

Microstructural white matter changes are correlated with the stage of psychiatric illness

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Microstructural white matter changes have been reported in the brains of patients across a range of psychiatric disorders. Evidence now demonstrates significant overlap in these regions in patients with affective and psychotic disorders, thus raising the possibility that these conditions share common neurobiological processes. If affective and psychotic disorders share these disruptions, it is unclear whether they occur early in the course or develop gradually with persistence or recurrence of illness. Utilisation of a clinical staging model, as an adjunct to traditional diagnostic practice, is a viable mechanism for measuring illness progression. It is particularly relevant in young people presenting early in their illness course. It also provides a suitable framework for determining the timing of emergent brain alterations, including disruptions of white matter tracts. Using diffusion tensor imaging, we investigated the integrity of white matter tracts in 74 patients with sub-syndromal psychiatric symptoms as well as in 69 patients diagnosed with established psychosis or affective disorder and contrasted these findings with those of 39 healthy controls. A significant disruption in white matter integrity was found in the left anterior corona radiata and in particular the anterior thalamic radiation for both the patients groups when separately contrasted with healthy controls. Our results suggest that patients with sub-syndromal symptoms exhibit discernable early white matter changes when compared with healthy control subjects and more significant disruptions are associated with clinical evidence of illness progression.

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Introduction

The ability to predict the trajectory of psychiatric illness is a crucial area of clinical research.¹ There is an increasing emphasis on how early intervention for psychotic disorders may reduce the subsequent severity and burden of illness and in some cases may delay the development of full-threshold disorders. This approach has been further developed and is now being applied to a wider range of more severe mood disorders. To date, delineation of risk factors or markers of early illness stages has focused largely on cognitive and psychosocial measures.² Although some have utility in the detection of early phases of illness, they may also belie (even) earlier changes in brain structure. Indeed there is increasing evidence that regional brain changes may precede the first overt signs of illness, and as such, it may be possible to identify 'at-risk' individuals, before the prodromal or first discrete clinical episodes.^{3,4}

To date, most brain imaging examining early illness phases has focused upon emerging psychotic disorders,^{5–8} and recent structural imaging studies using magnetic resonance imaging (MRI) have observed alterations in brain morphology at the very earliest phases of affective disorders.^{9,10} Moreover, loss of grey matter has been observed among adolescents and young adults presenting with a first episode

of either schizophrenia versus affective psychosis as well, relative to healthy controls.¹¹ Loss of grey matter volume has been reported across multiple structures, including frontal, insula, parietal and cerebellar cortex, with smaller right hippocampal volume correlated to poorer clinical outcome.¹² Fusar-Poli *et al.*¹³ reported a reduction in grey matter volume (in the prefrontal cortex), among individuals with prodromal psychosis symptoms, as well as reductions in brain activation (using functional MRI) within the same region that resolved with functional improvement. The latter was additionally observed in a separate study, with normalisation of activation within the anterior cingulate cortex following reduction in symptoms.¹⁴ Although these studies examined patient groups with at least mild symptomatology, evidence of structural abnormalities, including grey matter loss, have been observed among asymptomatic relatives of patients with schizophrenia, indicating a measurable genetic vulnerability.^{15,16} As discussed by Correll *et al.*,⁶ the rate of conversion to an established psychotic disorder from a state of high psychosis risk is relatively small, indicating that current measures of previous illness detection are limited.

Diffusion tensor imaging (DTI) is a new application of MRI that is sensitive to the microstructural organisation of white matter tracts. When reported as fractional anisotropy (FA), it

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provides insights into the role of structural (dis)connectivity at a much earlier stage of an illness, if not before its onset.^{17,18} Abnormalities to specific white matter tracts are increasingly being investigated as a means of identifying specific pathology, particularly within the early phases of schizophrenia. James *et al.*¹ identified a decrease in FA among adolescents with schizophrenia relative to healthy controls across multiple structures. Disruptions in white matter connectivity from parietal regions have been observed among children and adolescents following their first episode of schizophrenia, with this differing to that expressed among adults, where the disruptions in connectivity appear to be more diffuse.¹⁹ Comparing the first episode with high-risk groups (that is, prodromal symptoms with no evidence of a psychotic episode), Ota *et al.*²⁰ have recently reported brain alterations before illness onset and cited developmental mechanisms for bilateral changes in FA within the temporal lobes in patients.

FA is widely regarded a robust measure of white matter 'organisation' and indeed all of the aforementioned studies have reported abnormalities in FA across both prodromal as well as discrete phases of psychotic and affective illnesses. However, despite a confirmation of significant disruption to white matter integrity, little progress has been made delineating the underlying pathophysiology from measures derived solely from FA. Disruptions in white matter organisation, (as reflected in reductions in FA) can result from various mechanisms, including demyelination as well as discrete loss of axons and as such additional complementary DTI metrics that distinguish between these two mechanisms are essential. In this regard, quantitative measures of parallel (λ_{\parallel}) and radial (λ_{\perp}) diffusivity can also be obtained from DTI, and these measures describe water diffusion along (λ_{\parallel}) or across (λ_{\perp}) the axons, thus providing information thought to reflect the integrity of axons or myelin, respectively. Parallel diffusivity has been shown to be a robust measure of axon numbers and loss of axons are reflected in a decrease in this measure.^{21,22} Conversely, radial diffusivity characterises the diffusion across the myelin and thus disruptions in the myelin sheath are characterised by increased radial diffusivity.^{23–25}

