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Characterization of Pediatric Bipolar Disorder with Quantitative HARDI Tractography Metrics

Ryan Payne Cabeen[1], Daniel Dickstein[2], and David H Laidlaw[1]

[1]*Computer Science, Brown University, Providence, RI, United States,* [2]*Psychiatry & Human Behavior, Brown University, Providence, RI, United States*

Contributions: We computed and compared quantitative diffusion tractography metrics in children with bipolar disorder (BD) and typically-developing controls (TDC) without psychiatric illness. An automated process was used to choose tracks connecting the amygdala and accumbens, a track of interest (TOI) chosen a priori from previous findings in voxel-based morphometry (VBM) and resting state functional connectivity (RSFC) analysis.

Background: Bipolar disorder (BD) is among the most devastating psychiatric disorders, with great suffering, morbidity, mortality, and economic impact. Recent data indicate that pediatric BD is on the rise, now diagnosed in up to 20% of children and adolescents discharged from psychiatric hospitals today. Thus, there is a pressing need to understand the neural underpinnings of pediatric BD, so as to identify potential diagnostic markers and treatment targets. In this project, we explored differences in white-matter through quantitative tractography of high-angular resolution diffusion images (HARDI). We looked at a pair of gray matter regions-of-interest (ROIs) that are implicated in BD by previously published resting state functional connectivity (RSFC) and voxel-based morphometry (VBM) studies. In contrast to previous work that investigated BD with voxel-based analysis of diffusion MRI measures, we computed metrics from geometric models of the tracts connecting these ROIs.

Methods: BD and typically-developing control (TDC) participants ages 7-17 years old were enrolled in an IRB-approved protocol. MRI imaging was conducted on a Siemens Tim Trio 3 T scanner including a T1-weighted MPRAGE anatomical image ($TR_{epetition}$=2250ms, TE_{cho}=2.98ms, T1=900ms, flip angle=9^0, slices=160, field of view=256mm, voxels=1x1x1mm, duration=7.36min) and diffusion-weighted images (TR=10060ms, TE=103ms; slices=70; GRAPPA; 64 directions voxels=1.8x1.8x1.8mm; duration=12.56min). Diffusion images were corrected for motion and eddy current distortions using FSL's flirt and eddy_correct. Q-ball diffusion models were fit to the voxels using DTK with 181 output directions. Tracks were extracted from the Q-ball image using DTK with the second-order Runge-Kutta method, an angle threshold of 35 degrees, and two random seeds per voxel. A fractional anisotropy (FA) image was also computed using DTK. The high-resolution T1-weighted scan was segmented using FreeSurfer, and the resulting subcortical segmentation was mapped to the diffusion space using FSL's flirt. FreeSurfer's left and right amygdala and accumbens-area ROIs were used for the analysis, and tracks were included in the track-of-interest (TOI) if both ROIs contained an endpoint. FA was sampled at each vertex in each track in the TOI using linear interpolation. For each hemisphere, the mean FA and the sum of the track length weighted FA (sum wFA) of the TOI was computed using numerical integration along the tracks. Finally, the volumes of the subcortical ROIs were found from statistics reported by FreeSurfer.

Results: We found a strong difference between BD and TDC participants in several measures in left hemisphere tracks connecting the amygdala and accumbens. Both mean FA and the sum length-weighted FA were smaller in the BD group. Additionally, no differences were found in right hemisphere metrics. Neither the left nor the right subcortical volumes showed a difference between groups

Conclusions: Our results support previous findings, in which pathways between the left amygdala and left accumbens are thought to play a role in BD pathology. The lack of a significant difference in right hemisphere tracks reinforces these results. A possible bias for the sum metric is the subcortical volume, as this would increase the total number of seed points. However, we found no differences in subcortical volume to suggest such an effect. The small sample size, of course, limits the strength of the interpretation, but it does suggest that continuing research using these metrics has potential to characterize BD and other disorders. Furthermore, because the process is automated, this method scales efficiently as we consider larger populations.

References: Correia et al. NeuroImage. 2008; Dickstein et al. Arch Gen Psychiatry, 2005; Dickstein et al. Biological Psychiatry, 2010; Pavuluri et al. Biological Psychiatry, 2009

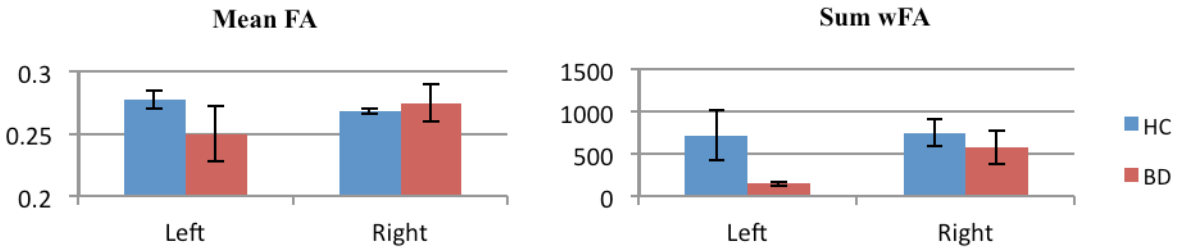

Figure: The mean and standard error of metrics of tracks between the accumbens and amygdala in the left and right hemispheres. We found the BD group to have decreased mean FA and sum track length-weighted FA in the left hemisphere.