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# Deficits in Neurite Density Underlie White Matter Structure Abnormalities in First-Episode Psychosis

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## ABSTRACT

**BACKGROUND:** Structural abnormalities across multiple white matter tracts are recognized in people with early psychosis, consistent with dysconnectivity as a neuropathological account of symptom expression. We applied advanced neuroimaging techniques to characterize microstructural white matter abnormalities for a deeper understanding of the developmental etiology 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, a multishell diffusion-weighted magnetic resonance imaging technique that distinguishes white matter fiber 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 control subjects 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 fiber bundle arrangement (orientation dispersion index). There was no direct relationship with active symptoms. FA decreased and orientation dispersion index increased with age in patients, but not control subjects, 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 neurite orientation dispersion and density imaging in psychosis, we found that processes compromising axonal fiber number, density, and myelination, rather than processes leading to spatial disruption of fiber organization, are implicated in the etiology of psychosis. This accords with a neurodevelopmental origin of aberrant brain-wide structural connectivity predisposing individuals to psychosis.

*Keywords:* Diffusion MRI, First-episode psychosis, Fractional anisotropy, Neurite density, Neurite orientation dispersion and density imaging (NODDI), White matter microstructure

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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 the brain are observed in post-mortem studies (7) and in vivo noninvasive 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 first-episode psychosis (FEP), preceding pharmacological treatment with neuroleptic medications (2,3,10).

The white matter abnormalities reported in FEP affect multiple fiber 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

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migration (18,19). Disordered axonal structure and fiber organization can result from such disruption. Thus, a key objective for understanding the nature, etiology, and implications of white matter abnormalities in FEP is to characterize microstructural differences in axonal structure, including axonal number, packing density, and myelination, and to differentiate these from variations in fiber 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, as indices estimated from a standard tensor model include contributions from both neurite density (ND) and fiber arrangement. More advanced analytic approaches can now model intracellular and extracellular water diffusion separately, enabling a more detailed description of white matter structure (20,21). Neurite orientation dispersion and density imaging (NODDI) applies a multicompartment model to separate contributions of neurite density and fiber orientation (Figure 1). Approaches such as NODDI benefit from long MRI acquisition times; however, newer clinically feasible protocols have been developed (21). These permit detailed characterization of white matter integrity that can shed light on the etiology 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 fiber geometry. This enables deeper characterization of white matter abnormalities than is possible with indices such as FA and MD. We hypothesized that specific NODDI signatures of microstructural integrity indicate the presence of a pathoetiological 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 preventive interventions.

## METHODS AND MATERIALS

### Participants

Patients with FEP were recruited from the Sussex Partnership National Health Service Trust Early Intervention in Psychosis service ($n$ = 35; 27 men, 8 women; mean age, 26.9 years; age range, 19–39 years; mean years of education, 13.4 years). The majority of patients (66%; 23 of 35) were 18–30 years old, and 34% (12 of 35) were 30–39 years old, suggesting heterogeneity within the FEP population (e.g., schizophrenia and affective psychosis). Diagnosis of psychotic episode was made by a U.K. psychiatrist. At the time of MRI, each patient remained under clinical care of the Early Intervention in Psychosis 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 men, 6 women; mean age, 24.7 years; age range, 18–38 years; mean years of education, 13.8 years). All participants gave written informed consent. The study was approved by the National Research Ethics Service Camden and Islington Research Ethics Committee.

### Clinical Assessments and Medication

On the day of MRI, symptom severity was assessed using the Positive and Negative Syndrome Scale short form (PANSS-S) (24) by a trained assessor (GD). We recorded any psychoactive medication and calculated olanzapine dose-equivalents (25). Of the patients, 11 were taking only antipsychotic medications, 7 were taking antipsychotics and additional psychoactive medications (e.g., serotonin reuptake inhibitors), 4 were taking psychoactive medications but no antipsychotics, and 13 were unmedicated, reflecting typical heterogeneity of early interventions within an FEP service (Table 1; see Supplemental Table S1 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 version 22 (IBM Corp., Armonk, NY) with olanzapine dose-equivalent as a dependent variable and PANSS positive, negative, and cognitive disorganization scores as independent variables.

### Diffusion MRI Data Acquisition

MRI data were acquired on a 1.5T MAGNETOM Avanto MRI scanner (Siemens Healthcare GmbH, Erlangen, Germany). Multishell diffusion-weighted data were acquired with single-shot, twice-refocused pulse gradient spin-echo echo planar imaging (voxel size 2.5 × 2.5 × 2.5 $mm^3$, 60 axial slices, matrix size 96 × 96, field of view 240 × 240 $mm^2$, repetition time = 8400 ms, echo time = 99 ms). Three b-value shells were acquired (9 directions with b = 300 $s/mm^2$, 30 directions with b = 800 $s/mm^2$, and 60 directions with b = 2400 $s/mm^2$), optimized for NODDI (21). Eleven images with no diffusion weighting (b ≈ 0 $s/mm^2$) were acquired. Total acquisition time was 17 minutes.

### Diffusion MRI Analysis

Data were processed and analyzed 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 (The MathWorks, Inc., Natick, MA; http://mig.cs.ucl.ac.uk/index.php?n=Tutorial.NODDImatlab) (21). DICOM images were converted to NIfTI images 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 version 22) indicated that as a group, patients did not move significantly more than control subjects (mean FEP displacement 57 mm, SD 11 mm; control 52 mm, SD 11 mm: $t_{52} = -1.749$, $p = .086$). 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 multistep image registration using FLIRT in FSL. Image