White Matter Microstructure in Early-Onset Schizophrenia: A Systematic Review of Diffusion Tensor Imaging Studies

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Objective: Neurodevelopmental processes and neural connectivity are thought to play pivotal roles in schizophrenia. This article reviews diffusion tensor imaging (DTI) studies of brain white matter connections and microstructure and their development in patients with early-onset schizophrenia (EOS), that is, schizophrenia with an age of onset before 18 years.

Method: A systematic literature search revealed 21 original case-control DTI studies of children and/or adolescents with EOS.

Results: Nearly all studies report significantly lower regional fractional anisotropy (FA) in patients with EOS than in healthy control participants. However, the anatomical locations and extent of these differences are highly variable across studies. Furthermore, consistent evidence for associations between DTI indices and age of onset, medication variables, and measures of symptomatology and cognition in EOS is lacking. Only 3 available studies have investigated cross-sectional age-related differences or longitudinal changes in DTI measures in adolescents with EOS. The results are mixed, with different studies indicating diverging, converging, or parallel developmental FA trajectories between patients and controls.

Conclusion: The study of brain structural connectivity, as inferred from DTI, and its development in EOS may inform us on the origin and ontogeny of schizophrenia. We suggest some directions for future research in this field and argue for increased focus on developmental questions. Specifically, further investigations of age of onset effects and multimethod longitudinal studies of structural and functional connectivity development before, at, and after onset of schizophrenia and related syndromes in children and adolescents are called for.

Key words: brain development, diffusion tensor imaging, early-onset, schizophrenia, white matter

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Various models of the ontogeny of schizophrenia are still debated, but one of the central perspectives remains the neurodevelopmental model, which, broadly stated, posits that the syndrome involves abnormal neurodevelopmental processes caused by an interplay of genetic and early environmental events that is set in motion before the brain approaches its adult anatomical state and/or psychosis onset.[1,2] Early-onset schizophrenia (EOS), defined as onset before age 18 years, occurs rarely. Psychoses have an estimated prevalence of 0.9 in 10,000 at age 13 years, showing a steady increase during adolescence, reaching a prevalence of 17.6 in 10,000 at age 18 years.[3] Patients with childhood-onset schizophrenia in particular present with more severe symptoms and have worse prognoses than patients with adult-onset schizophrenia.[4] However, patients with EOS and adult-onset schizophrenia share similar patterns of phenomenological, genetic, and cognitive abnormalities.[5] The study of brain structure and function in children and adolescents with schizophrenia, and, critically, the development of these, may provide important clues for understanding the origin of this major mental disorder.

Brain imaging in adult samples has delineated the neural systems involved in schizophrenia, including but not limited to prefrontal, medial temporal, and superior temporal regions.[6-8] Studies of children and adolescents with EOS overall implicate similar brain regions, although it is unknown whether the brain abnormalities are more or less severe than those observed in adult-onset schizophrenia.[9,10] Magnetic resonance imaging (MRI) studies of brain structure in children and adolescents with EOS also indicate altered developmental trajectories of gray matter volumes and regional cortical thickness.[11-14] Importantly, the distributed nature of the implicated brain regions may suggest that neural connectivity plays a central role.

The disconnection hypothesis of schizophrenia[15,16] suggests that some of the core symptoms relate to abnormal connectivity between multiple spatially distributed brain regions.[17-19] The hypothesis has been investigated in a substantial number of both functional and structural imaging studies at different stages of schizophrenia. Functional connectivity is currently typically measured using task or resting-state functional MRI (fMRI), whereas structural connectivity is often examined using diffusion tensor imaging (DTI), which is the focus of the current review. Briefly, the basis for DTI is the measurement of the diffusion, or random translational motion, of water molecules, and the technique indirectly characterizes tissue architecture at a micrometer scale (for more in-depth introductions to DTI and its biological basis, we refer the reader elsewhere[20-23]). When unconstrained, water diffusion is equal in all directions, that is, isotropic, whereas in brain tissue it reflects, to varying degrees, interactions with tissue compartments such as cell membranes, fibers, or macromolecules, and it may, because of these restricting structures, be directional or anisotropic. Commonly reported DTI measures include

fractional anisotropy (FA), indexing degree of net directionality in water diffusion, and mean diffusivity (MD), reflecting the overall magnitude of diffusion. Furthermore, measures of diffusion along (axial diffusivity [AD]) and across (radial diffusivity [RD]) the primary diffusion direction can yield additional information relevant for characterizing white matter microstructure. Although the results are not always consistent, the general consensus appears to be that, across different stages of the disorder and methods, schizophrenia is associated with abnormalities in neuroimaging measures that could be interpreted as connectivity alterations relative to healthy controls.[17] Specifically, DTI studies of patients with schizophrenia or related disorders have reported FA reductions in many different brain regions, most consistently in frontal and temporal white matter.[8,24] Many questions do remain, however, including the precise anatomical networks involved, the degree of regional specificity, and the relationships to clinical and cognitive manifestations and functions, developmental course, and outcome of the abnormal network connectivity.

