Deficits in neurite density underlie white matter structure abnormalities in first-episode psychosis

Article (Accepted Version)

Rae, Charlotte, Davies, Geoff, Garfinkel, Sarah, Gabel, Matthew, Dowell, Nicholas, Cercignani, Mara, Seth, Anil, Greenwood, Kathryn, Medford, Nick and Critchley, Hugo (2017) Deficits in neurite density underlie white matter structure abnormalities in first-episode psychosis. Biological Psychiatry. ISSN 0006-3223

This version is available from Sussex Research Online: http://sro.sussex.ac.uk/66732/

This document is made available in accordance with publisher policies and may differ from the published version or from the version of record. If you wish to cite this item you are advised to consult the publisher's version. Please see the URL above for details on accessing the published version.

Copyright and reuse:
Sussex Research Online is a digital repository of the research output of the University.

Copyright and all moral rights to the version of the paper presented here belong to the individual author(s) and/or other copyright owners. To the extent reasonable and practicable, the material made available in SRO has been checked for eligibility before being made available.

Copies of full text items generally can be reproduced, displayed or performed and given to third parties in any format or medium for personal research or study, educational, or not-for-profit purposes without prior permission or charge, provided that the authors, title and full bibliographic details are credited, a hyperlink and/or URL is given for the original metadata page and the content is not changed in any way.

http://sro.sussex.ac.uk
Deficits in neurite density underlie white matter structure abnormalities in first-episode psychosis (100 characters)

Charlotte L Rae*1,2, Geoff Davies3,4, Sarah N Garfinkel1,2, Matt C Gabel2, Nicholas G Dowell2, Mara Cercignani2, Anil K Seth1,5, Kathryn E Greenwood3,4, Nick Medford1,2,4, Hugo D Critchley1,2,4

1 Sackler Centre for Consciousness Science, University of Sussex, UK
2 Division of Neuroscience, Brighton & Sussex Medical School, UK
3 School of Psychology, University of Sussex, UK
4 Sussex Partnership NHS Foundation Trust
5 School of Engineering & Informatics, University of Sussex, UK

*corresponding author
Dr Charlotte L Rae
Sackler Centre for Consciousness Science, and
Clinical Imaging Sciences Centre
Brighton & Sussex Medical School
University of Sussex
Falmer
Brighton
BN1 9RR
UK

Telephone: +44(0) 1273 873787
Email: c.rae@bsms.ac.uk
Keywords: diffusion MRI; first-episode psychosis; fractional anisotropy; neurite density; neurite orientation dispersion and density imaging (NODDI); white matter microstructure

Number of words in abstract: 249
Number of words in main text: 4,000
Number of figures: 4
Numbers of tables: 2
Supplementary information: 1 table; 2 figures

Running title: NODDI in first-episode psychosis (max 55 characters)
Abstract

Background: Structural abnormalities across multiple white matter tracts are recognised in people with early psychosis, consistent with dysconnectivity as a neuropathological account of symptom expression. We applied advanced neuroimaging techniques to characterise microstructural white matter abnormalities for a deeper understanding of the developmental aetiology of psychosis.

Methods: Thirty-five first-episode psychosis patients, and 19 healthy controls, participated in a quantitative neuroimaging study using Neurite Orientation Dispersion and Density Imaging (NODDI), a multi-shell diffusion-weighted MRI technique that distinguishes white matter fibre arrangement and geometry from changes in neurite density. Fractional anisotropy (FA) and mean diffusivity images were also derived. Tract-based spatial statistics compared white matter structure between patients and controls and tested associations with age, symptom severity and medication.

Results: Patients with first-episode psychosis had lower regional FA in multiple commissural, corticospinal, and association tracts. These abnormalities predominantly colocalized with regions of reduced neurite density, rather than aberrant fibre bundle arrangement (orientation dispersion index). There was no direct relationship with active symptomatology. FA decreased and orientation dispersion index increased with age in patients, but not controls, suggesting accelerated effects of white matter geometry change.

