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# Shared White Matter Dysconnectivity in Schizophrenia and Bipolar Disorder with Psychosis

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Kraepelin; bipolar disorder; psychosis; dysconnectivity; diffusion tensor imaging; schizophrenia

## Introduction

The neurobiological continuum linking the two psychotic illnesses – schizophrenia and bipolar disorder - is elusive despite two decades of rapid advance in neuroscientific methods (Keshavan *et al*. 2011; Kaur *et al*. 2012). In the past, neuroimaging studies have mostly focused on trying to differentiate between schizophrenia spectrum and bipolar disorder, by aiming to identify disease-specific mechanisms in each of these disorders (Curtis *et al*. 2001; Whalley *et al*. 2009; Costafreda *et al*. 2009; Hall *et al*. 2010). Current evidence suggests that these two disorders share a significant overlap in genetic susceptibility (Craddock *et al.* 2005; Berrettini, 2011), pharmacological treatment responses (Murray *et al*. 2004), neuropsychological deficits (Hill *et al*. 2009), and epidemiological features and hence possibly a common pathophysiology, thereby challenging the so called Kraepelinian dichotomy (Kraepelin, 1919). In light of this, an emphasis on identifying the similarities and shared neural mechanisms between these two illnesses could aid the understanding of the pathophysiological basis of the clinical continuum of psychosis.

Along with functional imaging and grey matter alterations, studying changes in the white matter microstructure have provided valuable insights into the possible pathophysiology or course of these disorders. White matter abnormalities, observed using Diffusion Tensor Imaging (DTI) suggesting altered connectivity have been consistently reported in both bipolar disorder (Chan *et al*. 2010; Heng *et al*. 2010; Benedetti *et al*. 2011; Benedetti *et al*.

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2011) and schizophrenia (Chan *et al*. 2010; Kunimatsu *et al*. 2012; Mandl *et al*. 2013; Levitt *et al*. 2012). However, the literature on DTI-based direct comparison between schizophrenia and bipolar disorder is scarce. Four studies exist (McIntosh *et al*. 2008; Sussman *et al*. 2009; Lu *et al*. 2011; Cui *et al*. 2011) but have examined samples that differ in important respects. Two studies did not exclude patients without psychosis (McIntosh *et al.* 2008; Sussmann *et al*. 2009). The other two studies (Lu *et al*. 2011; Cui *et al.* 2011) have examined patients with first episode psychosis and hence might be biased against observing a dichotomy as the chronic time course that was a key feature of Kraepelin's concept of dementia praecox is less clearly discernible during the first episode.

The majority of DTI studies employ the measure of Fractional Anisotropy (FA) to study WM integrity. Though FA is a sensitive index of white matter microstructure, the neuronal interpretation of this measure is limited due to its composite nature. Pathological changes in FA can occur due to either axonal damage or myelin degradation and in order to decipher their relative contributions to FA change, along with calculating FA, it is necessary to also derive measures of Axial (AD) and Radial Diffusivity (RD) (Alexander *et al*. 2007; Seal *et al.* 2008). Secondly, FA alone cannot provide enough information about the microstructural architecture of the WM tracts. A newly developed tensor index called Mode of Anisotropy (MoA) can detect the predominance of crossing-fibre orientation in the white matter, thereby allowing for a more meaningful interpretation of FA results (Ennis & Kindmann, 2006; Jolapara *et al*. 2009). Although these indices have been employed in a number of recent DTI studies, a comprehensive analysis using multiple indices of WM integrity to identify the neural basis of psychotic continuum has not been reported yet.

Thus, to address these issues, we studied a sample representative of the two 'poles' of the 'Kraepelinian axis', with a focus on localizing brain regions which share altered white matter connectivity across the psychotic disorders. Such abnormalities, if identified, would represent the structural underpinnings of the putative Kraepelinian axis itself, rather than the correlates of one of the two poles of this axis. We aimed to delineate the WM abnormalities that are common to both poles of the axis initially by undertaking an exhaustive search for FA changes in the entire patient group when compared to non-psychotic healthy controls, followed by a comprehensive measurement of AD, RD and MoA in the regions showing a shared WM dysconnectivity. A prominent feature of Kraepelin's concept of dementia praecox was poor outcome (Heckers, 2008). Nonetheless, while outcome is generally better in bipolar disorder, the evidence indicates a continuum of symptomatic, cognitive and functional outcome (Johnstone *et al*. 1992). This suggests that the pathological process common to both disorders might be more strongly expressed in schizophrenia but nonetheless associated with indices of poor outcome across the spectrum psychotic disorders. We there predict that the severity of WM dysconnectivity would be related to the functional ability and persistent symptom burden in individuals with psychosis.