The current review focuses on DTI studies of white matter microstructure and its development in EOS. First, as we cannot understand how development may go awry in EOS and other disorders without first understanding the processes of normal development, we give an overview of DTI studies of white matter microstructure development in healthy children and adolescents. Second, a systematic review and critical discussion of DTI studies comparing children and adolescents with EOS and healthy controls is presented. Third, studies investigating relations between DTI indices and clinical and cognitive measures in EOS are reviewed. Fourth, studies investigating cross-sectional age-related differences or longitudinal changes in DTI measures of white matter microstructure in EOS are reviewed and discussed. Finally, some future directions for the field are suggested.

METHOD

An online search of the Scopus database was conducted on October 28, 2015 using the keywords "schizophrenia" AND "early-onset" OR "childhood-onset" OR "adolescent-onset" AND "DTI" OR "diffusion," and revealed 36 documents. For this review, articles were included if they met the following criteria: original research article; used DTI; included patients with early-onset (<18 years) schizophrenia spectrum disorders; included a healthy control group; performed case-control group comparisons of FA/MD/RD/AD: were written in English. This left only 16 studies published in the period 2004 to 2015. Reference lists of the identified publications and relevant review articles were then searched for additional studies, and 5 articles published in the period 2007 to 2015 meeting the above-listed criteria were identified, yielding a total number of 21 articles for the current review. Precise details regarding sample overlap between studies could not be consistently identified.

Studies or analyses investigating samples with an increased risk for developing schizophrenia, either individuals with relatives diagnosed with schizophrenia[25] or individuals showing specific symptoms or functional decline[26] or studies investigating other DTI indices than FA/MD/RD/AD,[27-29] were not included in the review. For reviews of DTI findings in early stages of schizophrenia, including both EOS and adult-onset schizophrenia, and in individuals characterized as genetic or clinically at high risk, we refer the reader elsewhere.[30,31]

A separate section of the review is devoted to cross-sectional studies investigating age-related differences and longitudinal studies investigating change in DTI measures over time, as these studies may shed light on whether white matter microstructural abnormalities in children and adolescents with EOS are stable over time or show a dynamic evolution reflecting altered trajectories of brain development. Two of the above-identified studies[32,33] and one additional study[34] were included in this section of the review.

NORMAL DEVELOPMENT OF WHITE MATTER MICROSTRUCTURE

The delineation of normal brain developmental trajectories provides an invaluable and necessary template for identifying possible atypical patterns of brain development in EOS and other disorders.[35] Beyond the very rapid changes seen in DTI indices in infancy,[36] cross-sectional studies have consistently documented age-related differences across children and adolescents in the form of FA increases and overall diffusivity decreases with increasing age in most white matter regions.[37,38] Studies with very wide age ranges have further extended these findings, indicating non-monotonic lifespan age trajectories of FA, MD, and RD characterized by 3 phases: initially fast but decelerating changes through childhood and adolescence and into young adulthood; relative stability in mid-adulthood; and reversed and accelerating changes in senescence.[39,40] Longitudinal developmental studies following the same individuals over time to measure within-person change are now also confirming widespread white matter FA increases and MD and RD decreases through childhood and adolescence, but the results for AD are less consistent.[41-45]

Importantly, the rates and timing of developmental DTI changes vary regionally in the brain. Studies have revealed a pattern of maturation in which major white matter tracts with fronto-temporal connections develop more slowly than other tracts.[37,41] Of the major fiber bundles, the cingulum appears to be among those with the most prolonged development of FA.[39] Crucially, individual- and age-related differences in DTI measures of white matter microstructure have also been linked to behavioral measures, documenting their functional consequences.[46-48]

Animal and post mortem human studies indicate that axonal membranes, density, and coherence, as well as myelin sheaths, are the main factors that drive diffusion anisotropy.[49] In tightly controlled model systems, modulating either axon fibers or myelin can be shown to have an impact at least somewhat specifically on specific DTI measures,[50] but these models do not necessarily generalize. For instance, it does not logically follow from animal studies that age-related differences in RD in healthy humans reliably indicate differences in myelination.[51] Developmental changes in DTI indices in white matter are mainly thought to relate to processes including increased relative axon caliber and myelin content, as well as changes in fiber packing density.[52] In addition, other factors such as brain water content, crossing or diverging fibers, and partial volume