Conclusions: Deficits in neurite density appear fundamental to abnormalities in white matter integrity in early psychosis. In the first application of NODDI in psychosis, we found that processes compromising axonal fibre number, density, and myelination, rather than processes leading to spatial disruption of fibre organisation, are implicated in the aetiology of
the disorder. This accords with a neurodevelopmental origin of aberrant brain-wide structural connectivity predisposing individuals to psychosis.
Introduction

Schizophrenia and related psychoses encompass a constellation of perceptual, cognitive and affective symptoms; with characteristic expression and maturational trajectories (1). Neuroimaging and pathological studies of patients and at-risk individuals indicate distributed neurobiological brain abnormalities (2-5). Psychosis has been considered a cardinal disorder of dysconnectivity (6), in which dysfunctional integration of mental processes arises from impaired functional neural communication. Correspondingly, structural abnormalities in white matter tracts across brain are observed in post-mortem studies (7) and in vivo non-invasive imaging using diffusion-weighted magnetic resonance imaging (MRI) (2, 8, 9). It is likely that white matter changes are present even before the experience of active symptoms at the onset of a first episode of psychosis (FEP), preceding pharmacological treatment with neuroleptic medications (2, 3, 10).

The white matter abnormalities reported in FEP affect multiple fibre bundles, including interhemispheric connections, corticospinal projections, and long-range association tracts (2, 11). These structural changes are associated with dysfunctional interactions between brain regions (12) and predict symptom severity in FEP (13). Moreover, neuroimaging indices of white matter integrity predict longer-term outcomes, including response to treatment (2, 14). White matter structural abnormalities may thus underpin early psychosis.

In vivo, white matter structure can be assessed using diffusion tensor imaging (DTI, 15). Quantitative DTI indices, including fractional anisotropy (FA) and mean diffusivity (MD), reflect microstructural features including myelination, axonal packing density and diameter, astrocytic morphology, and angiogenesis (16, 17). Genetic susceptibility to psychosis is linked to neurodevelopmental disruption of myelination, axonal guidance and neuronal migration (18, 19). Disordered axonal structure and fibre organization can result from such disruption. Thus, a key objective for understanding the nature, aetiology and implications of
white matter abnormalities in FEP is to characterise microstructural differences in axonal structure, including axonal number, packing density, and myelination, and differentiate these from variations in fibre geometry.

However, conventional DTI analyses model a single water compartment within each voxel. Thus, FA and MD measures cannot distinguish specific fine-grained contributions to white matter structure, since indices estimated from a standard tensor model include contributions both from neurite density and fibre arrangement. More advanced analytic approaches can now model intra- and extra-cellular water diffusion separately, enabling a more detailed description of white matter structure (20, 21). Neurite orientation dispersion and density imaging (NODDI) applies a multi-compartment model to separate contributions of neurite density and fibre orientation (Figure 1). Approaches like NODDI benefit from long MRI acquisition times; however, newer clinically feasible protocols have been developed (21). These permit detailed characterisation of white matter integrity that can shed light on the aetiology of brain disorders, and provide indicators for diagnosis, treatment response, and prognosis (14, 22, 23).

In this study of patients with FEP, we applied the NODDI technique (21) to distinguish changes in axonal microstructure from changes in fibre geometry. This enables deeper characterization of white matter abnormalities than is possible with indices such as FA and MD. We hypothesised that specific NODDI signatures of microstructural integrity indicate the presence of a patho-aetiological process of likely neurodevelopmental origin that underpins abnormalities across multiple white matter tracts at an early stage of illness. Ultimately, we seek mechanistic knowledge with clinical utility for biomarking and for developing new preventative interventions.
Methods and Materials