## Methods

### Participants

Patients undergoing treatment for psychotic disorders were referred by the Early Intervention in Psychosis teams and other community-based mental healthcare teams in

Nottinghamshire and Leicestershire, England. Upon referral clinical information was collected using retrospective review of case notes, discussion with referring clinicians and a video-recorded clinical interview using standardized symptom assessment procedure (Signs and Symptoms in Psychotic Illness Scale – SSPI) (Liddle *et al*. 2002). The clinical diagnosis was made in a consensus meeting in accordance with the best estimate procedure described by Leckman et al. (Leckman *et al*. 1982). Patients aged 18 to 50 years satisfying the DSM IV criteria for schizophrenia or schizoaffective disorder (SCZ), or bipolar disorder with psychotic features (BPP) were included in the study, provided they satisfied the following inclusion criteria: 1) IQ of at least 65 assessed using the Quick Test (Ammons & Ammons, 1962), 2) No lifetime history of substance dependence or harmful use in the past 6 months, 3) No history of significant head trauma or medical conditions likely to have appreciable neurological or psychiatric effects 4) No contraindications for MRI safety assessed by a standardized safety screening questionnaire.

All patients were in a stable phase of illness, defined as a change of no more than 10 points in their 'Global Assessment of Function' (GAF) (GAF, DSM-IV) (APA, 1994) score between assessment 6 weeks prior to and immediately prior to study participation. 55 out of 64 patients were receiving psychotropic medications. The median Defined Daily Dose (WHO-CCDSM, 2003) was calculated separately for antipsychotics, mood stabilizers including lithium and antidepressants and no patient had a change in any of these medications six weeks prior to participating in this study.

Healthy controls were recruited from the local community via advertisements and participants were recruited and group-matched to the patient group for age and parental socio-economic status (Rose & Pevalin, 2003). Controls satisfied the same inclusion and exclusion criteria as the patients, as specified above, and in addition did not have a personal or family history of psychotic disorders. A clinical interview by a research psychiatrist was employed to ensure that the controls were free from current axis 1 disorder and a history of either psychotic illness or neurological disorder. Handedness was assessed for both patients and healthy controls using the 12-items Annett scale (Annett, 1970). Social and occupational functioning in patients was evaluated using the SOFAS - Social and Occupational Functioning Assessment Scale (SOFAS - DSM IV) (APA, 1994). The clinical and demographic features of the sample are presented in Table 1.

The issue of appropriate matching to minimise risk of group differences in brain development unrelated to the pathophysiology of schizophrenia remains a subject of debate. There is consistent evidence that moderate lowering of IQ is related to the pathophysiology of schizophrenia and in particular, current IQ is influenced by factors such as age at onset of the disease, illness duration, severity of symptoms (Aylward *et al*. 1984; Woodberry *et al.* 2008). Therefore we did not match for IQ. Nonetheless, to avoid inclusion of cases with IQ deficits greater than those typically observed in schizophrenia, we excluded individuals with a proxy estimate of current IQ lower than 65, as measured by the Quick Test.

We used parental socio-economic status as a matching variable in this study. Parental occupational status might be expected to predict brain development (Noble *et al.* 2005; Farah *et al*. 2006). Although there is evidence that parental occupational status is at last

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weakly predictive of risk of schizophrenia or of severity of illness, the evidence is ambiguous (Parrott & Lewine, 2005). We therefore consider that matching groups for parental occupational status is the most appropriate way to minimise risk of group differences in brain development that are not directly related to the pathophysiology of schizophrenia.

The original sample consisted of 37 patients with schizophrenia, 6 with schizoaffective disorder, 22 patients with bipolar disorder and 41 controls, but 2 subjects with schizophrenia were excluded due to movement artefacts in the DTI scans, while 1 subject with schizophrenia did not complete the DTI acquisition protocol as planned, providing a final sample of 103 subjects (34 with schizophrenia, 6 with schizoaffective disorder, 22 with bipolar disorder and 41 controls). Functional connectivity findings from this sample have already been reported (Palaniyappan & Liddle, 2014).

Due to the small number of subjects with schizoaffective disorder, this group was included with schizophrenia group for further analysis; when undertaking direct comparison between BPP and SCZ, we conducted sensitivity analysis by excluding the schizoaffective patients from SCZ. The study was approved by the National Research Ethics Committee, Derbyshire, UK. Written informed consent was obtained from all study participants in accord with the procedure approved by the Ethics Committee.

