# Altered Development of White Matter in Youth at High Familial Risk for Bipolar Disorder: A Diffusion Tensor Imaging Study

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**Objective:** To study white matter (WM) development in youth at high familial risk for bipolar disorder (BD). WM alterations are reported in youth and adults with BD. WM undergoes important maturational changes in adolescence. Age-related changes in WM microstructure using diffusion tensor imaging with tract-based spatial statistics in healthy offspring having a parent with BD were compared with those in healthy controls. **Method:** A total of 45 offspring participated, including 20 healthy offspring with a parent diagnosed with BD (HBO) and 25 healthy control offspring of healthy parents (CONT). All were free of medical and psychiatric disorders. Mean fractional anisotropy (FA), radial diffusivity (RD), and longitudinal diffusivity were examined using whole-brain analyses, co-varying for age. **Results:** Group-by-age interactions showed a linear increase in FA and a linear decrease in RD in CONT in the left corpus callosum and right inferior longitudinal fasciculus. In HBO, there was a linear decrease in FA and an increase in RD with age in the left corpus callosum and no relation between FA or RD and age in the right inferior longitudinal fasciculus. Curve fitting confirmed linear and showed nonlinear relations between FA and RD and age in these regions in CONT and HBO. **Conclusions:** This is the first study to examine WM in healthy offspring at high familial risk for BD. Results from this cross-sectional study suggest altered development of WM in HBO compared with CONT in the corpus callosum and temporal associative tracts, which may represent vulnerability markers for future BD and other psychiatric disorders in HBO. J. Am. Acad. Child Adolesc. Psychiatry, J. Am. Acad. Child Adolesc. Psychiatry, 2010; 49(12):1249–1259. **Key words:** bipolar disorder, familial risk, white matter, diffusion tensor imaging, neurodevelopment

Bipolar disorder (BD) is a serious psychiatric illness affecting 1% to 3% of the adult population and remains a leading cause of morbidity, functional impairment, and completed suicide.[1] BD is characterized by difficulties in the regulation of emotions and behavior, as indicated by episodes of mania and depression. BD is highly heritable: the risk of BD is much greater in first-degree relatives of individuals diagnosed with BD.[2,3] Recent evidence has indicated that offspring of parents with BD are at increased risk for BD and other psychiatric disorders, including BD spectrum disorder, anxiety, and depression disorders.[2] Although genetic and environmental factors and their interactions are important in the development of BD, abnormalities of brain structure and function that most likely mediate these effects have yet to be elucidated. Converging evidence from epidemiologic, genetic, and neuroimaging studies has suggested that abnormalities in the development of white matter (WM) may play an important role in the neuropathophysiology of BD.[4] However, the extent to which WM development may be altered in offspring at high familial risk of BD has yet to be determined.


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Diffusion tensor imaging (DTI) is a noninvasive neuroimaging technique that uses the diffusion of water to investigate subtle changes in WM microstructural organization. DTI employs fractional anisotropy (FA), an index of the ratio of diffusional anisotropy in longitudinally aligned versus transverse directions of WM tracts. That is, voxels containing water moving predominantly along the principal diffusion direction, rather than the transverse directions, have a higher FA. Findings from previous DTI studies have suggested that adults with BD have WM abnormalities in prefrontal and subcortical regions implicated in emotional processing and emotion regulation. The majority of these studies, using a region-of-interest approach, have reported WM abnormalities in adults with BD in prefrontal regions,[5-12] including frontotemporal WM abnormalities in the uncinate fasciculus, a major WM tract connecting anterior temporal and orbitomedial prefrontal cortices.[7,10,11] Whole-brain studies in adults with BD have confirmed WM abnormalities, including increases and decreases in FA, in frontotemporal regions. [6,13,14] They also have reported abnormalities in fibers projecting to temporal[13] and occipital cortices.[6,13] Similarly, the few recent studies in pediatric BD also have reported an abnormally lower FA in prefrontal regions.[15-18] Furthermore, lower FA,[15,19] abnormal signal intensity,[20] and abnormal curvature shape[21] of the corpus callosum (CC) have been shown in youth with BD compared with healthy controls. FA decreases in fibers projecting to temporal,[16] frontal,[19] and occipital cortices[15,16] have also been reported in whole-brain studies in youth with BD compared with healthy controls.

One methodologic issue in DTI is the interpretation of changes in FA. A higher FA could reflect greater myelination of WM fibers, a larger number of myelinated fibers, or greater longitudinal versus oblique directional alignment of fibers. To improve the interpretation of changes in FA, including measurements of radial and longitudinal diffusivities (RD and L1, respectively)[22] has been recommended. L1 is an index of the principal—longitudinal—diffusion direction, whereas RD is an average of the transverse directions and an index of the diffusivity in directions that are perpendicular to the principal axis of diffusion. For example, changes in RD in the absence of changes in L1 have been associated with changes in myelin,[23] whereas changes in L1 in the absence of changes in RD have been associated with increases in axon diameter.[24] In a recent study with BD versus healthy adults,[6] we included RD and L1, which contributed to a better interpretation of group differences in FA.

Abnormalities in WM have been observed in individuals at risk for BD.[2,25,26] For example, one study reported decreased left hemispheric WM volume in adult patients with BD and their unaffected twin compared with age-matched healthy individuals.[27] We are aware of only one study to date that, using voxel-based DTI, examined WM tracts in offspring (4 to 12 years old) of parents with BD (n = 7) compared with children with BD (n = 10) and age-matched healthy controls (n = 8).[19] This study reported lower FA in bilateral superior longitudinal fascicule in the offspring of parents with BD and children with BD compared with healthy controls. However, like the children with BD, the majority of the offspring of parents with BD met criteria for another Axis I disorder (e.g., attention-deficit/hyperactivity disorder), which may have had an effect on the DTI findings in this group. Although offspring of parents with BD do exhibit higher levels of psychopathology than community controls,[2] focusing on *healthy* offspring with a parent diagnosed with BD is an important *first step* to improve the ability to identify potential neurodevelopmental vulnerability markers of BD and eliminate the possible confounding effects of psychopathology and/or psychotropic medication in offspring with BD on DTI measurements.

Another important issue is the extent to which WM tracts develop normally in youth at high familial risk of BD. A growing number of studies in healthy youth has suggested important maturational changes in WM during adolescence.[28,29] A recent DTI study reported age-related increases in FA (decreases in RD) in specific WM tracts across adolescence.[28] Given that adolescence is a vulnerable developmental window for the onset of mood disorders such as BD,[30] examining age-related changes in WM tracts in healthy offspring having a parent with BD across adolescence may help elucidate specific neurodevelopmental vulnerability markers of BD.

In this study, we used DTI to examine the development of WM microstructure in healthy offspring having a parent with BD (healthy bipolar offspring [HBO]) versus healthy control offspring of healthy parents (healthy control [CONT]). We conducted whole-brain analysis