Participants

Patients with FEP were recruited from Sussex Partnership NHS Trust Early Intervention in Psychosis service (N=35; 27 male, 8 female; mean age: 26.9 yrs, range 19-39 yrs, mean years of education 13.4 yrs). The majority 66% (23/35) were aged 18-30 yrs, and 34% (12/35) aged 30-39 yrs, suggesting heterogeneity within the first-episode psychosis population (e.g. schizophrenia and affective psychosis). Diagnosis of psychotic episode was made by a UK psychiatrist. At the time of MRI each patient remained under clinical care of the NHS service. Control participants, matched for age, gender, and years of education, with no history of psychiatric or neurological disorder, were recruited via advertisement within the local community (N=19; 13 male, 6 female; mean age: 24.7 yrs, range 18-38 yrs, mean years of education 13.8 yrs). All participants gave written informed consent. The study was approved by the NRES Camden & Islington research ethics committee.

Clinical assessments and medication

On the day of MRI, symptom severity was assessed using the Positive and Negative Symptom Scale-short form (PANSS-S) (24) by a trained assessor (G.D.). We recorded any psychoactive medication, and calculated olanzapine dose-equivalents (25). Eleven patients were taking only anti-psychotic medications, seven were taking anti-psychotics and additional psychoactive medications, four patients were taking psychoactive medications, e.g. serotonin reuptake inhibitors, but not anti-psychotics, and 13 patients were unmedicated, reflecting typical heterogeneity of early interventions within a first-episode psychosis service (Table 1; Supplementary Table 1 for individual patient data including duration of medication, onset of symptoms to MRI, and diagnosis).
Medication and symptom severity

We tested for a relationship between medication and symptom severity (PANSS-S), using multiple regression in SPSS (v22, IBM) with olanzapine dose-equivalent as a dependent variable, and PANSS positive, negative, and cognitive disorganisation scores as independent variables.

Diffusion MRI data acquisition

MRI data were acquired on a 1.5 T Siemens Avanto. Multi-shell diffusion-weighted data was acquired with single-shot, twice-refocused pulse-gradient spin-echo EPI (voxel size 2.5x2.5x2.5 mm³, 60 axial slices, matrix size 96x96, field-of-view 240x240 mm², TR = 8400ms, TE = 99ms). Three b-value shells were acquired (9 directions with b=300 s/mm², 30 directions with b=800 s/mm², and 60 directions with b=2400 s/mm²), optimised for neurite orientation dispersion and density imaging (NODDI, 21). Eleven images with no diffusion-weighting (b≈0 s/mm²) were acquired. Total acquisition time was 17 minutes.

Diffusion MRI analysis

Data were processed and analysed using FSL (version 5.0.7, http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/), DTI-TK (version 2.3.1, http://dti-tk.sourceforge.net/pmwiki/pmwiki.php), and in-house scripts with the NODDI matlab toolbox (Matlab Inc Nantick II) (http://mig.cs.ucl.ac.uk/index.php?n=Tutorial.NODDImatlab) (21).

DICOMs were converted to NIFTIs using mcverter (https://lcni.uoregon.edu/downloads/mriconvert/mriconvert-and-mcverter).

We computed head movement, using FSL eddy_correct to obtain motion indices in three translations (eddy_correct output logs). The root mean square of total motion was calculated, summing total displacement (26). A between-subjects t-test (SPSS, v22, IBM) indicated that as a group, patients did not move significantly more than controls (mean FEP displacement 57mm, SD=11mm; control 52mm, SD=11mm; t(52) = -1.749, p = 0.086).
However, individual differences in head movement can nevertheless contribute to estimations of diffusion indices (27). We therefore included a motion covariate in all statistical tests (see below).

To correct for motion and eddy currents, we implemented a multi-step image registration using flirt in FSL. Image contrast in diffusion-weighted imaging is strongly dependent on b-value. It was therefore not possible to reliably co-register all diffusion-weighted volumes to the same target image. Instead, a stepwise registration process was adopted. First, a mean image was generated for each shell \( (b = 0, 300, 800, 2400 \text{ s/mm}^2) \) by averaging the volumes for each diffusion direction in the corresponding shell. Next, a transformation matrix was computed to co-register each individual volume with the mean image for the corresponding shell. Another transformation matrix was computed to co-register the \( b = 300, 800 \) and 2400 \( \text{s/mm}^2 \) mean images with the mean \( b_0 \). Finally, the required transformation matrices were combined to transform each individual volume into the same space as the mean \( b_0 \) volume.

