A DTI tractography study of the cingulum in euthymic bipolar I disorder

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Introduction

Bipolar disorder (BD) is a major psychiatric illness characterised by uncontrollable changes in mood ranging from depression to mania and psychosis. Evidence from the field of structural neuroimaging implicates subtle grey and white matter abnormalities in BD in brain regions involved in affective regulation and executive function [1]. One region that emerges consistently is the cingulate cortex. Although several studies have demonstrated grey matter anomalies in the cingulate cortex in BD, only one study to date has investigated its major white matter tract, the cingulum bundle [2]. To our knowledge, this is the first study to employ DTI tractography to investigate the cingulum in BD in an entirely euthymic cohort of patients in order to identify trait related white matter microstructural abnormalities. Here we present preliminary data from a subset of the Galway Bipolar Study population of 60 BD and pair-wise matched healthy control (HC) subjects.

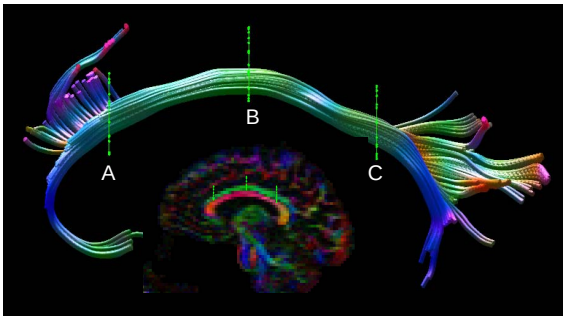
Method

Subjects: DTI data was acquired on 15 euthymic BD type I and 19 HC 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. Ethical approval was obtained from the University College Hospital Galway (UCHG) Clinical Research Ethics Committee. All subjects provided written informed consent

DTI data acquisition: DTI data was acquired on a 1.5T Siemens Magnetom Symphony MRI scanner (Erlangen, Germany), using an EPI diffusion sequence acquired using parallel imaging (GRAPPA, factor 2), 64 independent diffusion gradient directions, b = 1300 s/mm^2, with 7 reference non-diffusion weighted images, TR = 8100ms, TE = 95 ms, FOV=240×240mm², matrix = 96 × 96, in-plane resolution of 2.5mm^2, slice thickness = 2.5 mm, 60 axial slices, scan duration = 10:24 mins.

DTI data analyses: Whole brain tractography was performed using ExploreDTI (www.ExploreDTI.com) utilising a deterministic streamline method [3]. Following DWI data quality assessment and motion distortion correction, the cingulum bundle was extracted using three 'AND' regions-of-interest (ROI) gates (Fig 1). Due to inter-individual differences in the extent of the cingulum tracked and to reduce interference from lower FA frontal projecting fibres, the calculation of FA and ADC was restricted to the dorsal portion of the cingulum between gates A and C. ROIs were defined by a single blinded rater.

Fig1. The position of AND gates along the dorsal cingulum



Gate A was defined by the most posterior slice in which the genu of the corpus callosum (CC) was seen in full profile. Gate B, by the most anterior slice in which the splenium of the CC was seen in full profile. Gate B, the mid-point between gates A and C.

Statistical analyses: Analysis of covariance (ANCOVA) models were used to investigate the influence of diagnosis on the mean (across groups) of the individuals' median FA and ADC values in the left and right cingulum controlling for age and gender. Individuals' median FA and ADC values were used to account for the non-parametric distribution of diffusion parameters within the cingulum. An asymmetry index: *[(2x(Left-Right)/(Right+Left)]x100* was used to compare FA and ADC between hemispheres. Statistical significance was set at $p < 0.05$.

Table 1:Comparison of diffusion metrics in the cingulum bundle between BD and controls

	Mean of the median values (Mean ± SE)	Group differences (F, p)	AI Left –Right (Mean ± SE)	Hemisphere Differences L>R (T.p)	AI Group Differences (T, p)
Fractional Anisotropy					
Control Left Right	 0.50 ± 0.11 0.45 ± 0.10	0.10, 0.76	11.33 ± 1.88	6.01, 1.11x10^{-5}	-0.056, 0.96
Bipolar Left Right	 0.50 ± 0.10 0.45 ± 0.09	0.10, 0.76	11.18 ±1.72	7.10, 5.34x10^{-6}	
Apparent Diffusion Coefficient (10^{-3}mm^2/s)					
Control Left Right	 0.71 ± 0.05 0.71 ± 0.06	0.59, 0.45	-0.25 ± 0.74	-1.27, 0.28	1.23, 0.23
Bipolar Left Right	 0.71 ± 0.04 0.71 ± 0.05	0.22, 0.64	1.03 ± 0.71	0.77, 0.45	

Results: Tractography reliability was determined by blinded re-tracking of bilateral cingulums in 10 subjects (intra-class coefficient >.95). There were no significant group differences in age (p=0.999) or gender (p=0.798). There was no significant difference in the mean median FA or ADC between groups in either the left or the right cingulum (Table 1). There was, however, a significant effect of age on FA in the right cingulum (p=0.01). An inter-hemispheric asymmetry (Left>Right) in FA but not ADC was detected in both groups (Tpaired=8.8; p=3.5x10^{-10}).

Discussion: We detected left-sided laterality in FA of BD and HC groups which may reflect the known morphological asymmetry of the cingulate cortex. However, this preliminary sample size may not have provided the power to detect group based differences in FA or ADC in the cingulum bundle. Nonetheless, the mean FA and ADC are similar across groups. This is consistent with Wang et al [2] who reported no difference between posterior cingulum (including portions of the dorsal cingulum) FA in BD versus controls. However, the latter authors also detected reduced FA in the anterior cingulum of subjects with BD. The cingulum bundle has a complex architecture with many efferent and afferent trajectories joining and leaving the main bundle at different points. This presents challenges to DTI-based fibre tractography due to its inherent limitations in modelling crossing fibres. Taken together these data suggest further refinement of the spatial extent of cingulum regions examined in BD, are warranted. The reduction in FA and increase in ADC with age is consistent with previous studies[4]. Future work will expand the sample size studied, incorporate parcellation of the cingulum into more precisely defined sub-sections, such as rostral and parahippocampal divisions, and explore HARDI based estimations of the diffusion signal as a means to improve the sensitivity of tractography based analyses.

References

[1] Emsell L et al, *Int Rev Psychiatry*, (*in press);* [2] Wang F et al, *Br.J.Psychiatry*,193(2):126-9, 2008;.[3] Basser PJ et al, *Magn Reson Med 44*:625-632, 2000.[4] Mosely,M, NMR Biomed, 15(7-8):553-60, 2002