Previously, we have applied a clinical staging model in a grey matter volumetric study of young people with affective disorders and identified grey matter loss occurring with later clinical stage.¹⁰ The present study sought to investigate white matter changes in early 'sub-syndromal' individuals, as compared with those who had progressed to later more severe stages of illness (that is, an established disorder), and separately contrast both of these groups to healthy controls. Traditional diagnostic measures of psychiatric illness, such as the Diagnostic and Statistical Manual of Mental Disorders (DSM)²⁶ or the International Classification of Diseases (ICD),²⁷ have limited scope for examination of the early 'sub-threshold' phases of illness. Consequently, our group has developed and tested a clinical staging model^{28,29} as an adjunctive mechanism for rating syndrome progression in young subjects with emerging psychotic or severe mood disorders. Thus it provides a suitable clinical framework for comparison of emergent brain alterations, such as those which may be observed with DTI. In the present study, we used a whole-brain voxel-based spatial analysis to determine

the locale of any significant microstructural changes within the white matter across these two patient groups. We then sought to derive measures of λ_{\parallel} and λ_{\perp} to better characterise these white matter changes and, finally, we conducted an analysis of the influence of crossing fibres on the derived DTI measures.

In accordance with our previous work on clinical staging,^{10,29,30} we hypothesised that there would be a gradation of white matter changes associated with early, as compared with later, clinical stages. More specifically, we predicted that more extensive white matter deficits would be evident in patients with established disorders (and as such defined at a later stage of illness), as compared with those patients with earlier sub-syndromal or attenuated syndromes. Moreover, we also predicted that these deficits would be predominantly confined to prefrontal regions, which have previously been identified as abnormal,¹⁰ thus supporting the premise that the evolution of psychiatric disease is predicted on evolving structural change within the prefrontal cortex.

Materials and methods

Participants. Seventy-four patients categorised as having attenuated syndromes aged 14–30 years and 69 patients diagnosed with an established affective or psychotic disorder were recruited from a specialised tertiary referral service for assessment and early intervention of mental health problems in young people^{31,32} as part of a longitudinal study of youth mental health at the Brain and Mind Research Institute (BMRI), Sydney, Australia. Inclusion criterion for this sub-study were: (i) persons aged 12–30 years seeking professional help primarily for significant anxiety, depressive, hypomanic or psychotic symptoms, and (ii) willingness to participate in other neurobiological and longitudinal research within the BMRI, related to clinical outcomes.³³ As such, this cohort represents a selected sub-set of a much broader cohort ($n=1483$) who presented to our services for clinical care during the same time period.³¹ In addition, 39 healthy control subjects (age range 15–30 years and all screened for psychiatric illness) were recruited via snowballing techniques and advertisement in community newspapers.

Subjects were excluded if they did not have sufficient English-language skills or had insufficient intellectual capacity to participate in the neuropsychological aspects of the concurrent studies.³⁴ The Human Research Ethics Committee of the University of Sydney approved this study, and all patients gave prospective written informed consent for their clinical data to be used for research purposes. Parental consent was obtained for patients <18 years of age.

All patients who entered the services were assessed and managed by medically and/or psychologically trained health professionals.³⁵ In this study, an independent psychiatrist or trained research psychologist also conducted a structured clinical interview, focusing on assessment of the detailed criteria developed for formal application of our clinical staging framework.^{28,29,35,36} For those assessed in clinical environments, discrete categories (Stages 1–4; whereby, Stage 1A = 'help-seeking'; Stage 1B = 'attenuated syndrome'; Stage 2 = 'discrete or established disorder'; Stage

3 = 'persistent or recurrent illness'; and Stage 4 = 'chronic debilitating illness') were described. On examination, Stage 1B patients had persistent attenuated syndromal symptoms, which significantly impacted on major aspects of their psychosocial function but these were distinct from patients with an established disorder (Stage 2). Stage 1B patients were also categorised on the basis of the development of more specific depressive or mixed syndromes of at least moderate severity, including: (a) depressive syndromes associated with persistently depressed mood, anhedonia, suicidal ideation or thoughts of self-harm and/or some neurovegetative features, (b) hypomanic symptoms of < 4 days duration during any specific episode and (c) brief duration psychotic symptoms. A key point of differentiation, however, was between those early 'attenuated syndrome' (that is, Stage 1B) and the onset (Stage 2) of a more discrete or established disorder. Importantly, assignment to Stage 1B or 2/3 was not simply analogous to, or defined by, meeting existing DSM-IV or ICD criteria for a specific mood or psychotic disorder. Within the clinical staging model, it is possible to differentiate prodromal, sub-syndromal or 'attenuated syndrome' states from first major, acute or recurrent episodes (that is, 'discrete disorders'), largely independent of diagnostic considerations. This is primarily due to the assumption that the 'attenuated syndrome' stage is (by its nature) non-specific, that is; individuals within this stage would share a range of symptoms and be similarly impaired (in terms of their functioning) but not necessarily 'at risk' for a specific psychiatric disorder. Indeed, most young people who present for care with early but disabling forms of mental disorder have admixtures of anxiety, depressive or brief hypomanic or psychotic symptoms and are at risk of developing a broad range of adverse psychological, physical health and functional outcomes. At the time of scan, 74 patients were identified to be at the 'attenuated syndrome' (Stage 1B) and 69 were rated to be within the 'discrete disorder' (Stage 2) or 'persistent or recurrent illness' (Stage 3) stage. The Stage 2/3 cohorts included patients with a formal diagnosis of bipolar disorder, severe depression or psychotic disorder. We have established the inter-rater reliability of our clinical staging methods during the earlier development of this process.²⁸