Following motion and eddy current correction, diffusion data were skull-stripped using bet2 in FSL, and a brain mask was derived to constrain anatomical fitting of DTI and NODDI parameters. Diffusion tensors were fitted using dtifit in FSL, providing output maps of the three diffusion tensor eigenvectors \((\varepsilon_1, \varepsilon_3)\) and eigenvalues \((\lambda_1, \lambda_3)\), FA, and MD. NODDI models diffusion according to three tissue compartments: intra-cellular restricted diffusion, modelled by sticks; extra-cellular hindered diffusion, modelled by parallel and perpendicular diffusion in an anisotropic tensor; and cerebrospinal fluid free diffusion, modelled by an isotropic tensor (Figure 1). The restricted diffusion of the intra-cellular component gives rise to intracellular volume fraction maps, which index neurite density; while both restricted and hindered diffusion of the intra- and extra-cellular components give rise to orientation dispersion index maps, which index fibre arrangement. The NODDI ‘WatsonSHStickTortIsoV_B0’ model (21) was applied, providing output maps of neurite
orientation dispersion index (ODI; indexing fibre arrangement), and intracellular volume fraction (ficvf; indexing neurite density, ND).

To compare DTI indices between patients and controls, we used tract-based spatial statistics (TBSS, 28) in FSL, with DTI-TK tensor-based registration, in a hybrid DTI-TK–TBSS pipeline. DTI-TK uses the full tensor for registration, rather than FA only (29). This improves registration accuracy compared to conventional TBSS registration using FA (30). A tensor image was created for each participant by converting diffusion eigenvectors and eigenvalues with fsl_to_dtitk in DTI-TK. A study-specific population template was created from participants’ tensor images, by iterative affine, then diffeomorphic, registration to the group mean. This population template was registered to the Illinois Institute of Technology IITmean_tensor.nii mean tensor template (version 4.1, https://www.nitrc.org/projects/iit/), in MNI space, to create the final study template. These two stages generated matrices of transformations from each individual’s native space to the population template, then to standard space. These matrices were used to calculate a deformation field capturing transformations from native to standard space in one interpolation for each participant (see 31, 32).

Following tensor-based registration, in DTI-TK a mean FA map was calculated from the final tensor template. This was skeletonised using tbss_skeleton in FSL to create a mean FA skeleton. Individual participants’ FA maps were calculated in DTI-TK from standard-space registered tensor images, and merged into a 4D file of all participants’ FA maps for entering to TBSS. FA maps were then projected onto the mean FA skeleton using tbss_4_prestats with a threshold of FA>0.3.

Deformation fields, capturing transformations from native to standard space, were applied to each participant’s MD, ODI and ND images to test for group differences in MD and NODDI indices. The skeleton distance maps calculated for the FA images in tbss_4_prestats were
then applied to the MD, ODI, and ND images using \textit{tbss\_skeleton} in \textit{FSL}, to project the non-FA images onto the mean FA skeleton (see 33).

\textit{Voxel-wise statistics}

Voxel-wise statistics were carried out using \textit{palm} in \textit{FSL} (34). Four design matrices tested (1) group difference, with images categorised as ‘patient’ or ‘control’; (2) group difference, with age covariates entered separately for patients and controls; (3) correlation with olanzapine dose-equivalent in the patient group only; (4) correlation with the positive, negative, and cognitive disorganisation scores of the PANSS-S, including olanzapine dose-equivalent as a covariate, in the patient group only. The high correlation between the PANSS subscales, indicating shared variance (see Results), necessitated the use of three different design matrices for ‘positive’, ‘negative’, and ‘cognitive disorganisation’ scores.

