Evidence of White Matter Pathology in First-Episode Manic Adolescents with Bipolar Disorder: A Diffusion Tensor Imaging Study

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Background: Several recent studies have identified neuroanatomic and neurofunctional changes in patients with bipolar disorder, involving what appear to be core areas of emotional and cognitive neural processing. While the bulk of recent research findings have focused on identifying specific regional abnormalities in patients with bipolar disorder, we and others have hypothesized that affective symptomatology may be related to dysfunctional networking between these areas of the brain. Nonetheless, few studies to date have examined the white matter pathways linking these structures. Several lines of evidence suggest the presence of white matter pathology in patients with bipolar disorder. Increased numbers of white matter hyperintensities (WMH) for instance, a possible indicator of white matter pathology, have been reported in patients with bipolar disorder. More directly, studies have reported decreased whole brain white matter volume and density in bipolar patients, compared with healthy controls. Differences appear to be subtle however, as other studies examining both whole brain and frontal white matter failed to replicate these findings, as did a study examining T1 proton relaxation times, another measure of white matter integrity. These differences in study findings may be due to the insensitivity of the measures employed. Diffusion tensor imaging (DTI) is a relatively new magnetic resonance based technique that utilizes measures of water diffusion to study the structural integrity and coherence of white matter. Using DTI, we have previously observed decreased fractional anisotropy (FA) in patients with bipolar disorder, suggestive of white matter pathology. It remains unclear however, whether abnormalities in white matter tracts are a result of pathological changes linked to illness progression or an innate feature of bipolar disorder. Resolving this issue would have significant implications for our understanding of the neurophysiology of bipolar disorder at the time of illness onset. In this study, we utilized DTI to study regional white matter in first episode manic adolescents with bipolar disorder.

Methods: Eleven adolescents with bipolar I disorder who were mood-stabilizer and neuroleptic naïve, hospitalized for the first time for a manic/mixed episode, and a demographically matched group of seventeen healthy controls were recruited. Diffusion-weighted spin-echo single-shot echo-planar twenty-five gradient DTI and high-resolution T1-weighted 3-D brain scans were acquired. Regions-of-interest (ROIs) were identified in prefrontal and posterior white matter tracts. Regions chosen were contiguous with areas previously observed to be abnormally activated in functional neuroimaging studies. FA and trace apparent diffusion coefficient (TADC) were compared by ROI between study groups.

Results: Adolescents with bipolar disorder showed significantly decreased FA in portions of frontal white matter tracts, with the largest difference in the frontal cortex 19-24 mm above the anterior-posterior commissural (ac-pc) plane ($t=2.84$, $df=26$, $p<0.005$). Findings were bilateral but particularly significant on the left. TADC did not significantly differ between groups in any region tested. No changes in the FA or TADC of posterior cortical white matter tracts were found.

Conclusion: These findings suggest that white matter abnormalities are non-uniformly present early in the course of bipolar disorder. Because differences were found in FA, which may be more sensitive to a loss of axonal coherence, without corresponding group differences in the TADC, these findings suggest that white matter changes may consist largely of axonal disorganization. Observing these changes in young first-episode patients further suggests that white matter pathology may be a core feature of bipolar disorder.