The clinical interview included the Hamilton Depression Rating Scale (HAMD, 17-item)³⁷ to quantify current (over the past 7 days) mood symptoms; the Brief Psychiatric Rating Scale (BPRS)³⁸ to quantify general psychiatric symptoms at the time of assessment; and the Social and Occupational Functioning Assessment Scale (SOFAS),³⁹ where a patient's functioning was rated from 0 to 100, with lower scores suggesting more severe impairment. Patients also completed the Kessler-10 (K-10),⁴⁰ a brief self-report instrument designed to detect psychological distress.⁴¹ Statistical analyses were performed using SPSS for Windows 20.0 (IBM, Chicago, IL, USA). Group differences in demographic and clinical variables were assessed with one-way analysis of variance or chi-square tests where relevant. If equality of variance was compromised (according to Levene's test), the corrected degrees of freedom and *P*-values were reported.

MRI acquisition. All imaging was performed on a 3T GE Discovery MR750 scanner (GE Medical Systems,

Milwaukee, WI, USA) at the BMRI imaging facility. Whole-brain diffusion-weighted images were acquired using an echo planar imaging sequence with the following image parameters: repetition time = 7000 ms; echo time = 68 ms; slice thickness = 2.0 mm; field of view = 230 × 230 mm; acquisition matrix = 256 × 256; 69 gradient directions. Two images without gradient loading (B_0 s mm^{-2}) were acquired before the acquisition of 75 images (each containing 55 slices) with uniform gradient loading ($B_0 = 1000$ s mm^{-2}). In addition to diffusion-weighted images, we also acquired T1-weighted structural images for the purpose of anatomical localisation.

Tensor calculations. All data were analysed using the FMRIB Software Library (FSL version 4.1.9; <http://www.fmrib.ox.ac.uk/fsl>).⁴² Firstly, the FMRIB's Diffusion toolbox was used to correct all data for spurious eddy current distortions as well as motion artifacts by applying affine alignment of each diffusion-weighted image to the first volume of the diffusion data without gradient (that is, the $b=0$ image). The Brain Extraction Tool was then used to generate a binary brain mask from the $b=0$ image. Next DTIfit was used to independently fit the diffusion tensor to each voxel that yielded voxelwise maps of FA, radial diffusivity (λ_{\perp}) and parallel diffusivity (λ_{\parallel}).

Tract-based spatial statistics. Voxelwise statistical analysis of FA was carried out using tract-based spatial statistics within FSL¹² using the following routine. Firstly, the FA image of each subject was aligned to a 1-mm isotropic target FA image (FMRIB58_FA) using nonlinear registration by using a b-spline representation of the registration warp field.⁴³ The data was visually inspected to ensure accuracy of the transformations and then all of the aligned FA images were transformed into the 1-mm isotropic MNI152 (Montreal Neurological Institute) template by means of affine registrations.⁴³ A mean FA skeleton image representative of all tracts with a common centre was created from all subjects and individual subject FA images were projected onto this skeleton. Voxelwise statistics across subjects (co-varying for age and gender) were then run for each point on the mean FA skeleton using permutation-based non-parametric testing (RANDOMISE as implemented in FSL), using a 5000 permutation set⁴⁴ for contrasting differences between healthy controls versus patients with a confirmed discrete disorder (Stages 2/3). Family-wise error (FWE) correction⁴⁵ was used to correct the threshold for multiple comparisons across space and threshold-free cluster enhancement was employed to assess cluster significance.⁴⁶ The significant *P*-value with the FWE-corrected threshold was set at $P < 0.05$. Statistical significant white matter regions identified for the healthy controls versus Stage 2/3 patient group were then used to formulate the *a priori* hypothesis for healthy controls versus attenuated syndromes (Stage 1B) contrast. The transformation matrices that were created for registration of the FA maps were then applied to determine λ_{\parallel} and λ_{\perp} and white matter skeletons for each were created. Finally, to further characterise observed changes in FA, non-parametric testing of both λ_{\parallel} and λ_{\perp} was undertaken and mean values for FA, λ_{\parallel} and λ_{\perp} were derived from significant clusters.

Connectivity-based probabilistic tractography. Probabilistic tractography was then undertaken to explore the effects of crossing fibres on FA in region of interest (ROI) that were found to have significantly decreased FA across the statistical contrasts conducted in the RANDOMISE step. A single significant ROI was found in the left anterior corona radiata (ACR) (see results below). This significant ROI was manually traced out to form a seeding mask. Using the JHU (Johns Hopkins University) DTI-based white-matter atlases,^{47–49} we approximated that this ROI predominately comprised of the anterior thalamic radiation (ATR), inferior fronto-occipital fasciculus (IFOF) and uncinate fasciculus (UF) of the left hemisphere (see Figure 1), and target masks were created to isolate these respective tracts. Diffusion probabilistic tractography was then performed using a Bayesian approximation as implemented by the Bedpostx application. Specifically, we fitted a three-fibre orientation diffusion model⁵⁰ to estimate probability distributions on the direction of fibre populations for ATR, IFOF and UF at each brain voxel in the diffusion space of each subject. To interpret the probabilistic tractography in standard space, we used standard-to-diffusion matrices and the corresponding inversed matrices. Tractography was then performed in standard space from every voxel of the seed ROI to the ATR, IFOF and UF classification target masks. For each tractography, we generated 5000 samples from each seed voxel to build up a connectivity distribution.