Age, gender, and total head movement were entered as nuisance covariates in each design matrix. All covariates were mean-centred across participants. These design matrices were applied to the FA, MD, ODI, and ND images using \textit{palm} with 10,000 permutations, tail acceleration (35), and threshold-free cluster enhancement (36). The option ‘-corrcon’ was applied to correct for multiple contrast testing (35). Statistic images were thresholded at p<0.05 with Family Wise Error Correction for multiple voxel comparisons (FWE). Significant voxels were ascribed anatomical labels using \textit{atlasquery} in \textit{FSL} with the JHU ICBM-DTI-81 White Matter Labels and JHU White Matter Tractography atlases and a minimum likelihood of at least 0.1\% (Table 2). To test for overlap between significant voxels in different contrasts (Figure 2E, Supplementary Figure 1), statistic images were thresholded at p<0.05 FWE, binarised, summed, and the resulting image thresholded at a voxel value of k, where k = number of input statistic images (i.e. testing for voxels present in all k original contrasts at p<0.05 FWE).
Rae et al

ROI comparison

We extracted the mean FA, MD, ODI, and ND for controls and FEP in the corpus callosum body (JHU ICBM-DTI-81 atlas), masking the ROI by the mean_FA_skeleton_mask to include only skeleton voxels (Supplementary Figure 2).
**Results**

*Medication and symptom severity*

Multiple regression revealed no simple relationship between olanzapine dose-equivalent and symptom severity on the three PANSS-S subscales ($F(3) = 0.21, p = 0.891$). Nevertheless, PANSS-S scores correlated with each other: positive symptoms with negative symptoms ($r = 0.35, p = 0.020$), positive symptoms with cognitive disorganisation ($r = 0.45, p = 0.004$), and negative symptoms with cognitive disorganisation ($r = 0.66, p < 0.001$).

*Poorer white matter structure in FEP indicated by reduced neurite density*

Patients with FEP showed abnormalities across multiple white matter tracts with lower FA, and greater MD, compared to controls (Figure 2A, 2B; Table 2). NODDI analyses showed no significant group differences in ODI (Figure 2C), yet the patients had lower neurite density (ND, Figure 2D; Table 2). This overlapped anatomically with many regions of lower FA (Figure 2E), and furthermore also regions of higher MD (Supplementary Figure 1).

Interhemispheric connections, corticospinal projections, and association fibres showed these group differences in FA, MD, and ND (Table 2; also see example ROI of corpus callosum skeleton voxels, Supplementary Figure 2). These data suggest that white matter abnormalities in patients with FEP chiefly reflect reduced neurite density, rather than abnormalities in geometrical organization and angular variation of fibres, suggesting a distinct developmental cause (37).

*Orientation dispersion index correlates with age*

We tested for an association between age and white matter structure, first across all participants (FEP and controls). Age correlated positively with ODI, in the anterior corpus callosum (Figure 3A, Table 2). This suggests that white matter structural geometry changes with increasing age (even within a relatively young adult cohort), expressed as disruption of fibre orientation (21).
We next tested for an association between age and white matter structure in FEP patients and in controls separately, and examined age-by-group interactions to evaluate whether age-related changes ODI were accelerated in patients with FEP. In controls, there were no significant correlations with age. In patients with FEP, however, age correlated negatively with FA in the corpus callosum, and association fibres (Figure 3B, Table 2), and positively with ODI in the anterior corpus callosum (Figure 3C, Table 2). The age-by-group interactions for FA and ODI were below threshold significance.

Impact of medication
Within the patient group, we tested for associations between medication and white matter structure, using correlations of olanzapine dose-equivalent with FA, MD, ODI, and ND. Olanzapine dose-equivalent correlated negatively with FA (Figure 4) within specific white matter tracts, linking higher medication dose to poorer white matter structure (Table 2). There were no significant correlations with MD, ODI or ND.

