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Neuroimaging Findings Specific for Bipolar Disorder in Children: Quantitative Structural and Diffusion Tensor Imaging

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Purpose: Bipolar disorder (BD) manifests in children as a severe behavioral disturbance characterized by paroxysmal outbursts of disproportionate rage separated by intervening periods of more stable mood with or without depressive symptoms. A major clinical problem in child psychiatry is the differentiation of children with BD from those with ADHD. Misdiagnosis is common and incorrect treatment of children who in fact have bipolar disorder may lead to poor outcomes. We have evaluated a group of patients meeting research diagnostic criteria for the pediatric bipolar core phenotype. The aim of this study is to determine if asymmetry of limbic brain structures occurs in children with BD and if these findings are related to abnormalities of white matter integrity as shown by diffusion tensor imaging (DTI).
Materials and Methods: 10 children (ages 8-16) were identified by a behavioral neurologist and referred for imaging at 1.5 T. Standardized research-clinical evaluations confirmed the diagnosis of Pediatric BD core phenotype. Whole brain volumetric imaging was accomplished using a 3D FSPGR acquisition acquired at 1 mm^3 isotropic resolution. Quantitative volumetric measurement of amygdala, hippocampus and cingulate gyrus was performed after segmentation of grey/white/CSF by experienced raters using validated criteria and 3D SLICER. Whole brain DTI was acquired with b=1000 and 25 independent diffusion directions. Regions of interest were placed in the frontal white matter for assessment of mean fractional anisotropy (FA). Asymmetry was assessed using paired samples T-test.
Results: Initial review of brain images by a CAQ certified Neuroradiologist identified striking asymmetry of mesial temporal structures. Quantitative measurements confirmed statistically significant asymmetry of amygdala ($p<0.0001$), hippocampus ($p<0.001$) and cingulate gyrus ($p=0.04$). In addition, greater asymmetry of anterior cingulate gyrus compared to posterior cingulate gyrus was suggested. ROI

measurements of FA suggested lower FA in left frontal white matter.
Discussion: These findings show a striking structural brain abnormality in a carefully screened patient group. The abnormal brain structures are putative substrates of neuropsychological domains found to be dysfunctional in children with BD and implicated in its pathogenesis. The asymmetry of mesial temporal structures is particularly striking in light of data from epilepsy research that demonstrates symmetry of these regions in normal young subjects. Suggestion of abnormality in the anterior, but not the posterior portion of the cingulate gyrus is consistent with reported implication of the anterior cingulate in processing of emotion and the posterior cingulate in motor function. Finding asymmetry of frontal white matter using DTI potentially implicates fronto-limbic circuits in the pathogenesis of the disorder. This is consistent with existing hypotheses regarding the brain substrates of the disorder. Perhaps most importantly, these results indicate that specific imaging findings may be useful in psychiatric differential diagnosis and may ultimately provide a diagnostic tool for resolving an important clinical problem in child psychiatry.

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