Multiple-subjects connectivity-based parcellation was estimated as described by Jbabdi *et al.*⁵¹ Specifically, each seed-to-target image was thresholded to include only the voxels with the top 1% of the robust range of probability. To identify the predominate tract within the ACR ROI, the volume of each seed-to-target image was extracted for statistical comparison. For illustrative purposes, subject's total tracts pathway images were also thresholded to the top 1% of probability, concatenated and thresholded again to show voxels that were common across subjects. A one-way analysis of variance of the seed-to-target image volumes was used to determine what percentage of the ROI was parcellated to the ATR, IFOF or UF for each cohort. Where the assumption of equal variances did not hold, the Welch statistic and Games–Howell *post hoc* analysis was used. Significance was set at $P < 0.05$ (two-tailed).

Results

Group characteristics. The comparisons and characteristics across the three groups (Stage 1B, Stage 2/3 and controls) are reported in Table 1. Levene's test indicated unequal variances for the HAMD, SOFAS, K-10 and BPRS, so Welch's statistic was used for these variables. A one-way between subjects analysis of variance revealed significant between-group differences for age ($F(2,178) = 5.77$; $P = 0.004$), HAMD ($F(2, 100.91) = 105.6$; $P < 0.001$), SOFAS ($F(2, 109.93) = 295.54$; $P < 0.001$), K-10 ($F(2, 104.21) = 44.17$; $P < 0.001$), BPRS ($F(2, 101.23) = 97.21$; $P < 0.001$) and level of education ($F(2, 175) = 15.70$; $P < 0.001$), see Table 1. *Post hoc* comparisons using Tukey's Honestly Significant Difference and Game's Howell statistics indicated that the age of the control group ($M = 23.82 \pm 2.52$) was significantly higher than that of the Stage 1B ($M = 21.3 \pm 3.51$; $P < 0.003$), however, it was not significantly different from that of the Stage 2/3 patients ($M = 22.4 \pm 4.35$, $P = .155$). The control group had significantly lower scores on the HAMD ($M = 1.93 \pm 2.02$), SOFAS ($M = 92 \pm 3.36$), K-10 ($M = 14.89 \pm 5.68$) and the BPRS ($M = 26.79 \pm 3.00$) compared with the Stage 1B patients ($M = 12.42 \pm 7.19$, $P < 0.001$; $M = 63.70 \pm 11.57$, $P < 0.001$; $M = 28.04 \pm 9.52$, $P < 0.001$; $M = 40.55 \pm 9.81$, $P < 0.001$), respectively, and group 2/3 ($M = 13.39 \pm 7.53$, $P < 0.001$; $M = 62.26 \pm 13.65$, $P < 0.001$; $M = 25.02 \pm 8.98$, $P < 0.001$; $M = 43.61 \pm 11.33$, $P < 0.001$), respectively. Moreover, the control group ($M = 15.05 \pm 1.86$) had significantly more years of education than the Stage 1B ($M = 12.60 \pm 2.48$, $P < 0.001$) and Stage 2/3 ($M = 12.81 \pm 2.27$, $P < 0.001$) patients. There were no significant differences between the Stage 1B and 2/3 patient groups on any of the aforementioned variables.

For symptoms potentially indicative of more severe syndromes, 78% of the Stage 1B group reported affective-like symptoms compared with 61% of the Stage 2/3 group; whereas only 22% of the Stage 1B group reported psychotic symptoms compared with 39% of the Stage 2/3 group. With regards to medication, a chi square test was used to determine whether there was a significant difference between Stage 1B and Stage 2/3 patients in terms of their medication status and a significant difference was found for antidepressants ($\chi^2(1) = 9.59$, $P = 0.002$), anti-psychotics

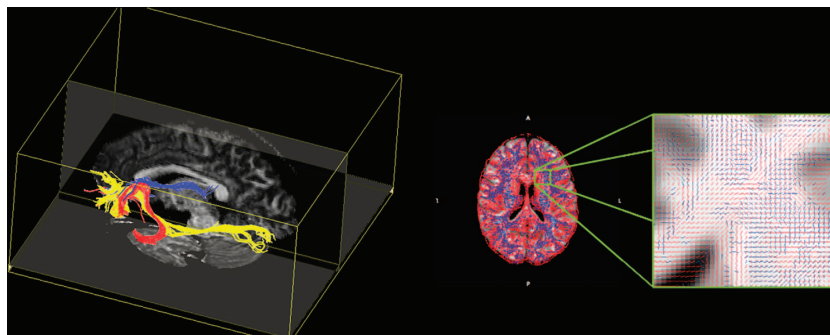


Figure 1 The left anterior corona radiata (ACR), the region of significantly decreased fractional anisotropy is the conjunction of three major association fibres, the anterior thalamic radiation (blue), the inferior fronto-occipital fasciculus (yellow) and the uncinate fasciculus (red). The green box illustrates the ACR region of interest and a magnified view of the crossing fibres.