PANSS-S scores
We observed no suprathreshold correlations between PANSS-S positive, negative, and cognitive disorganisation scores with FA, MD, ODI, or ND.
Discussion

We found anatomically widespread white matter structure alterations in people with FEP. Using diffusion imaging combined with neurite orientation dispersion and density imaging (NODDI) analysis, we demonstrated these white matter alterations as primarily reflecting reduced neurite density. This observation can be attributed to specific changes that include lower axonal count, reduced packing density, and lower myelination (21). Thus we provide an important first demonstration that white matter disturbance in FEP is driven by these microstructural features rather than fibre orientation, which standard diffusion tensor-derived parameters, notably FA, cannot distinguish. In patients, age impacted on fibre geometry: Fibre orientation dispersion increased with age, an effect not present in the controls. Together these findings provide fresh insight into the nature of the biological disruption underpinning white matter abnormalities in psychosis.

Our findings have implications for understanding psychosis as a neurodevelopmental dysconnectivity syndrome. They highlight the value of fine-grained characterisation of white matter abnormalities, including neurite density, to yield insights into pathoetiologial mechanisms that can determine patients’ long-term prognosis and response to treatment.

Psychosis as a neurodevelopmental dysconnectivity risk syndrome

Disrupted white matter structure is likely to precede the onset of a first-episode of psychosis (2). In adolescent cohorts within the general population, alterations in white matter structure associated with psychotic experience can be observed before diagnosis of a mental health condition (3, 10). This suggests that an aberrant neurodevelopmental risk state, centred upon a structural vulnerability that compromises functional connectivity, can predispose to psychotic symptoms, which in some individuals, may progress to a diagnosed disorder.
In order to better understand the origins of structural dysconnectivity in psychosis, we sought a more detailed characterisation of the microstructural abnormalities that underpin white matter differences (notably, fractional anisotropy, FA; and mean diffusivity, MD) previously reported using diffusion MRI (2, 8). Using the NODDI technique, we modelled intra- and extra-cellular contributions to diffusion. This permitted us to differentiate changes to neurite density versus fibre orientation. Our *in vivo* observation of reduced neurite density might arise from alterations developmental processes such as neuronal migration, axon guidance, myelination, and synaptic pruning (18, 19, 38). For example, aberrant neuronal migration may reduce the number of neurites within a fibre bundle, while excessive synaptic pruning may lead to withdrawal of axonal projections.

It is noteworthy that we did not observe significant group differences in neurite orientation dispersion, except in regard to age. Developmental insults can theoretically affect neurite orientation, e.g. through disruption of brain matrix and/or programmed migration path. However this does not reliably determine risk of early psychosis. Nevertheless, alterations in fibre arrangement can still foster processes that lead to secondary (age-related) organizational disruption. In the general population, while neurite density increases logarithmically throughout adolescent life, the orientation dispersion index decreases exponentially from early adulthood into later life (37, 39). In light of this, our results suggest a core deficit in neurite density during early development in individuals with psychosis, yet the experience of a psychotic episode may encourage premature age-related changes in white matter geometry, reflected by increasing fibre orientation dispersion with age.

Future imaging studies of at-risk populations should usefully integrate genotyping of specific polymorphisms linked to neuronal development, with estimation of NODDI parameters from diffusion MRI, and nonlinear modelling of relevant demographic features, to gain more precise insight into the developmental origins and biological nature of microscale disruptions in white matter relevant to psychosis.
**Distribution of network abnormalities**

We observed reductions in white matter fractional anisotropy and neurite density within all lobes, affecting interhemispheric, corticospinal, and association tracts. Our findings are inconsistent with focal concentration of structural dysconnectivity in frontal and temporal lobes (8), and fit with the observed broader distribution of white matter changes across multiple regions in psychosis (2, 9). This widespread expression of structural connectivity abnormalities suggests a shared, and perhaps early, aetiology that accords with the diverse expression of symptoms, including alterations to conscious experience, in psychosis. Moreover, the structural connectivity abnormalities likely underpin concomitant dysfunctional network interactions, observed in fMRI (10, 12, 40), which in turn can reflect symptom experience, severity of psychosis, and response to treatment (2, 13, 41).