## Image Acquisition

All scans were conducted at Sir Peter Mansfield Magnetic Resonance Centre, University of Nottingham using 3T Philips Achieva MR Scanner ({Philips Medical Systems, Best, The Netherlands). Diffusion-weighted images were acquired using a single-shot, spin-echo, echo planar imaging (EPI) sequence in alignment with the anterior commissure - posterior commissure (AC-PC) plane. The acquisition parameters were as follows: Repetition Time (TR) = 8.63 s, Echo Time (TE) = 56.9 ms, voxel size = 2mm isotropic, 112 × 112 matrix, Field of View (FoV) = 224 × 224 × 104, flip angle = 90°, 52 slices, 32 directions with a b-factor of 1000s/mm$^2$, EPI Factor = 59, total scan time = 6.29 min. Scans were inspected immediately after each acquisition, and if motion was detected, scans were repeated.

## Data Pre-processing

Diffusion weighted data were converted from DICOM in order to analyze images. FSL (FMRIB) was used for all data pre-processing and analysis (www.fmrib.ox.ac.uk/fsl). FSL's Diffusion Toolbox (FDT) was used in order to correct for head motion and eddy current distortions (Behrens *et al*. 2003). In order to remove non-brain voxels, the Brain Extraction Tool (BET) was used to create a binary mask from the non-diffusion weighted data (Smith, 2002). Diffusion tensor and associated parameters such as Fractional Anisotropy, Axial and Radial Diffusivity and Mode were then calculated by applying a single tensor model using the DTIFIT tool in FSL. In preparation for tractography, the data was also run through the program BEDPOSTX to build probability distributions on diffusion parameters and model for crossing fibres at each voxel (Behrens *et al*. 2007).

FA ranges from 0 to 1, where 0 indicates regions with isotropic diffusion and 1 indicates perfect linear diffusion that is expected along the WM fibers. Radial diffusivity is considered to represent the integrity of myelin while axial diffusivity is considered to represent axonal integrity. MoA varies from −1 to +1, with values closer to −1 indicate regions where high number of crossing fibers can be expected and +1 indicate regions where one fiber orientation predominates (Douaud *et al*. 2011). Lower MoA values observed within a specific WM region in group comparisons may indicate that the underlying architecture of the WM fibers in this region may be 'disorganised' in one group compared to the other.

### Tract-Based Spatial Statistics

Tract-Based Spatial Statistics (TBSS) (Smith *et al*. 2006) was used in order to analyze the DTI data. First, the FA data were pre-processed in order to remove likely outliers from the diffusion tensor fitting. Non-linear transformation and affine registration was then performed in order to align all FA images to a standard space (Andersson *et al*. 2007; Andersson *et al*. 2007). Following registration, the mean FA image and skeleton which represents the centres of all tracts common to the group were created. The mean FA skeleton was then thresholded at 0.2, after which each subject's aligned FA data was projected onto this skeleton, allowing for further voxelwise statistical analysis. A similar approach for transformation and registration followed by projection on to the TBSS skeleton was applied for the AD, RD and MoA images.

### Statistical Analysis

Voxelwise statistical analysis were conducted using TBSS, in order to compare whole brain group level differences in FA between the two groups – all patients with psychosis (PSY) and healthy controls (HC). A t-test was used for the comparison with age and gender as covariates. A Threshold-Free Cluster Enhancement (TFCE) approach was adopted with 10,000 permutations to correct for multiple comparisons without having to specify an initial cluster-forming threshold, with equal weighting for the peak height and extent of clusters (Smith *et al*. 2006). We also used this statistical design to directly compare the two diagnostic groups: SCZ and BPP. We repeated this comparison initially by excluding the 6 subjects with schizoaffective disorder from the SCZ group, and then by including these 6 subjects in the BPP group.

Clusters surviving TFCE corrected $p$=0.05 from PSY vs. HC comparison were used to obtain individual binary masks to extract cluster specific mean FA, RD, AD and MoA values for each subject. FA, RD, AD and MoA from the clusters were compared using separate ANOVAs with diagnosis (HC, SCZ or BPP) as the independent variable and age and gender as covariates. Holm-Sidak corrected follow-up t-tests were applied to detect differences among the three diagnostic groups (Sidak, 1967). Multiple regression analyses used to predict symptom scores, number of episodes and functional outcome measured using SOFAS is described in the Results section below.

We used probabilistic tractography to visualise the connectivity of clusters showing significant group differences. The maxima of clusters surviving TFCE correction for the

PSY vs. HC comparison in the TBSS analysis of FA were used to generate 3-mm radius spherical seed regions of interest (ROI). Probabilistic tractography (seed to rest of the brain) was carried out for each ROI using the FSL's PROBTRACKX2 tool (5000 samples from each seed voxel; step length = 0.5 mm; curvature threshold = 0.2). The resulting connectivity maps were thresholded at 10% of the total generated tracts to remove voxels that showed extremely low connectivity, and to retain the major white matter pathway passing through the seed regions. Each subject's FA map was transformed to standard space using the FMRIB Non-Linear Image Registration Tool (FNIRT).