Table 1 Patient demographic and instrument scores and their associated significance level

	Controls (n = 39) Mean (s.d.) (61.5% F: 38.5% M)	Stage 1B patients (n = 73) Mean (s.d.) (67.1% F: 32.9% M)	Stage 2/3 patients (n = 69) Mean (s.d.) (46.4% F: 53.6% M)	Significance (df) (P)
Age	23.82 (2.52)	21.36 (3.51)	22.45 (4.35)	F (2, 178) = 5.77 (0.004) ^b
HAMD	1.93 (2.02)	12.42 (7.19)	13.39 (7.53)	F (2, 154) = 30.80 (0.001) ^{a,c}
SOFAS	92.0 (3.36)	63.70 (11.57)	62.26 (13.65)	F (2, 175) = 96.0 (0.001) ^{a,c}
K-10	14.89 (5.68)	28.04 (9.52)	25.02 (8.98)	F (2, 163) = 27.26 (0.001) ^{a,c}
BPRS	26.79 (3.00)	40.55 (9.81)	43.61 (11.33)	F (2, 154) = 30.13 (0.001) ^{a,c}
Education	15.05 (1.86)	12.60 (2.48)	12.81 (2.27)	F (2, 175) = 15.70 (0.001) ^{a,c}
IQ	106.96 (7.51)	104.57 (7.98)	105.06 (9.90)	F (2, 161) = 0.76 (0.469)

Abbreviations: BPRS, Brief Psychiatric Rating Scale; Education, years of education; F, female; HAMD, Hamilton Depression Rating Scale; IQ, predicted Intelligence Quotient; K-10, Kessler-10; M, male; SOFAS, Social and Occupational Functioning Assessment Scale.

^aPost hoc test revealed a significant difference ($P < 0.001$) between control and Stage 1 participants. ^bPost hoc test revealed a significant difference ($P < 0.01$) between control and Stage 1 participants. ^cPost hoc tests revealed a significant difference ($P < 0.001$) between control and Stage 2/3 patients.

Table 2 Patient medication levels

	Any anti-depressant, % (number of patients)	Any anti-psychotic, % (number of patients)	Any mood stabiliser, % (number of patients)
Stage 1B (attenuated syndrome)	65.75 (48)	34.25 (25)	16.44 (12)
Stage 2/3 (discrete disorder)	39.13 (27)	73.91 (51)	31.88 (22)
Total	52.82 (75)	53.52 (76)	23.94 (34)

Cross-tabulation of clinical stage group by current medication.

($\chi^2(1) = 23.53, P < 0.001$) and mood stabilisers ($\chi^2(1) = 4.87, P = 0.027$). Specifically, 66% versus 39% of Stage 1B and 2/3 patients, respectively, used antidepressants. On the other hand, antipsychotic use was 34% versus 74% for Stage 1B and Stage 2/3, respectively, and mood stabiliser medication was distributed to 16% versus 32% for use in patients with Stage 1B and Stage 2/3, respectively (see Table 2).

DTI tract-based spatial statistics. A significant decrease in FA was found in a confined region of white matter within the ACR for the Stage 2/3 patients when contrasted with controls. More specifically, this region of significantly decreased FA (FWE-corrected $P < 0.033$ and MNI coordinates –22, 32, 4) was the conjunction of the ATR, IFOF and the UF—all on the left side (see Figure 1). Significantly, decreased FA (uncorrected $P = 0.01$) was also identified for the Stage 1B patients within the same region of white matter to that for the Stage 2/3 patients (Figure 2).

With regards to radial and parallel diffusivity, a significant cluster was identified for λ_{\perp} in the ACR in the left hemisphere for the Stage 2/3 group (Figure 3). The Stage 2/3 group had significantly increased λ_{\perp} (FWE-corrected $P < 0.037$) compared with controls. This region of significantly increased λ_{\perp} was confined to the ACR, which had previously been identified as having a decreased FA. However, no significant changes were observed for the Stage 1B group, and neither group displayed any significant changes for λ_{\parallel} when contrasted with healthy controls (see Table 3). Similarly, no significant changes were identified for the contrast between Stage 1B and 2/3 patients.

The results of the Bayesian modelling of the three white matter tracts that traversed through the ACR ROI indicated that the ATR accounted for 94% of the white matter fibres followed by 5% for the IFOF and 1% for the UF. When the ACR ROI was masked and the average FA values for controls, Stage 1B and Stage 2/3 were determined, a significantly decreased FA was found for the Stage 2/3 group when compared with controls (separately) after correcting for the relative contributions of the three crossing white matter tracts (Figure 4). The corrected FA for Stage 1B group was not significant ($P = 0.058$).

Discussion

This study sought to investigate microstructural changes in the white matter of young outpatients diagnosed with an admixture of affective and psychotic symptoms and contrast these findings with a group of patients, which at the time of scanning, did not meet the diagnostic criteria for an established psychiatric disorder. Patients classified by our clinical staging model^{28,29} for psychiatric disorders as Stage 2/3 (those meeting diagnostic criteria for an established psychiatric condition) had significantly reduced FA within the ACR on the left when compared with healthy controls. The ACR is known to be the conjunction of three long-range association fibre tracts, namely the ATR, IFOF and the UF, that converge through this region. Similarly, for the patients that were classified as Stage 1B (those not meeting diagnostic criteria for an established psychiatric disorder but instead exhibiting significant sub-syndromal symptoms), a similar pattern of decreased FA was identified within this same anatomical region, although the extent of white matter involvement was less in overall volume to that of the Stage 2/3 patients. In order to delineate the nature of these white matter changes in addition to FA, we calculated both λ_{\parallel} and λ_{\perp} within the ACR and found a significantly increased λ_{\perp} for the Stage 2/3 group. However, as overlapping white matter fibre tracts have the potential to artifactually decrease FA, we sought to confirm that the observed decrease in FA within the ACR was resultant from physical changes in the integrity of the white matter and not a spurious decrease in FA due to crossing fibres. In doing so, we undertook further analysis to determine the percentage of involvement of the three white

