

White Matter Alterations in Euthymic Bipolar I Disorder, a DTI Voxel-Based Analysis

L. Emsell^{1,2}, W. Van Hecke^{3,4}, C. Langan¹, G. Barker⁵, A. Leemans⁶, S. Sunaert³, P. McCarthy¹, R. Skinner¹, D. M. Cannon¹, and C. McDonald¹

¹NUI Galway, Galway, Co. Galway, Ireland, ²Developmental & Functional Brain Imaging, Murdoch Children's Research Institute, Melbourne, Victoria, Australia, ³Dept of Radiology, University Hospital Leuven, Belgium, ⁴University of Antwerp, Belgium, ⁵Institute of Psychiatry, London, United Kingdom, ⁶Imaging Sciences Institute, University Medical Center Utrecht, Utrecht, Netherlands

Bipolar Disorder (BD) is a complex psychiatric disorder characterised by periods of relative stability termed euthymia. The euthymic state presents an opportunity to investigate potential underlying trait abnormalities of the illness. To date most studies on brain structure in BD have investigated small cohorts of mixed mood state and clinically heterogeneous populations and have yielded contradictory results. The most consistent findings suggest alterations in white matter (WM) underlying limbic networks (1). This study sought to clarify the extent of such WM change in a Diffusion Tensor Imaging (DTI) voxel-based analysis (VBA) of 35 prospectively confirmed euthymic patients and 44 controls.

Method: Clinical Subjects: DTI data was acquired on 35 euthymic BD type I and 44 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.

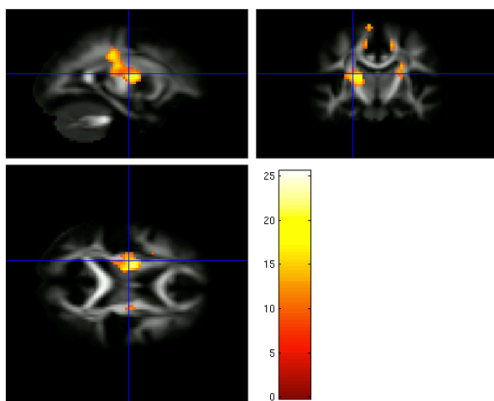
Diffusion tensor imaging data acquisition: DTI data was acquired on a 1.5T MRI scanner along 64 independent diffusion gradient directions, $b = 1300 \text{ s/mm}^2$, 7 b_0 images, TR = 8100ms, TE = 95 ms, FOV = 240 × 240 mm², matrix = 96 × 96, in-plane resolution of 2.5 mm², slice thickness = 2.5 mm, 60 axial slices, scan duration = 10:24 mins

VBA: Each dataset was corrected for motion and distortion including b-matrix rotation and signal intensity modulation using ExploreDTI(2), non-linearly coregistered to a template atlas generated from the study population (3), visually assessed for registration quality, anisotropically smoothed (4) by 6mm and then with a further 4mm gaussian kernel to meet the requirements for GLM based statistical analysis.

Statistical processing was performed using SPM8 (FIL,UK). The resulting data were masked using an FA threshold of 0.15 to restrict the analysis to WM. Independent t-tests with age, gender and total brain volume (TBV) as covariates were used to examine group differences and F-constrasts to examine variable effects. Family-wise error was controlled using a random field theory uncorrected p-value threshold of 0.005, cluster threshold of 30 voxels with surviving clusters deemed statistically significant at $p < 0.05$.

Results: Patients demonstrated bilateral reduction in FA relative to controls in the callosal splenium (cluster-level), $p\text{FDR-corr} < 0.026$, posterior cingulum, $p\text{FDR-corr} < 0.007$, lower corticospinal tract, $p\text{FDR-corr} 0.0029$ and cerebellar WM, $p\text{FDR-corr} < 0.007$ with subthreshold clusters in the prefrontal WM $p\text{FDR-corr} < 0.06$ (fig 1). There were no areas in which patients had higher FA compared to controls. Across the study population, FA was significantly related to age, gender and total brain volume. In patients, a higher FA in the posterior limb of the internal capsule and corticospinal tract was correlated with increasing illness duration $p\text{FDR-corr} < 0.026$ (fig 2). There were no significant correlations between lithium status and FA.

Fig.2 Areas of FA increase in BD patients with increasing illness duration overlaid on FA map of population atlas.



interpretation of the results. In addition to the selection of a well characterised and homogeneous clinical population and rigorous data preprocessing, by employing anisotropic smoothing (4) and a sophisticated non-linear registration (3) to a study specific population atlas to minimise registration error, this VBA study was able to include as much of the total WM in the analysis as possible. Further analysis including other diffusion metrics e.g. mean diffusivity, will help to clarify the nature of WM structural alterations in this population.

References: 1. Mahon et al, (2009) *Neurosci Biobehav Rev.* **34**(4): p. 533-54 2. Leemans et al, (2009) *17th Annual Meeting of Intl Soc Mag Reson Med*, p. 3537, Hawaii, USA, 3. Van Hecke, et al. (2007) *IEEE Trans Med Imaging.* **26**(11): p. 1598-612. 4. Van Hecke, et al., (2008) *Neuroimage*, **43**(1): p. 69-80 5. Mahon et al, (2009) *Neuropsychopharmacology*, **34**(6): p590-600

Fig.1 Areas of FA reduction (pink) in BD patients compared to controls overlaid on first eigenvector FA map of population atlas.