## Results

### TBSS Voxelwise Statistical Analysis – Group Differences

Patients with psychosis had 5 significant clusters with reduced FA compared to controls. Clusters were located at diverse locations embracing longitudinal and interhemispheric tracts. These results are presented in Table 2 and Figure 1. In all of these regions both SCZ and BPP had reduced FA when compared with controls, with BPP vs. HC comparisons reaching statistical significance at clusters A, B and D (corrected $p<0.05$), and showing a trend towards significance in clusters C and E (corrected $p=0.06$). FA reduction was accompanied by an increase in RD and a reduction in MoA in both patient groups, but reaching statistical significance only in patients with schizophrenia. However, inspection of the values for FA in each diagnostic group at the local maxima within each of the 5 clusters reveals no consistent trend for the abnormalities to be greater in SCZ, indicating that the greater statistical significance in the contrast of SCZ with HC compared with the contrast of BPP with HC is due to the greater statistical power in the larger sample of SCZ. The spread of FA values in the three groups is shown in Figure 2.

We did not find any brain regions showing statistically significant differences in FA when directly comparing SCZ and BPP. Even when the significance threshold was lowered to $p=0.15$, we did not observe differences between the two groups. The inclusion of schizoaffective patients in either SCZ or BPP did not alter this null observation.

**WM Integrity Factor—**In the PSY group, FA, AD, RD and MoA values for the clusters were all correlated with each other (mean absolute Pearson's correlation value $|r| = 0.33$); this allowed us to extract a general principal component that explained 36.2% of the variance in the WM integrity measures across the clusters using unrotated Principal Component Analysis (Table 3). This component loaded positively on all the FA values of all clusters, and negatively on the RD values; thus the factor scores of this component represented the shared WM integrity across all patients. Patients with higher scores on this factor had intact WM structural integrity characterised by higher FA, MoA, AD and lower RD. This distribution of this factor was not different between SCZ and BPP ($t=0.13$, $p=0.9$). 6 separate multiple regression analyses were conducted to predict the SSPI scores of Reality Distortion, Disorganisation, Psychomotor Poverty, Anxiety/Depression, Psychomotor Excitation and the SOFAS scores and number of episodes in the PSY group, using the shared WM integrity factor and diagnostic status (SCZ and BPP) as predictors and age, gender and the combined daily dose of psychotropics (antipsychotics/mood stabilisers or

antidepressants) as covariates. All variables (predictors and covariates) were entered in a single step in the regression analyses after ruling out multicollinearity among predictors using Statisstical Package for Social Sciences (version 21) . The results of this analysis are presented in Table 4. WM integrity predicted SOFAS but not the number of episodes or symptom scores. Reality Distortion, Psychomotor Poverty and Excitation were predicted by diagnostic classification (for both symptoms, SCZ > BPP), but not by WM integrity.

No correlation was noted between the WM integrity factor and DDD of antipsychotics, mood-stabilisers and antidepressants (p values ranging from 0.2-0.8).

## Discussion

Using microstructural indices derived from DTI, we have shown that reduced integrity in callosal, fronto-occipital and paralimbic WM, as indexed by FA, is a feature of psychosis, irrespective of the categorical diagnostic boundaries. This abnormality is specifically associated with an increase in radial diffusivity and reduction in the mode of anisotropy, suggesting defects in myelination along with a degree of ‘disorganisation’ in the underlying fibre structure in patients with psychosis.

The distribution of the WM factor scores that explain higher FA (and less RD) predicted the interindividual differences in the functional measure SOFAS after taking into account the variance explained by categorical diagnosis, age, gender and medication use. In other words, the degree of aberration in a neurobiological measure associated with the presence of psychosis relates to the degree of functional impairment that results from the illness.

We did not find any relationship between the WM factor and symptom clusters of Reality Distortion, Psychomotor poverty, Disorganisation, Anxiety/Depression or Excitation. This observation is consistent with the similar severity of the white matter abnormality in the two patient groups that differ in symptoms. On the other hand, the white matter abnormality was correlated with severity of occupational and social dysfunction demonstrating a relationship with clinical features present in both disorders. Nevertheless, it is important to note that our sample consisted of clinically stable patients in a medicated state. As a result, the degree of inter-individual variation in the severity of symptoms assessed on the day of the scan was modest.

