White Matter Abnormalities Detected in Very Early-Onset Bipolar Disoder

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Objectives: Structural and functional magnetic resonance imaging (MRI) studies in youths with bipolar disorder (BD) have found abnormalities in the prefrontal cortex (PFC), parietal lobe (PL), temporal lobe (TL), and limbic (amygdala and hippocampus) structures. Furthermore, a recently submitted volumetric analysis of the corpus callosum (CC) in youths with BD compared to healthy controls (HC) found smaller body and posterior CC regions in youths with BD. Two diffusion tensor imaging (DT-MRI) studies in youths with BD also found abnormalities in the body of the CC and in major frontal white matter (WM) tracts. These findings suggest intra- and interhemispheric dysconnectivity may be involved in the pathophysiology of early-onset BD. To date, no study has assessed both cortical grey matter (GM) and white matter (WM) in a sample of very-early onset BD (onset before age 13) to investigate whether or not abnormalities could be detected in gray matter (GM) and its associated WM connections in the same sample. This study presents whole brain high resolution volumetric and DT-MRI analysis in a cohort of very-early onset BD.

Methods: Twelve children with BPD I and 10 HC matched for sex and age (9.8±2.2 years), had MRI scans on a 3T magnet which included a T-1 weighted scan (3D MPRAGE grappa sequence acquired sagitally (TE/TR/TI/=2.74ms/2.1s/1.1s, 12° flip angle, echotrain length=5, acquisition matrix=256x168)) and a DT-MRI sequence (72 directions, b=1000 sec/mm^2, TE/TR=91msec/5sec; matrix=128x128 on 240x240 FOV; slice thickness=1.9 with 0 gap). Structural and FA data was analyzed using FSL's VBM and TBSS, respectively, [Please see website for detailed methods and reference list- http://www.fmrib.ox.ac.uk/fsl]. FA data was processed with the tools FDT, BET and FNIRT for fitting a tensor model to the raw diffusion data, brain-extraction and nonlinear registration. Next, the mean FA skeleton was created which represents the centers of all tracts common to the group. Each subject's aligned FA data was then projected onto this skeleton and the resulting data fed into voxelwise cross-subject statistics. Structural data was analyzed with FSL-VBM using BET for brain-extraction and FAST4 for tissue segmentation. The resulting grey-matter partial volume images were then aligned to MNI152 standard space using the affine registration tool FLIRT followed by nonlinear registration using FNIRT, which uses a b-spline representation of the registration warp field. The resulting images were averaged to create a study-specific template. The modulated segmented images were then smoothed with an isotropic Gaussian kernel with a sigma of 4 mm. Voxel-wise GLM was applied using permutation-based non-parametric testing utilizing Threshold-Free Cluster Enhancement in the RANDOMISE program in FSL for both VBM and TBSS. Significant regions of interest (ROI) were created for the body of the CC (voxel 75,118,106) and the right frontal WM (voxel 62,138,104), using a 5x5x5 box centered on a significant voxel. These ROIs were then used to calculate FA values for these areas on all subject's original FA data and correlations with age were performed.

Results: Relative to HC, BPD children trended toward a decrease in FA in right frontal WM tracts (p=0.06) and the right body of the corpus callosum (p=.06) (See Figure 1). Age was not significantly correlated with FA in the BD or HC group in either the CC or frontal WM region. There were no significant GM differences for any region between groups.

Figure 1. Voxel-wise group comparisons showing a significant trend in (p =.06) FA reductions in BD compared to HC in regions of the right body of the corpus callosum and in right frontal WM tracts. The red regions are significant at the p=0.06 level and are superimposed on the mean FA skeleton (green) and mean FA background image which were constructed from the study population. Figure 2. Figures showing ROI placement for the A) corpus callosum body (blue) and B) frontal white matter (teal).

Figure 1.

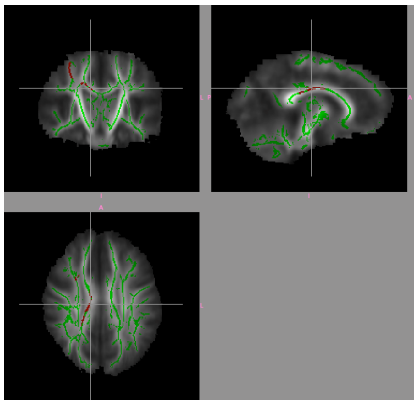
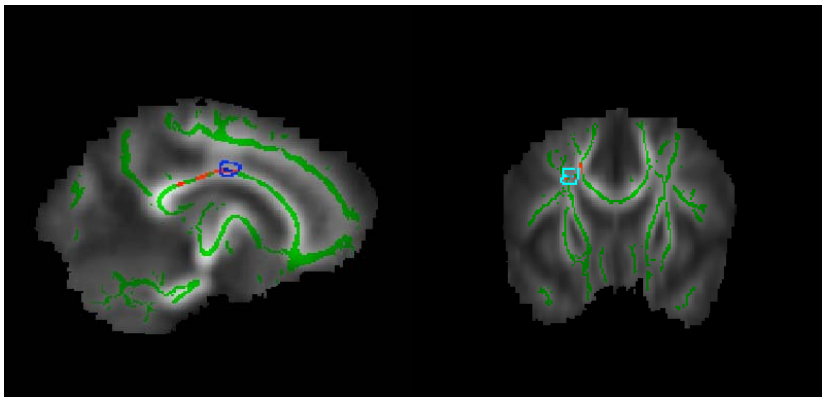


Figure 2.



Conclusion: Our results showed that very-early onset BD may have abnormalities in frontal WM tracts having fronto-parieto and fronto-limbic intra-hemispheric connectivity. These finding are consistent with adolescent and adult studies. In addition, we found a trend toward a reduction in the integrity of the body of the CC, which connects interhemispheric parieto-temporal regions. In contrast to prior structural neuroimaging studies, no regional abnormalities in GM volumes were found in youths with early-onset BD. This may indicate that changes in GM volumes are associated with other factors such as illness chronicity or medication use. However, the lack of GM findings may also be due to the inherent limitations of VBM analysis, our small sample size and the robust brain changes occurring in early childhood. Cortical thickness evaluation of this data set is currently underway to verify the VBM findings. Additional studies utilizing multiple MR approaches with larger sample sizes and longitudinal assessments are warranted to assess for GM and WM abnormalities in pediatric BD.

Select References:

1. Frazier JA, et al. White matter abnormalities in children with and at risk for bipolar disorder. Bipolar Disorder. 2007;9:799-809.
2. Smith SM, et al. Advances in functional and structural MR image analysis and implementation as FSL. NeuroImage, 23(S1):208-219, 2004.