White matter impairments as an endophenotype of bipolar disorder – A diffusion imaging study of patients with bipolar 1 disorder and their unaffected relatives.

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Background: Bipolar disorder is a common psychiatric condition, diagnosed in 1-2% of the population, and characterized by fluctuating affective states. It is highly hereditary (1), and there is evidence of an overlap in susceptibility genes between bipolar disorder and schizophrenia (2). Early studies assessing white matter pathologies in bipolar disorder found an increased prevalence of white matter hyperintensities, and Diffusion Tensor Imaging (DTI) data have identified reductions in Fractional Anisotropy (FA) in prefrontal (3,4) and thalamo-cortical projections (5). The current study uses whole brain voxel-based analyses of FA, providing evidence of areas of FA reduction that are associated with increasing genetic risk of bipolar disorder.

Methods: **Subjects:** A diffusion weighted scan was acquired on 19 Bipolar (I) Disorder patients, 20 unaffected relatives and 18 healthy comparison volunteers. There were no significant differences seen in age, gender, handedness, years of education or parental social class between the groups.

DTI acquisition: Data were acquired using a GE Signa 1.5T MRI system. Whole brain coverage was achieved with an isotropic image resolution ($2.5mm^3$) using a protocol of 7 non-diffusion images (b=0) followed by 64 images acquired with gradients applied in optimized diffusion directions (6). The acquisition was peripherally gated to the cardiac cycle. Using in house software, image distortions introduced by the diffusion-weighting gradients were corrected, non-brain tissue was removed, and the diffusion tensor was determined at each voxel (7). FA images (8) were then computed, along with the mean of the 7 T2-weighted (b=0) images.

Preprocessing of DTI data: Mapping of the data to standard space was performed in SPM2 (Wellcome Department of Imaging Neuroscience, UCL). A custom FA template was created by normalizing each subject's T2-weighted image to the T2* template in SPM2, with the resulting transformation parameters applied to the corresponding FA images, which were then averaged and smoothed by 8mm FWHM. FA images in native space were then normalized to the custom FA template, with the resulting images smoothed by 4mm FWHM and masked by each subject's white matter segment, constraining the analysis to relevant tissue.

Voxel based statistical analyses: Between group differences of FA were assessed using XBAM v 3.4 (Brain Image Analysis Unit, IoP), by fitting an ANOVA at each intracerebral voxel. A permutation based analysis with a threshold of $p<0.05$ was used to identify voxels showing significant differences, which were then combined to form 3D clusters, described by their cluster mass (9). These were then tested against the null hypothesis of no group difference by permutation at cluster level. The cluster level significance was selected so that the expected number of false positives was less that one per analysis.

Genetic Liability Scale: We modeled the likely variation in the level of genetic risk among subjects using a continuous quantitative measure of genetic liability based on each individual's affection status and the number, affection status, and genetic relatedness of all adult members of each family as far as second degree from the index patient (10). Multiple regression models were then specified to estimate the association between genetic liability and FA variation, using a similar permutation based method as described above. To stop the analysis being driven simply by differences in FA between the bipolar group and relatives, each groups genetic liability score was standardized (z-score) around independent means.

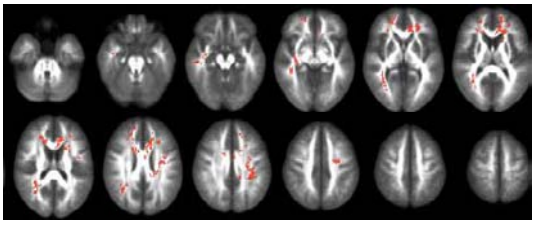

Figure 1. Clusters of decreased FA in bipolar (*I*) disorder

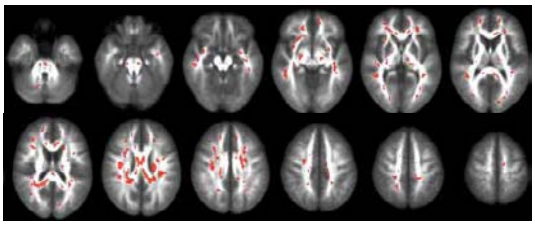

Figure 2. Clusters of decreased FA associated with increased genetic liability to bipolar disorder