In the context of predictive coding accounts of psychosis (42-44), these widespread reductions in neurite density may result in network-wide failures to balance ascending sensory ‘prediction error’ signals against descending top-down perceptual predictions (45). These failures may arise from a reduced capacity to modulate synaptic gain, as a result of reduced efficiency of impoverished modulatory axonal projections.

**Disorder severity & interaction with medication**

We found that in a subset of white matter tracts, FA was associated with neuroleptic dose level. The question arises as to whether white matter abnormalities may be more extreme in patients who require higher levels of neuroleptic therapy and/or whether such medications alter white matter.

In our sample, we did not observe significant correlations between PANSS scores and white matter. Previous diffusion imaging studies in FEP report correlations between white matter structure and PANSS scores (13, 46). In medicated patients, drug therapy typically improves symptoms, hence the PANSS-S may not reflect severity at presentation and diagnosis,
constraining the interpretation of correlations between symptom severity score and white matter structure.

Nevertheless, anti-psychotics may change white matter, according to animal models (47) and human imaging (48-50). The mean duration of medication for the 18 medicated patients was over a year, which may be sufficient time for neuroleptic-induced plasticity or changes, although there were individual patient differences. However, it is interesting that there were no effects of medication on neurite density or orientation dispersion, which suggests effects on FA do not relate to axonal structure or fibre geometry. At present evidence for the impact of neuroleptics on white matter appears to be equivocal (2) and may index historical patterns of medication use.

To further address how anti-psychotic use relates to microstructural features, longitudinal studies of larger cohorts may permit examination of sub-groups of patients differentiated according to precise anti-psychotic medication taken, and relative expression of symptoms, alongside pre- and post-medication quantification of white matter structural integrity including NODDI measures.

Predictive value for prognosis and treatment response

White matter structure at FEP is likely to relate to long-term prognosis and response to treatment (2). It is essential that the biological nature of white matter aberration is understood if microstructural measures are to prove valuable as clinical biomarkers. The multi-compartment model of the NODDI technique is particularly valuable in this regard, given that it can identify in greater detail the nature of the neuroanatomical change in white matter, beyond diffusion tensor-derived indices such as FA. Patients with reduced neurite density may be less likely to respond to drug therapies if a decrease of axonal bundles has already occurred, while patients may be poised to respond well if they exhibit a relative preservation of neurite density, whereby the function of the remaining neurons can be
boosted. In following a longitudinal outcome, if neurite density continues to decline with repeated episodes, the potential for recovery may diminish.

Treatments typically focus on managing symptoms after they have emerged. However, prevention is an ultimate ambition. Perhaps by identifying those most at risk of psychosis through expression of developmental dysconnectivity, interventions can be implemented before onset of psychosis. Here, we highlight the overarching contribution of disordered neurite density (rather than fibre geometry) to dysconnectivity at a first episode of psychosis. Effective early treatment interventions might usefully target the prevention of neurite depletion as a therapeutic target.

The identification of imaging biomarkers that can be acquired in a short acquisition time will help characterise the neurobiology of poor white matter structure, and thereby inform the development of new targeted early interventions. Practically, a brief imaging protocol is necessary for patients who may have problems tolerating longer imaging times. Even if scanning is broadly tolerated, movement and other artefacts may compromise data quality. Including motion covariates remains important, as head movement impacts estimation of diffusion indices (27). It is also important to consider trade-offs between impact of high b-values and number of directions on accuracy of tensor and other model fits (26, 51). Nevertheless, a multi-shell diffusion acquisition with NODDI analysis offers biologically more insightful indices of white matter structure than is possible with a single shell, yet requires only a modest increase in acquisition time, particularly with simultaneous multi-slice acquisition (52). NODDI thus provides a practical route to address microstructural abnormalities in investigations of white matter structure in patients with psychosis or other neuropsychiatric disorders.
Limitations of the present study