No differences were observed in FA between SCZ and BPP, even at a lenient threshold. This observation is in agreement with previous reports of lack of differences in FA in both TBSS and tractographic studies (McIntosh *et al*. 2008; Sussman *et al*. 2009). In contrast, Lu *et al.* detected differences in FA between the two diagnostic groups in a first episode sample (Lu *et al*. 2011). In contrast to the TBSS approach used in our study, Lu *et al.* employed a voxel-based analysis which is more sensitive for changes in peripheral white matter, but is associated with reduced spatial (tract-to-tract) correspondence (Zalesky, 2011).

These results are also consistent with findings reported in some fMRI studies (Palaniyappan & Liddle, 2014; Argyelan *et al*. 2014; Brandt *et al*. 2014), which show that neural deficits in schizophrenia and bipolar disorder lie on a continuum, though in general abnormalities are more marked or more widespread in schizophrenia. However, other studies report more

distinct, abnormalities in schizophrenia compared to bipolar disorder (Curtis *et al*. 2001; Costafreda *et al*. 2009; Whalley *et al*. 2009; Hall *et al*. 2010). It is likely that there are some brain features that do differ between the two disorders, though it should be noted that the finding of excessive activation of frontal cortex during task performance in bipolar disorder (e.g. Curtis *et al.* 2001; Costafreda *et al.* 2009) in contrast to underactivity often reported in schizophrenia does not exclude a continuum. Much evidence indicates that mild or moderate cortical inefficiency is associated with increased activation whereas severe disorder is associated with underactivity (Liddle *et al.* 2012).

A specific strength of this study is the use of MoA, which allowed us to meaningfully interpret FA changes in regions with predominant crossing fibres. Furthermore, the use of a TBSS approach has certain advantages. TBSS allows for microstructural evaluation of white matter tracts, while effectively dealing with alignment inaccuracies and spatial smoothing, which are issues common with VBM-based methods.

Several limitations must be considered while interpreting these findings. This study has a relatively small sample size, particularly for the bipolar group, and it is possible that significant differences between the two diagnostic groups might be detected with larger samples. Nonetheless, such results would not exclude a continuum in which the disorder might be more severe in schizophrenia. Most patients were medicated, with the majority of SCZ patients taking antipsychotics and many BPP patients taking mood stabilizers. A number of studies have shown an effect of prescribed psychotropics on white matter in the brain (Brambilla *et al*. 2009). For instance, some studies have shown a normalizing effect of lithium on FA values, with higher FA values observed in bipolar patients taking lithium as opposed to those on other medication (Hafeman *et al*. 2012). However, in our sample, we did not find any significant correlations between antipsychotic DDD or mood stabilizer DDD and white matter indices. Despite this, we cannot completely exclude the effect of prescribed medications on the current observations. Fewer females were included in the study compared to males, and hence all statistical procedures were undertaken by using gender as a covariate. Nevertheless, caution must be exercised when generalising these results to mixed samples.

Additionally, we acknowledge the possibility that the shared reduced white matter integrity found in patients with schizophrenia and bipolar disorder in our sample is a feature of psychiatric illness in general and not psychosis in particular as we did not include non-psychotic bipolar patients in our study. Furthermore, another study has shown no relationship between FA and values and lifetime history of psychotic symptoms in bipolar patients (McIntosh *et al*. 2008) and similar results have been found in a largely overlapping sample (Sussmann *et al.* 2009).

To conclude, similar white matter connectivity abnormalities in callosal, paralimbic and fronto-occipital regions are observed across the spectrum of psychotic illnesses. This shared dysconnectivity predicts functional outcome in psychosis, better than the clinical diagnostic boundary. Poor outcome is seen as the central feature of Kraepelin's conception of dementia praecox (Heckers, 2008). While conventional diagnostic descriptions have failed to capture Kraepelin's concept in a convincing fashion, augmenting this clinical information with

neurobiological observations such as the one reported here brings new hopes for making progress in understanding psychosis.