Results: **Group Comparisons**: Reductions in FA were found in Bipolar I disorder when compared to the healthy comparison group (Fig. 1). Three clusters were identified - a bilateral frontal cluster, that extended to include the genu of the corpus callosum and a portion of the internal capsule; a right temporal cluster which incorporated inferior temporal regions and extended towards the occipital lobe; and a superior frontal cluster, that incorporated white matter in the insula. There were no clusters of increased FA detected in the bipolar and control comparison. The group comparison of the unaffected relatives of the bipolar disorder patients compared to the healthy comparison group did not find any clusters of significant FA differences. However a significant linear relationship was observed between the three groups($R^2=0.298$, $p<0.01$) when FA values were extracted from these clusters.

Correlation to genetic liability scale: Genetic risk to bipolar I disorder was associated with distributed FA reductions along many of the major white matter pathways. Reduced FA associated with increased genetic risk to bipolar disorder was identified in - small clusters in the cerebellum and brainstem; bilaterally in temporal lobe regions, most likely corresponding to the inferior longitudinal fasciculus and uncinate; in bilateral frontal regions, corresponding to the anterior regions of the frontal-occipital fasciculus, genu of the corpus callosum, and the right external capsule; in posterior brian regions including bilateral portions of the inferior frontal-occipital and inferior longitudinal fasciculi; splenium of the corpus callosum; and in superior brain regions, corresponding to the superior-longitudinal fasciculus and corona radiata.

The FA value was extracted from each of the clusters in this correlational analysis, and a weighted mean was calculated for each subject with respect to the volume of the cluster. The average value of these clusters was then plotted against the standardized genetic liability scale (Figure 3.). There was a significant negative correlation ($p<0.001$) between FA and genetic liability in both the patient ($R^2=0.733$) and relative groups ($R^2=0.423$).

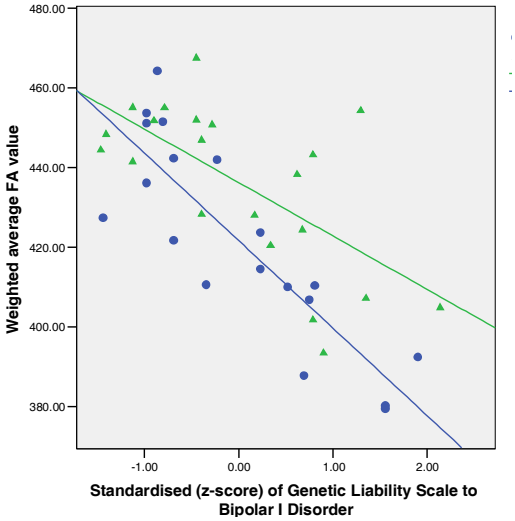

Figure 3. FA of clusters negatively correlated to genetic liability plotted against the z-score of this scale.

Conclusions: Bipolar disorder is associated with widespread differences in FA which are related to the genetic liability to the disorder. All patients with bipolar disorder had a history of psychosis in illness exacerbation, and therefore this data raises the question whether the FA reductions are related to the instability of mood or the association with psychosis. Candidate genes affecting neuronal migration, oligodendrocyte function, and myelination should be considered as potential risk factors for the development of bipolar disorder and their effects in future imaging studies should be assessed.

References: (1) **Cardno** et al, (2002) Am J Psychiatry. 159: 539-45. Craddock et al (2006) Schiz Bull. 32: 9-16. (3) **Adler** et al, (2004), Bipolar Disord. 6: 197-203. (4) **Adler** et al (2006), Am J Psychiatry. 163: 322-4. (5) **Haznedar** et al (2005), Biol Psychiatry. 57: 733-42. (6) **Jones** et al (2002), Hum Brain Map. 15: 216-30. (7) **Basser** et al. (1994), J Magn Reson B. 103: 247-54. (8) **Peirpaoli** and Basser (1996), Magn Reson Med. 36: 893-906. (9) **Bullmore** et al (1999), IEEE Trans Med Imag. 18: 32-42. (10) **Mcdonald** et al (2004), Arch Gen Psychiatry. 61: 974-84.