented by a single trained rater using ITK-SNAP. ***ROI definition***. The hippocampus was defined as Ammon's horn, dentate gyrus, and most of the subiculum. The alveus, fimbria and fornix and entorhinal cortex were excluded. Tracing was performed predominantly in the sagittal plane. Anterior border: demarcated by the alveus. Posterior border: with reference to external structure,the point where the greatest continuation of the fornix was visible as grey gives way to white matter. Medial border: the open end of the hippocampal and uncal fissures and the medial aspect of the ambiens gyrus.Lateral border: inferior horn of the lateral ventricle and adjacent white matter.Superior border: the alveus and inferior border of the white matter between the hippocampus and the underlying parahippocampus.

Fig. 1 Hippocampal segmentation in 3 orthogonal views and resulting 3D reconstruction.

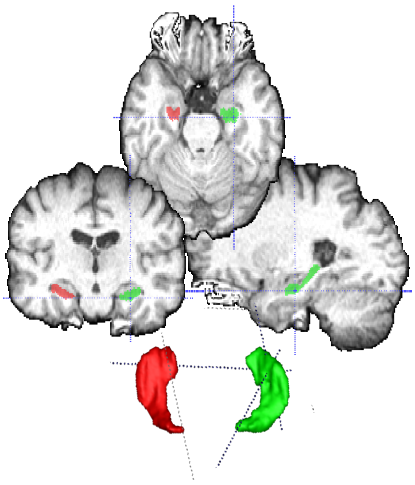
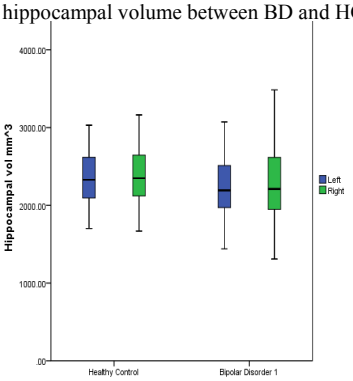


Fig 2. Differences in left and right hippocampal volume between BD and HC



Results: Intra-rater reliability was determined for a single-blinded tracer segmenting 10 images on two separate occasions α=0.93(left and right). There were no differences in mean age or proportion of gender between groups (gender, χ^2=0.000), p=0.572; age t=0.085, p=0.932). Employing a repeated measures ANCOVA statisical analysis with diagnosis, gender and hemisphere as fixed factors, and covarying for age and total intracranial volume, a diagnosis of bipolar disorder had a statistically significant effect on the volume of the hippocampus (F=4.07, p=0.046) reflecting an estimated decrease in hippocampal volume of 122 mm^3 in the patient group. There were no significant interactions between any within or between-group factors and diagnostic status: p<0.05 e.g. volumes did not differ significantly in bipolar males compared to bipolar females and there were no significant laterality effects. *Post-hoc tests*: No differences in volume were attributable to illness duration, or medication status, including current lithium use (p<0.05).

Discussion: The finding of a subtle reduction in hippocampal volume is consistent with three other studies investigating the structure using ROI based methods. Decreased volume has also been reported in both major depression and schizophrenia. However, these findings conflict with the majority of other studies which report preservation of hippocampal volume in bipolar disorder(2). The most recent study with comparable methodology matched 24 BDI patients to 24 controls based on age, gender and education,and reported volumetric increase (3). The hippocampus is a region of considerable plasticity and volume is likely to reflect the combined influences of a number of environmental factors. One hypothesis for the apparent preservation of hippocampal volume proposes that deficits associated with longer illness duration and episodes are masked by the competing action of neurotrophic medications. A number of studies have associated lithium use with hippocampal increase(2). However, the present study investigating 46 lithium treated subjects detected no such effect with lithium status (p=0.731). It is worth noting however that the present study was not specifically designed to test the effects of lithium or any other potential neurotrophic agents *per se* and therefore disambiguating the competing effects of pharmacological treatment and any underlying structural abnormality becomes problematic. The nature of structural abnormalities in BD in the hippocampus remains unclear. Longitudinal studies would further clarify the effects of medication, illness duration and frequency of episodes on hippocampal volume.

References: 1.Hallahan, B et al, (2010) 'Structural Magnetic Resonance Imaging in Bipolar Disorder: An International Collaborative Mega-Analysis of Individual Adult Patient Data', *Biological Psychiatry*,Epub ahead of print: http://dx.doi.org/10.1016/j.biopsych.2010.08.029 2**.** Emsell, L & McDonald, C.(2009) 'The structural neuroimaging of bipolar disorder' *Int Rev Psychiatry*,21:4,297-313. 3. Javadapour, A., et al., (2010) Hippocampal volumes in adults with bipolar disorder. *J Neuropsychiatry Clin Neurosci*. **22**(1): p. 55-62.