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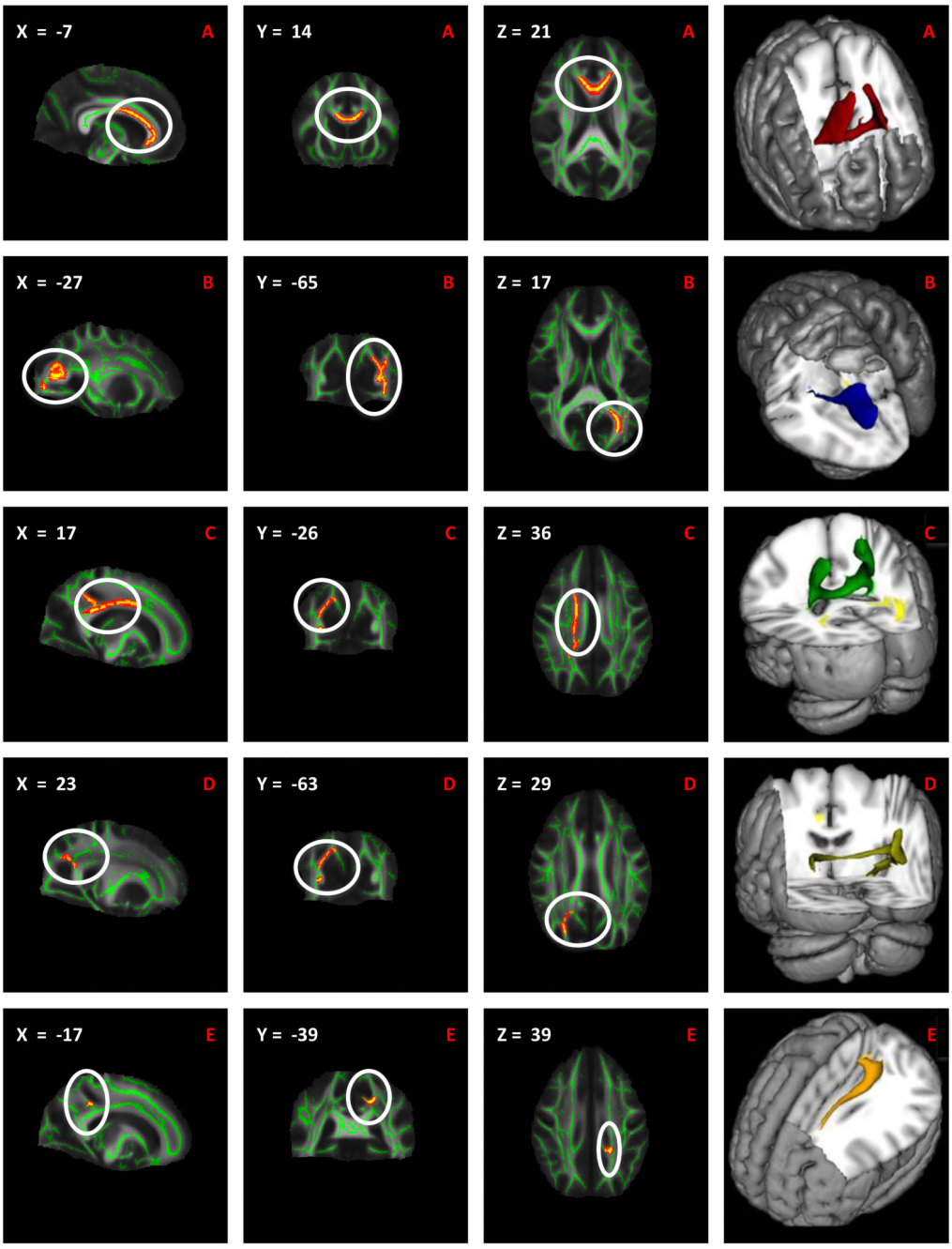


**Figure 1.**

Clusters from the voxelwise analysis showing significant reduction in FA in psychotic patients (PSY) (n = 62) compared to healthy controls (HC) (n = 41). Results are shown overlaid on the mean FA image with the mean FA skeleton in green, using the COG co-ordinates, TFCE corrected $p < 0.05$ and have been thickened using the tbss_fill script in FSL. Left-right orientation is in accordance with radiological convention. Figures in right column shows 3D visualisation of tracts generated from probabilistic tractography overlaid

on a standard MNI brain. For visualisation purposes, tracts displayed are those present in at least half of the subjects.



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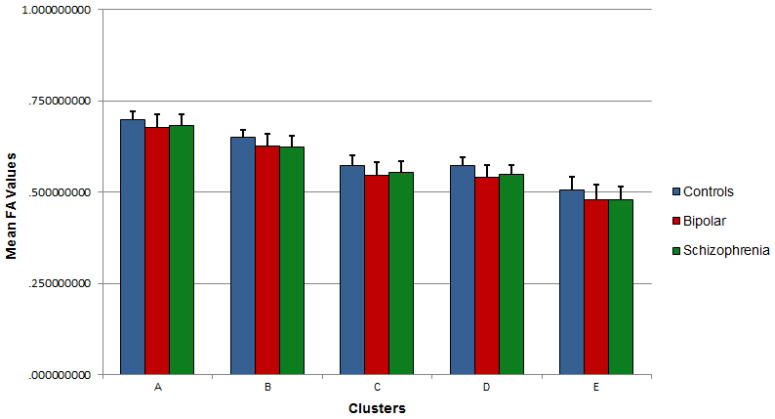


**Figure 2.**

Mean FA values for the 5 clusters obtained from the TBSS analysis for each of the 3 groups – healthy controls (HC), schizophrenia (SCZ) and bipolar disorder (BPP). Error bars represent standard deviation (SD) values.



