White matter microstructural changes in bipolar disorder: A HARDI CSD tractography study

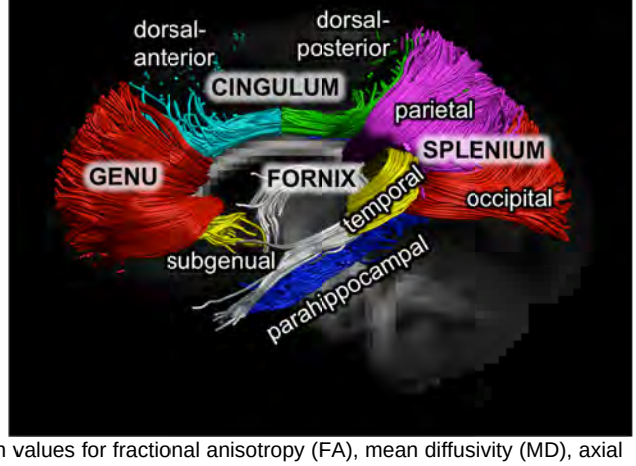
Louise Emsell[1,2], Alexander Leemans[3], Wim Van Hecke[4,5], Camilla Langan[2], Gareth J Barker[6], Peter McCarthy[2], Stefan Sunaert[1], Dara Cannon[2], and Colm McDonald[2]

[1]*Radiology, KU Leuven, Leuven, Belgium,* [2]*NUI Galway, Ireland,* [3]*Image Sciences Institute, UMC Utrecht, Netherlands,* [4]*University Hospital Antwerp, Belgium,* [5]*icoMetrix, Belgium,* [6]*Department of Neuroimaging, King's College London,Institute of Psychiatry, United Kingdom*

Introduction: White matter (WM) changes detected by MRI have been reported in bipolar disorder (BD). However the location, extent and direction of these differences varies considerably between studies (1). Research to date has focused predominantly on small patient populations and has used diffusion tensor imaging (DTI) based analysis, therefore the effect of clinical heterogeneity and the limitations of the tensor model may have contributed to these variable and discrepant findings. In a previous DTI voxel-based analysis, we reported fractional anisotropy reductions and radial diffusivity increases in posterior limbic WM in a large clinically homogeneous sample of remitted bipolar I disorder patients (2). Our present work aimed to clarify the location of these diffusion changes using a high angular resolution diffusion imaging (HARDI) tractography analysis to improve fibre-tracking in regions of crossing-fibres. To increase specificity, we examined anatomically defined segments of the corpus callosum, cingulum bundle and the fornix.

Method: ***Clinical Subjects****:* DTI data were 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 imaging data acquisition***: DWI data was acquired on a 1.5T MRI scanner along 64 independent diffusion gradient directions, b = 1300 s/mm^2, 7 b0 images, TR = 8100ms, TE = 95 ms, FOV=240×240mm², matrix =96 × 96, voxel-size 2.5 mm^3, 60 axial slices. ***Tractography:*** Each dataset was corrected for motion and distortion using ExploreDTI(3) and non-linearally coregistered to a study population atlas (PA)(4). Whole brain tractography was performed on the atlas using a deterministic constrained spherical deconvolution (CSD) approach (5,6). Tract masks of the **cingulum**: *subgenual, dorsal anterior, dorsal posterior* and *parahippocampal* divisions; **corpus callosum**: *genu, parietal, occipital* and *temporal splenium* projections, and bilateral **fornix** were created in atlas space using data driven customised inclusion and exclusion regions based on expert anatomical knowledge (figure 1)(7). In summary, the tract masks were modulated by the track density of each bundle to weight the diffusion metrics towards those voxels most likely to contain reliable portions of the tract in every individual. Median values for fractional anisotropy (FA), mean diffusivity (MD), axial (AD) and radial diffusivity (RD) were then extracted from voxels included in the weighted masks in each subject's PA registered dataset.

Fig. 1 CSD derived tract masks on population atlas FA map



Statistical processing: A global assessment of each tract was obtained using repeated measures ANCOVA models, with hemisphere and tract division as within-subject variables, diagnosis and gender as between-subject fixed factors, and age and total brain volume as covariates. Post hoc MANCOVAs with the same between-subject factors were used to investigate differences in the tract segments between patients and controls. Bonferroni correction for multiple comparisons was applied. Statistical significance was set to p=0.05.

Table 1: (a) Differences in BD and controls across the entirety of each tract, (b) across callosal segments

Tract	FA	MD	AD	RD
Cingulum	F=2.621 p=0.110	F=1.557 p=0.216	F=0.033 p=0.857	F=2.433 p=0.123
Corpus callosum	F=10.56 **p=0.002***	F=7.386 **p=0.008***	F=1.264 p=0.265	F=10.26 **p=0.002***
Fornix	F=3.849 p=0.054	F=5.442 **p=0.022***	F=4.572 **p=0.036***	F=5.588 **p=0.021***

Segment	FA	MD	AD	RD
Genu	F=8.195 **p=0.005***	F=3.406 p=0.069	F=0.049 p=0.825	F=6.073 **p=0.016***
Parietal	F=6.075 **p=0.016***	F=4.826 **p=0.031***	F=0.581 p=0.448	F= 6.572 **p=0.012***
Occipital	F=6.765, **p=0.011***	F=5.285 **p=0.024***	F= 0.625 p=0.432	F=7.566 **p=0.007***
Temporal	F=7.111 **p=0.009***	F=9.174 **p=0.003***	F= 3.084 p=0.083	F=11.57 **p=0.001***

Results: We detected significant FA reductions and increases in diffusivity metrics in patients throughout the corpus callosum (table 1a,b) and fornix (table 1a). Despite the lack of a global finding in the cingulum, we detected significant FA reduction, MD and RD increases in the left subgenual (F=5.964, p=0.017, F=6.508, p=0.013, F=8.736 p=0.004) portion. We also detected decreased FA and increased AD in patients relative to controls in the right, dorsal anterior segment of the cingulum (F=5.161 p=0.026, F=5.161 p=0.026).

Discussion: The detection of diffusion changes in each of these key limbic tracts supports and extends not only our previous VBA results but the emerging view that bipolar disorder is characterised by trait white matter microstructural alterations that may hinder emotional and cognitive regulation. Alterations in the corpus callosum are one of the most consistent findings in BD. We detected FA decrease and increased diffusivity in not only the genu, but in all callosal splenium projections suggesting potential deficits are not localized to the forceps major, but are more widespread. The fornix seldom emerges in DTI studies as partial volume and smoothing make this relatively small bundle difficult to detect. However, using CSD, which seems to be less sensitive to partial volume effects in this region, we were able to track the fornix successfully and found significant diffusivity changes throughout the tract. The majority of previous work has focused on FA changes. We also report consistently more significant radial relative to axial diffusivity increases in patients, suggesting a potentially consistent microstructural paradigm alteration in BD. However, the biological interpretation of changes in the relationships between eigenvalues remains challenging (8). Future work using HARDI and non-Gaussian, rather than DTI, derived measures will provide new insights into the nature of such diffusivity changes in BD.

References: (1) Emsell & McDonald), Int Rev Psychiatry, 2009 (2) Emsell et al, ISMRM, 2010, (3) Leemans et al, ISMRM, 2009, (4) Van Hecke et al, Neuroimage, 2008, (5) Jeurissen et al, Human Brain Mapping, 2011, (6) Tournier et al, Neuroimage, 2007, (7) Verhoeven et al, Human Brain Mapping, 2010, (8) Vos et al, Neuroimage 2011