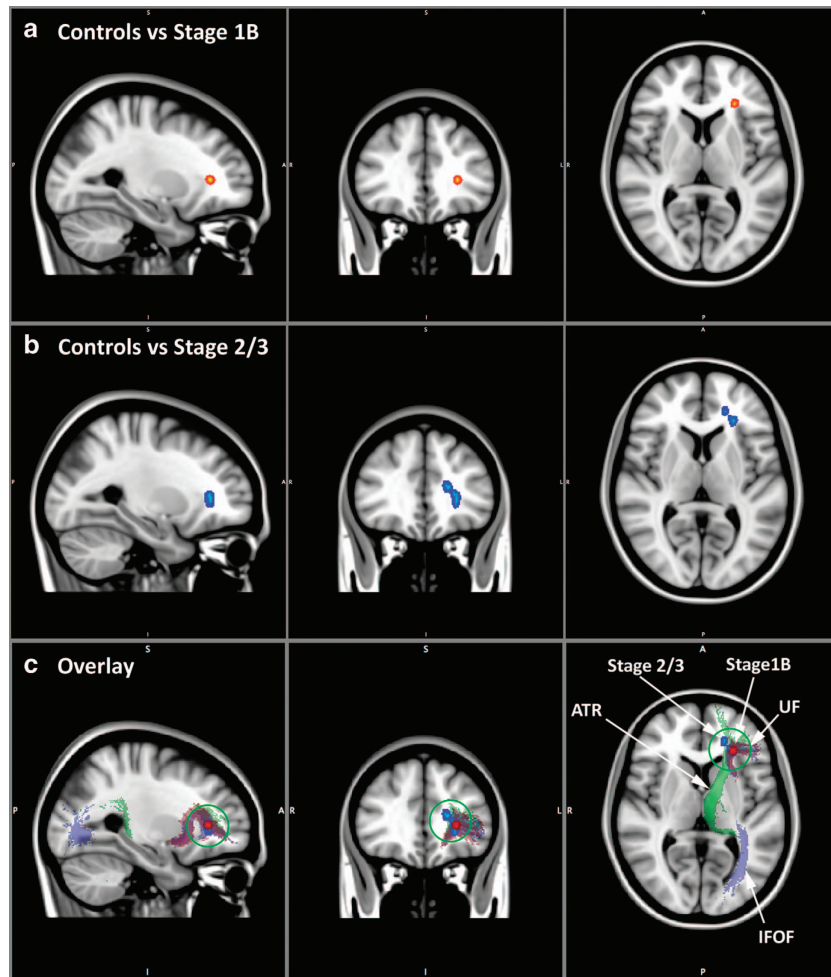


Figure 2 Panel (a): The top row displays the contrast between controls and Stage 1B patients and shows a regions of decreased ($P=0.01$ uncorrected) fractional anisotropy (FA) in the left anterior corona radiata for the Stage 1B patients. Panel (b) displays the contrast between controls and Stage 2/3 patients that highlights the involvement of the identical region, which has significantly decreased FA ($P=0.033$, corrected). Panel (c) is a graphical overlay of the FA results for Stage 1B and Stage 2/3 patients along with the coregistered fibre tracts for anterior thalamic radiation (ATR), inferior fronto-occipital fasciculus (IFOF) and uncinate fasciculus (UF). Both contrast shown in panels (a) and (b) have undergone threshold free cluster enhancement. All images are radiologically oriented.



Figure 3 Illustrates the region of significantly increased λ_{\perp} for the Stage 2/3 group that is constrained within the anterior corona radiata region of interest, which indicates abnormal diffusion of water across the myelin sheath. The three converging fibre tracts are superimposed (anterior thalamic radiation—green; inferior fronto-occipital fasciculus—purple; uncinate fasciculus—red). The contrast has undergone threshold free cluster enhancement. All images are radiologically oriented.

matter tracts known to traverse the ACR. By employing a Bayesian methodology, we modelled the overlapping white matter tracts within the ACR and identified that the ATR constituted 94% of the ACR ROI. The results of the present

study confirm that patients at a more advanced illness stage are characterised by greater changes in frontal lobe white matter integrity as indicated by lower FA and increased λ_{\perp} metrics compared with healthy controls. Our results

corroborate the recent work that has reported discernable white matter changes in high-risk individuals for schizophrenia with prodromal symptoms, as well patients with schizophrenia in the very early stages of their illness.⁵² The significantly increased λ_{\perp} in the presence of a decreased FA (and normal λ_{\parallel}) indicates increased diffusion of water across the myelin sheath and thus is consistent with the interpretation of demyelination of fibre tracts.²² The observed changes in white matter integrity within the ACR (94% of which is comprised of the ATR) would be expected to significantly impact projections from the thalamus to the frontal lobes, which ultimately manifests as cognitive and psychiatric symptoms.⁵³

There is a confluence of evidence from neuroimaging, neuropathological and genetic association studies suggesting that oligodendrocytes and myelin dysfunction may underpin the observed white matter aberrations in psychiatric cohorts. Recent neuroimaging studies have reported deficiencies in myelin along with changes in the white matter volume across a range of psychiatric illness, including schizophrenia,⁵⁴ bipolar disorder⁵⁵ as well as unipolar depression.⁵⁶ Similarly, recent neuropathological studies have reported decreased oligoden-

drocyte density across these same psychiatric conditions⁵⁷ and, finally, genetic studies have demonstrated that oligodendrocyte and myelin-related genes are genetically associated with schizophrenia, with one of the more robust findings involving the Neurogulin 1 gene and its receptor (ErbB4),⁵⁸ both of which are known to be involved in oligodendrocyte development.^{59,60} Although the aforementioned studies provide strong evidence that oligodendrocytes and myelin assume a significant role in the evolution of psychiatric symptoms, several studies have also investigated white matter changes in non-psychiatric conditions. For example, leukodystrophies and leukoencephalopathies, both of which are demyelinating diseases characterised by progressive degeneration of the white matter, are frequently associated with psychotic symptoms.⁶¹ Indeed psychotic features have also been reported in patients with multiple sclerosis who have presented with white matter lesions to the frontal and temporal lobes.⁵³ Collectively, these studies provide strong evidence that abnormalities in oligodendrocyte and/or myelin are at the core of the observed white matter changes. Our finding of increased λ_{\perp} within the ACR for the Stage 2/3 patient group (compared with healthy controls) further strengthens the conception of oligodendrocyte/myelin pathology and the resultant impact on white matter connections.