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## Table 1

### Clinical and Demographic Features

| Features | Patients (N = 62) | | Controls (N = 41) Mean/N (SD) |
|---|---|---|---|
| | SCZ (N = 40) Mean/N (SD) | BPP (N = 22) Mean/N (SD) | |
| Gender (Male/Female) | 30/10 | 15/7 | 30/11 |
| Handedness (R/L) | 35/5 | 19/3 | 37/4 |
| Age | 33.5 (9.02) | 34.72 (10.51) | 33.24 (9.04) |
| Parental NS-SEC | 2.47 (1.50) | 1.70 (1.17) | 1.97 (1.29) |
| Quick Test (IQ) | 95.76 (13.48) | 102.80 (14.59) | 105.78(11.72) |
| Mean Illness Duration (Years) | 9.92 (7.57) | 10.68 (8.35) | - |
| Number of Episodes | 2.36 (1.51) | 3.40 (1.69) | - |
| DDD Antipsychotics | 1.29 (1.09) | 0.47 (0.59) | - |
| DDD Mood Stabilizers | 0.06 (0.24) | 0.91 (0.63) | - |
| DDD Antidepressants | 0.32 (0.66) | 0.07 (0.32) | - |
| DDD (all psychotropics) | 1.67 (1.33) | 1.46 (0.97) | - |
| SOFAS Score | 53.75 (12.32) | 61.04 (13.14) | - |
| Reality Distortion | 2.50 (2.62) | 0.57 (1.46) | - |
| Psychomotor Poverty | 2.80 (3.48) | 0.42 (1.20) | - |
| Disorganization | 1.57 (1.87) | 1.14 (1.98) | - |
| Anxiety/Depression | 2.05 (1.99) | 1.23 (1.48) | - |
| Psychomotor Excitation | 1.15 (1.33) | 3.23 (3.44) | - |
| SSPI Total Score | 11.5 (7.53) | 8.57 (8.12) | - |

NS-SEC: National Statistics Socio-Economic Classification; SSPI: Signs and Symptoms of Psychotic Illness; DDD: Defined Daily Dose; SOFAS: Social and Occupational Functioning Assessment Scale.

## Table 2
### Regions showing FA reduction in patients with psychosis

| Index | | A | B | C | D | E |
|---|---|---|---|---|---|---|
| **MNI co-ordinates of COG in x, y, z** | | **−7, 14, 21** | **−27, −65, 17** | **17, −26, 36** | **23, −63, 29** | **−17, −39, 39** |
| **WM tract labels** [a] | | **Body of the Corpus Callosum** | **Left Posterior Thalamic (optic) Radiation, Forceps Major** | **Body of the Corpus Callosum** | **Right Inferior Fronto-occipital Fasciculus** | **Left Cingulate Gyrus Corona Radiata** |
| **Cluster Extent** | | **3212** | **1585** | **1428** | **822** | **110** |
| **FA** | Mean (SD) CTRLS | 0.697 (0.025) | 0.649 (0.025) | 0.572 (0.032) | 0.574 (0.025) | 0.506 (0.038) |
| | Mean (SD) SCZ | 0.682 (0.025) | 0.624 (0.025) | 0.555 (0.032) | 0.548 (0.025) | 0.479 (0.038) |
| | Mean (SD) BPP | 0.679 (0.028) | 0.627 (0.028) | 0.548 (0.028) | 0.542 (0.023) | 0.481 (0.038) |
| | Diagnosis | F = 6.903 * | F = 15.970 * | F = 5.614 * | F = 10.930 * | F = 4.649 * |
| **AD** | Mean (SD) CTRLS | 0.150 (0.006) | 0.143 (0.006) | 0.128 (0.006) | 0.129 (0.006) | 0.117 (0.006) |
| | Mean (SD) SCZ | 0.151 (0.006) | 0.141 (0.006) | 0.129 (0.006) | 0.126 (0.006) | 0.118 (0.006) |
| | Mean (SD) BPP | 0.151 (0.004) | 0.141 (0.004) | 0.129 (0.004) | 0.126 (0.004) | 0.118 (0.004) |
| | Diagnosis | F = 0.231 | F = 1.800 | F = 0.773 | F = 2.900 | F = 0.474 |
| **RD** | Mean (SD) CTRLS | 0.380 (0.006) | 0.420 (0.006) | 0.460 (0.006) | 0.460 (0.006) | 0.500 (0.006) |
| | Mean (SD) SCZ | 0.410 (0.006) | 0.460 (0.006) | 0.500 (0.006) | 0.500 (0.006) | 0.540 (0.006) |
| | Mean (SD) BPP | 0.400 (0.004) | 0.440 (0.004) | 0.490 (0.004) | 0.490 (0.004) | 0.530 (0.004) |
| | Diagnosis | F = 6.070 * | F = 6.887 * | F = 4.667 * | F = 4.373 * | F = 3.165 * |
| **MoA** | Mean (SD) CTRLS | 0.885 (0.032) | 0.728 (0.051) | 0.685 (0.064) | 0.594 (0.077) | 0.559 (0.115) |
| | Mean (SD) SCZ | 0.870 (0.031) | 0.685 (0.050) | 0.648 (0.063) | 0.540 (0.076) | 0.495 (0.113) |
| | Mean (SD) BPP | 0.873 (0.032) | 0.708 (0.051) | 0.646 (0.061) | 0.539 (0.075) | 0.530 (0.117) |
| | Diagnosis | F = 3.235 * | F = 6.691 * | F = 4.644 * | F = 7.050 * | F = 2.277 |

