

## An MRI study of the caudate nucleus 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. Evidence from structural MRI implicates subtle grey matter abnormalities in BD in brain regions involved in affective regulation and executive function. However such studies are often underpowered with highly heterogeneous patient populations [1]. An important yet often neglected structure is the caudate nucleus which forms a subcortical component of and modulator within anterior limbic networks[2]. To our knowledge this study represents the largest case-control population (n=118) investigation of caudate nucleus volume in euthymic bipolar I disorder.

**Method:** *Subjects:* MRI data was acquired on 59 euthymic BD type I and 59 individually age and gender matched control subjects. Diagnosis of BD-I was determined by DSM-IV SCID and euthymia confirmed both 1 month 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) with the following sequence parameters: 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<sup>3</sup> using a 6-parameter affine transformation (FLIRT/FSL,FMRIB). The caudate was manually segmented using ITK-SNAP.

*ROI definition:* The first slice was defined by the grey matter of the caudate head being clearly distinguished from the surrounding frontal white matter anteriorly, anterior commissure, posteriorly, internal capsule laterally, and thin strip of WM medially in the axial plane. The last slice was defined as the point at which the caudate body was no longer clearly visible laying medial to the lateral ventricle. To improve accuracy, the tracing was refined in all three orthogonal planes viewed simultaneously and raw volumes were corrected for total brain volume (TBV): (individual volume /individual TBV) x mean TBV.

**Results:** Intra-rater reliability was determined for a single-blinded tracer segmenting 10 images on two separate occasions: 0.99. There were no differences in mean age or proportion of gender between groups (gender,  $\chi^2=0.000$ ,  $p=0.572$ ; age  $t=0.085$ ,  $p=0.932$ ). A main effect of gender was detected in the right ( $F=8.676$ ,  $p=0.004$ ) and left caudate ( $F=8.642$ ,  $p=0.004$ ). These findings can be accounted for by females with BD having both greater right ( $t=-2.61$ ,  $p=0.012$ ) and left caudate volume ( $t=-2.42$ ,  $p=0.019$ ) relative to the males with BD. Female controls did not differ significantly from male controls (right,  $t=-0.592$ ,  $p=0.556$ , left,  $t=-0.841$ ,  $p=0.404$ , Fig 2) Left and right caudate volume correlated significantly with age (right,  $r^2=0.07$ ,  $p=0.005$ , left,  $r^2=0.07$ ,  $p=0.004$ ). A main effect of diagnostic group was not detected in either right ( $F=0.007$ ,  $p=0.932$ ) or left caudate ( $F=0.014$ ,  $p=0.906$ ). *Post-hoc tests:* No differences in volume were attributable to illness duration, age of onset, or medication status, including current lithium use ( $p<0.05$ ). There was a significant effect of family history in the right caudate ( $F=3.992$ ,  $p=0.051$ ) and a gender by family history interaction also in the right ( $F=6.555$ ,  $p=0.013$ ).

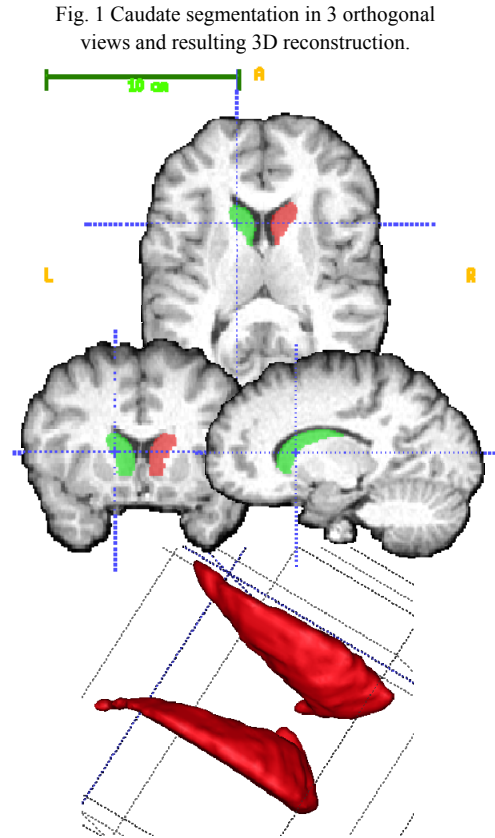
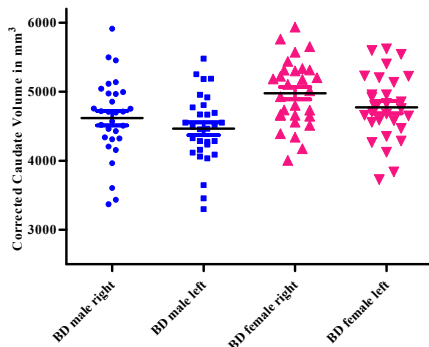


Fig. 1 Caudate segmentation in 3 orthogonal views and resulting 3D reconstruction.

Fig. 2 Gender differences in caudate volume in BD



### Discussion:

A main effect of gender was detected overall: females > males although this was not significant amongst controls. This was accounted for by males with BD having lower bilateral caudate volume relative to females with BD and may reflect underlying sexual dimorphism in the limbic system. However, there were no overall differences between controls and BD consistent with the majority of previous studies investigating much smaller sample sizes[1]. Increased caudate volume has been associated with medication use[1], however, we found no difference between subjects currently on lithium and those having remote or no exposure to lithium. The significant negative correlation with age is consistent with previous reports of volume reduction in the caudate during adulthood [3]. Although we detected a significant effect of family history in male patients only, a recent high risk study of affected, unaffected relatives of BD patients and controls found no significant differences between groups [4]. Future work on this sample will attempt to characterise the contribution of genetic load to caudate volume, investigate other morphological parameters within the caudate such as shape, and perform longitudinal assessment of morphology in the same patient group during mood episodes to examine state versus trait differences.

**References:** [1]Emsell, L & McDonald, C.(2009) 'The structural neuroimaging of bipolar disorder' *Int Rev Psychiatry*,21:4,297-313 [2] Bonelli, R.M et al (2006) 'Basal ganglia volumetric studies in affective disorder: what did we learn in the last 15 years. *J Neural Transm*, 113:255-268 [3]Jernigan, T.L.& Gamst, A.C,(2005) 'Changes in volume with age-consistency and interpretation of observed effects', *Neurobiology of Ageing*, 26,1271-1274[4] Hajek, T et al,(2009) 'Striatal volumes in affected and unaffected relatives of bipolar patients – high risk study' *J Psychiatr Res*, 43(7):724-9