Our FA findings are consistent with the recent study by Carletti *et al.*⁵ who reported qualitatively similar white matter changes in an 'ultra high-risk' group that subsequently transitioned to full-threshold schizophrenia, with more severe changes evident following transition. Anatomically, our results are distinct from that of Carletti *et al.*;⁵ however, they bear similarities in the sense that they are present in our sub-syndromal patients that have not transitioned to a

Table 3 Statistical values for the corrected DTI measures corrected for ATR

	FA	λ_{\perp}	λ_{\parallel}
Controls versus Stage 1B	0.058	0.18	0.425
Controls versus Stage 2/3	0.033	0.037	0.682
Stage 1B versus Stage 2/3	0.266	0.471	0.867

Abbreviations: ATR, anterior thalamic radiation; DTI, diffusion tensor imaging; FA, fractional anisotropy.

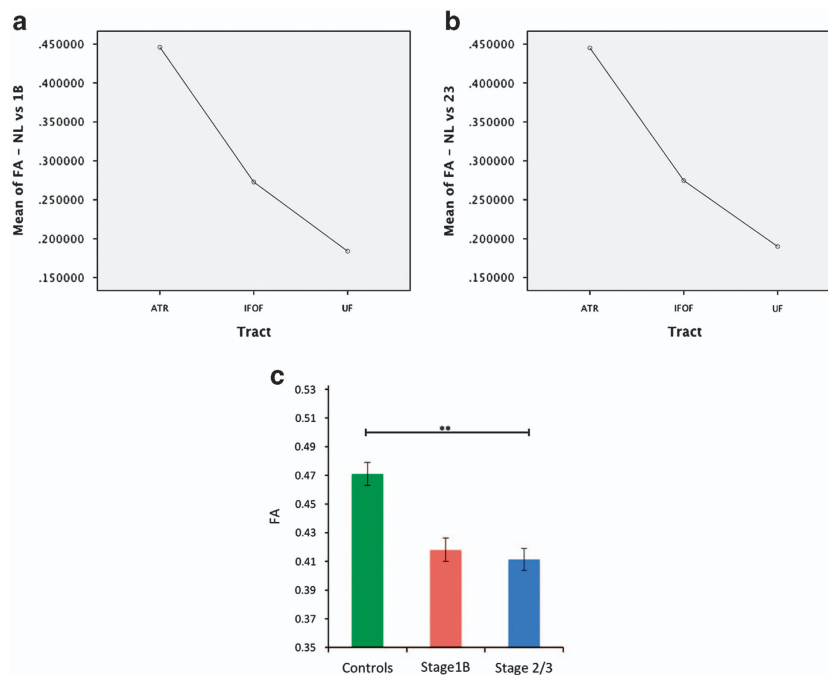


Figure 4 Illustrates the relative contribution of the anterior thalamic radiation (ATR), inferior fronto-occipital fasciculus (IFOF) and the uncinate fasciculus (UF) fibre tracts that converge through the anterior corona radiata region of interest. Panels (a) and (b) illustrate that the ATR is the predominant fibre tract that contributes to the mean fractional anisotropy (FA) across the groups. Panel (c) illustrates the corrected FA measures for the controls (NL), Stage 1B and Stage 2/3 groups. ** $P < 0.05$.

full-threshold psychiatric disorder. A recent tractography study that contrasted white matter changes in patients with schizophrenia and bipolar disorder with healthy controls reported significant reductions in the UF and ATR, which were common to both the patient groups.⁶² The results of our current study corroborate these findings and together with our previous work¹⁰ further strengthen the notion that the observed white matter changes may represent a shared disease mechanism underpinning the emergence of major psychiatric disorders. Indeed aberrations in oligodendrocytes density, number and spacing as well as myelin production have been reported across a range of psychiatric conditions.⁵⁷ The loci of white matter changes reported in our current study confirms our hypothesis that patients at a more advanced stage of illness exhibit greater white matter changes compared with controls and that the FA results for the sub-syndromal patient group suggest an overlapping or progressive mechanism. Notably, our data were covaried for the effects of age, thus eliminating the possibility that age effects may have contributed to the observed result.