All clusters survived FWE corrected p value <0.05.

[a] White matter labels are provided in accordance with JHU White Matter Tractography Atlas and the ICBM DTI-81 White Matter Labels Atlas (Mori *et al.* 2005). Only tracts with >5% probability are included in the labels.

* Denotes p<0.05 for F tests.

## Table 3

**Factor loading on the principal component (first unrotated factor) relating to WM integrity in patients with psychosis (PSY)**

| Variables | Factor loading | Interpretation of the principal factor based on major components (variables with loading >0.4) |
|---|---|---|
| ***WM integrity (36.2% of variance)*** | | Higher factor scores seen in patients with more anisotropic diffusion (higher FA), more prominent single fiber orientation (higher MoA), and uncompromised myelin integrity (lower RD). |
| FA Cluster A | +0.75 | |
| FA Cluster B | +0.79 | |
| FA Cluster C | +0.73 | |
| FA Cluster D | +0.80 | |
| FA Cluster E | +0.59 | |
| RD Cluster A | −0.83 | |
| RD Cluster B | −0.80 | |
| RD Cluster C | −0.84 | |
| RD Cluster D | −0.84 | |
| RD Cluster E | −0.82 | |
| AD Cluster A | −0.12 | |
| AD Cluster B | +0.34 | |
| AD Cluster C | −0.10 | |
| AD Cluster D | +0.33 | |
| AD Cluster E | −0.10 | |
| MoA Cluster A | +0.43 | |
| MoA Cluster B | +0.46 | |
| MoA Cluster C | +0.37 | |
| MoA Cluster D | +0.48 | |
| MoA Cluster E | +0.33 | |

FA: Fractional Anisotropy, RD: Radial Diffusion, AD: Axial Diffusion, MoA: Mode of Anisotropy.

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## Table 4

**Multivariate analysis predicting functional status (SOFAS), SSPI syndrome scores and number of episodes in patients with psychosis**

| | | Independent Variables | | | | |
|---|---|---|---|---|---|---|
| | | **WM Integrity** | **Diagnosis (BPP = 0, SCZ =1 )** | **Age** | **Gender** | **DDD Psychotropics** |
| **Dependent Variables** | **SOFAS score** **$R^2$=0.25** β (p value) | **0.31(0.02)** | **−0.25(0.04)** | 0.02 (0.89) | **0.34(0.01)** | −0.07(0.93) |
| | **Reality Distortion** **$R^2$=0.18** β (p value) | −0.08(0.56) | **0.29(0.03)** | −0.12(0.41) | −0.05(0.69) | 0.19 (0.15) |
| | **Disorganization** **$R^2$=0.05** β (p value) | −0.11(0.45) | 0.01(0.97) | −0.08(0.58) | −0.19(0.18) | −0.08(0.59) |
| | **Psychomotor Poverty** **$R^2$=0.20** β (p value) | −0.25(0.08) | **0.32(0.02)** | −0.19(0.18) | −0.11(0.39) | −0.07(0.62) |
| | **Anxiety/Depression** **$R^2$= 0.14** β (p value) | −0.26(0.06) | 0.13(0.32) | −0.22(0.13) | −0.18(0.89) | 0.22(0.10) |
| | **Psychomotor Excitation** **$R^2$= 0.27** β (p value) | −0.13(0.30) | **−0.49(0.0001)** | **−0.26(0.05)** | −0.12(0.32) | 0.07(0.54) |
| | **Number of Episodes** **$R^2$= 0.29** β (p value) | −0.12(0.36) | −0.11(0.35) | **0.41(0.003)** | 0.17 (0.15) | −0.05(0.68) |