While this is the first demonstration of neurite density deficits in FEP, it is relevant to consider the heterogeneity of the sample, with varied diagnostic outcomes including schizophrenia, affective psychosis, and substance-induced psychosis (Supplementary Table 1). The age distribution also reflected such heterogeneity, encompassing a period of 20 years. Larger patient samples and longitudinal studies may permit greater power and deeper insight into how NODDI indices may differ in clinical sub-categories and at varying timepoints across the lifespan. Beyond NODDI analyses, a future goal of diffusion modelling is to further dissect contributions of myelination, axonal number, packing density, and diameter, to neurite density (16, 17). Multi-modal functional and structural datasets can provide mechanistic insights, where multiple testing on non-normally distributed data will benefit from non-parametric approaches such as permutations tests (34).

Conclusions

NODDI separates changes in neurite density relating to axonal structure from alterations in fibre geometry. In first-episode psychosis, neurite density is reduced across anatomically distributed white matter tracts, and overlaps anatomically with changes in fractional anisotropy. This accords with evidence that psychosis is a neurodevelopmental dysconnectivity risk syndrome, in which reduced brain-wide structural connectivity and impairment of axonal structure increases the likelihood of developing abnormal conscious experiences of the self and of the world.
Acknowledgements

This work was funded by a donation from the Dr Mortimer and Theresa Sackler Foundation. HDC and SNG are supported by an ERC Advanced Grant (324150 CCFIB, Cardiac Control of Fear in the Brain). Thanks to Abigail Wright for assistance with patient diagnosis records.
Financial Disclosures

Dr Rae, Dr Davies, Dr Garfinkel, Mr Gabel, Dr Dowell, Prof Cercignani, Prof Seth, Dr Greenwood, Dr Medford, and Prof Critchley reported no biomedical financial interests or potential conflicts of interest.
References


**Figure Legends**

**Figure 1.** The NODDI technique and how it differs from traditional diffusion tensor imaging (DTI). In DTI, a diffusion tensor models three orthogonal axes of diffusion (V1, V2, V3), from which fractional anisotropy (FA) and mean diffusivity (MD) can be estimated. NODDI models diffusion according to three compartments: restricted diffusion in the intra-cellular compartment, hindered diffusion in the extra-cellular, and free diffusion in cerebrospinal fluid (CSF). From this model, parameter maps representing neurite density (ND) and orientation dispersion index (ODI) can be estimated. Yellow circles highlight region where changes in FA can be accompanied by changes in both ND and ODI.

**Figure 2.** Group difference between first-episode psychosis (FEP) and controls: (A) reduced FA, (B) increased MD, (C) no significant group differences in ODI, (D) reduced ND, (E) overlapping voxels of reduced FA and reduced ND. (A-D) shown at p<0.05 FWE with threshold-free cluster enhancement. Tracts with bilateral white matter abnormalities shown here include the corpus callosum, corticospinal tract, anterior thalamic radiation, inferior fronto-occipital fasciculus, superior longitudinal fasciculus, and inferior longitudinal fasciculus (also see Table 2). Slice labels (0-40) indicate z co-ordinate in MNI space.

**Figure 3.** Age and white matter structure. (A) positive correlation with ODI, in both FEP and controls, in the anterior corpus callosum; (C) negative correlation with FA in FEP only, (D) positive correlation with ODI in FEP only. (A-C) shown at p<0.05 FWE with threshold-free cluster enhancement. Slice labels (0-20) indicate z co-ordinate in MNI space.

**Figure 4.** Medication level (olanzapine dose-equivalent) and white matter structure: negative correlation with FA (p<0.05 FWE threshold-free cluster enhancement) in the internal capsule, corticospinal tract, anterior thalamic radiation, inferior fronto-occipital fasciculus,
and superior longitudinal fasciculus (also see Table 2). Slice labels (0-40) indicate z coordinate in MNI space.