Following modelling of the crossing fibres at the site of convergence in the ACR, we found that the ATR accounted for 94% of the fibres running through this ROI. The ATR is a glutamatergic thalamocortical pathway comprising association fibres that putatively form part of a series of five thalamocortical circuits that describe precise anatomical projections from the thalamus to the cortex and back again.⁶³ Four of these five thalamocortical loops project to the frontal cortex, and these circuits are thought to be integral to the processing of salient information as well as modulating behaviour. Disruptions to these pathways have been associated with the emergence of positive symptoms that accompany psychotic disorders, including auditory hallucinations.⁶⁴ Not surprisingly, abnormalities in the ATR have been reported in patients with schizophrenia, bipolar disorder, unipolar depression⁶² as well as in subjects at ultra high risk for psychosis.⁸

The second fasciculus found to project through the ACR was the IFOF, although it accounted for only 5% of the total fibres. A recent study by Carletti *et al.*⁵ reported reduced FA values in patients with first-episode psychosis but only 'intermediate' FA values for the ultra high-risk subjects within the IFOF.⁵ The IFOF forms a putative 'connection' between the frontal, temporal and occipital lobes and, as such, is one of the major efferent and afferent neuronal projections to the frontal lobes. Despite being a major association pathway between the frontal and occipital lobes, the precise role of the IFOF is unknown. A recent study has conjectured an association between the IFOF, semantic processing and attentional set-shifting;⁶⁵ however, this finding requires replication and further investigation to delineate what the exact relationship might be in the context of our own results.

The final fasciculus that traverses the ACR ROI is the UF, which is a fronto-striatal white matter tract that connects the anterior most aspects of the temporal lobe with the inferior frontal gyrus and the ventral surfaces of the frontal lobe. Anatomically, it arises lateral to the amygdala and hippocampus and projects along a superior pathway behind the external capsule inward of the insular cortex to the posterior part of the orbitofrontal gyrus. Abnormalities in the UF have been

documented across several psychiatric conditions, including more recent studies investigating patients at ultra high risk of developing schizophrenia.^{8,62,66,67} Moreover, separate to white matter structural abnormalities, there are also reports of functional impairments arising within this same network that subserves mainly executive functions,^{68–70} providing further evidence for the involvement of the UF in the development of psychiatric sequelae. Interestingly, in healthy controls, the UF exhibits greater FA on the left compared with the right side,⁷¹ thus the decrease in FA observed on the left for both our patients cohorts might be suggestive of a preferential targeting of the left hemisphere by the disease process.

The absolute contribution of the aforementioned white matter tracts to the observed decrease in FA in the ACR ROI cannot be fully explicated from our current study; however, using Bayesian modelling, we calculated that the ATR was the predominant fibre tract and that it constituted 94% of the total volume of the ROI. As such, crossing fibres were unlikely to have significantly influenced the observed decrease in FA within the ACR. Instead, the observed ACR findings more likely indicate a region of white matter disconnection in our Stage 2/3 patient group, and similarly the ACR may represent a region of anatomical vulnerability or possibly a harbinger to developing a psychiatric condition for the sub-syndromal patients. A better understanding of the relative contributions of these fasciculi may be obtained in future studies by employing white matter tractography to examine the developmental trajectory of each of these individual tracts in a longitudinal study.

It should be borne in mind that membership to both the patient cohorts was based solely on cross-sectional ratings of our clinical staging criteria rather than formal diagnostic frameworks, such as DSM-IV. Thus the inclusion of affective and psychotic disorders in both the cohorts suggests that this region of lower FA identified (for both the cohorts) may evolve as a general precursor to developing a major mental illness but may not be specific to any one particular psychiatric disorder.

There were several limitations associated with our study that warrant discussion. Firstly, the potential confound of the effects of medication on the final FA results cannot be entirely discounted. The Stage 2/3 patients were, on average, taking more medication than the Stage 1B patients, and so it is possible that the microstructural white matter changes that we are reporting may be impacted by medication. However, it is important to highlight that there were significant differences in both the class (and dosages) of the medications between the Stage 2/3 and 1B cohorts. Indeed, if medication was a contributing factor to these observed results, we would expect a differential pattern of microstructural changes in line with the variable nature of the medication regimens, which was not observed in this study. The two main medication types that the patients were taking at the time of scanning were antipsychotics and lithium. In this regard, studies have reported that antipsychotic medications, have no significant effects on FA,⁷² and separate studies have shown that lithium has trophic effects on deep white matter and the oligodendrocyte network.^{73,74} Finally, our current study was cross-sectional in nature and as such limits our ability to comment on illness trajectory. If indeed our findings (which require

replication) represent a common structural diathesis, then longitudinal experimental designs with large cohorts are urgently needed. Incorporating a longitudinal design with DTI scanning before and following transition to a full-threshold psychiatric illness, and including patients who move to different eventual disorder outcomes, such as bipolar and other discrete psychotic disorders, would aid the separation of early shared changes from those that may be more characteristic of either later stages of illness or isolated to particular clinical phenotypes.

In conclusion, our study builds on an emerging literature that heralds the importance of clinically staging patients based on illness progression, in order to gain a better understanding of the nature and timing of the mechanisms that underpin the transition to psychiatric disorders. The results of our study indicate that patients with established psychiatric disease have significantly lower FA but increased λ_{\perp} within frontal lobe white matter tracts when compared with controls. Moreover, the significantly increased λ_{\perp} in the presence of reduced FA but normal λ_{\parallel} suggests a demyelinating process that underpins the pathophysiology and thus implicates oligodendrocytes and myelin as key factors. Our results further indicate that patients exhibiting sub-syndromal psychiatric symptoms also exhibit early (albeit less severe) signs of white matter disruption in a similar region to the more severe patient group. This study highlights the importance of investigating patients before the onset of a full-threshold psychiatric disorder and, to our knowledge, this is the first study to map a region of anatomical concordance of white matter changes between patients at risk of developing a significant psychiatric condition and those patients with a confirmed discrete psychiatric disorder. Finally, the results of our study provide evidence that our sub-syndromal patients also exhibit early signs of white matter disconnection within the ACR and that these changes may act as surrogate markers for the disease stage.

Conflict of interest

The authors declare no conflict of interests.

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