Disruption of commissural white matter tracts in pediatric bipolar disorder

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Introduction

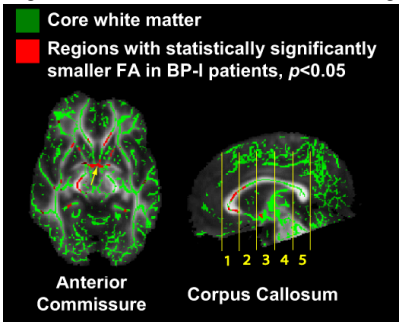
Bipolar disorder (BP) is a serious, chronic illness that significantly impacts the quality of life of an individual. Studies have revealed that 15% to 28% of adults experienced an onset of their illness prior to 13 years of age. Those with childhood versus adult onset have more severe, complicated, and adverse course of bipolar illness. Thus, identifying early signs of bipolar disorder is important because it may enable health care providers to intervene earlier and prevent progression of increased morbidity and personal dysfunction. Fractional anisotropy (FA) of diffusion tensor imaging (DTI) is sensitive to white matter structural changes. Commissural tracts including corpus callosum (CC) and anterior commissure (AC) play important roles in connecting and coordinating the two cerebral hemispheres. These tracts have been less focused on in childhood bipolar cases and are the research target in this study. Disruption of CC has been reported to have abnromal integerity in a DTI study on adult bipolar patients [1]. Investigators also reported smaller FA values at the junction of the fornix and corpus callosum for adolescent bipolar patients [2]. However, no detailed analysis at the multiple segments of CC has been found for pediatric bipolar cases. AC, connecting the temporal lobes of both sides which are involved in the important emotion circuits, has been overlooked for a long time due to the relatively small size of this tract. Most clinical DTI data could not reach the resolution to detect the changes of this small tract. In our study, we acquired high resolution DTI with resolution of $2x2x2mm^3$ from 10 bipolar patients and 10 age matched control subjects. TBSS method was used to normalize the data and project the white matter to the skeletons. We further segmented midsagittal CC into five compartments and compared FA difference of segmented CC and AC. We found that AC and anterior segment of CC has statistically significant smaller FA. Compared to DTI result of adult BP [1, 3], the disruption pattern caused by BP demonstrates anterior to posterior pattern from childhood to adult.

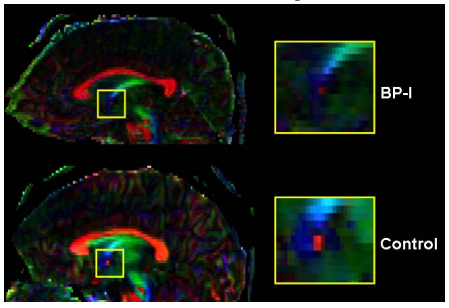
Methods

Subjects and data acquisition: 10 bipolar patients (age: 13.9±2.7; 9 BP-I and 1 BP-NOS) and 10 age-matched normal subjects (age: 13.6±3.6) were recruited for this study from Children's hospital. The diagnosis of BP-I was confirmed with a structured diagnostic evaluation using The Schedule for Affective Disorders and Schizophrenia for School-aged Children - Present and Lifetime Versions (K-SADS-PL). A 3T Philips Achieva MR system was used. DTI data was acquired using a single-shot echo-planar imaging (EPI) sequence with SENSE parallel imaging scheme (reduction factor =2.3). DWI parameters were: FOV=256/256/130mm, in plane imaging matrix = 128× 128, axial slices thickness = 2 mm without gap, 30 independent diffusion-weighted directions with b-value = 700 sec/mm^2, TE=97ms, TR=7.6s. To increase signal noise ratio (SNR), two repetitions was performed. *FA measurement of CC and AC:* With a control child data as the template, TBSS was used to normalize the data and project the FA to the core of white matter. FA measurements of AC and CC were based on the values of core white matter after the skeletonization step of TBSS. AC was measured in a small rectangular region of interest (ROI) in the axial slice at the AC plane, pointed by the yellow arrow in the left panel of Fig. 1. The ROI of AC is limited inside the white matter skeleton. In the midsagittal slice, CC is evenly segmented into five compartments from its most anterior to most posterior boundary, as shown in the right panel of Fig. 1.

Results

Fig. 1 shows the statistically significant lower FA values at the anterior commissure and corpus callosum. In the left panel of Fig. 1, the cluster of voxels covering the entire middle AC display red color, indicating the disrupted AC at this area. In the right panel of Fig. 1, it is clear that abnormality occurs only at the anterior CC with middle and posterior CC intact. As AC is relatively a small white matter tract and more susceptible to the registration errors in the group analysis, we further checked midsagittal and axial slices of DTI colormaps, where AC can be clearly identified, from all subjects by direct observations. Darker AC can be seen in DTI colormaps of most BP subjects. Midsagittal slices of a BP patient and a control subject are shown in Fig. 2 as an example to directly demonstrate that AC in the BP patient has the integrity change. The small rectangular areas with the AC as the center were magnified to the same extent and displayed in the right panels of Fig. 2. It is evident from Fig. 2 that midsagittal AC of the control subject is much brighter and larger than that of BP patient. With the ROI placed at the AC and segmentation of CC into five compartments, we measured the FA of each segment of CC and AC as shown in Fig. 3. AC and the most anterior segment of CC have statistically significant changes of FA. BP patients have smaller average FA in the middle and posterior four segments of CC, but the difference is not significant.





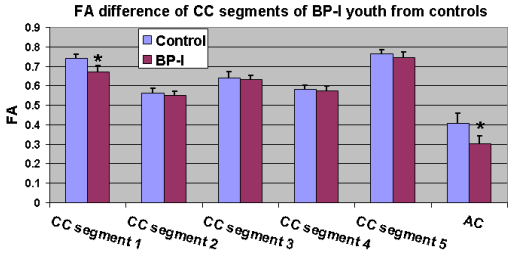


Fig. 1(left): Group analysis with TBSS shows the statistically significantly lower FA values at AC and anterior CC for BP patients. The yellow arrow in the left panel points to the ROI of FA measurement for AC. The right panel indicates the segmentation of midsagittal CC into five compartments.
Fig. 2 (middle): The midsagittal slices of a BP-I patient and a control subject in the left panel directly demonstrate the darker and smaller AC in the DTI colormap of BP-I patient. The right panel shows the enlarged yellow box with AC as center.
Fig. 3 (right): Difference of FA measurements at each segment of CC and AC. Asterisk indicates significantly FA difference with p<0.05.

Conclusion and discussion

Although childhood BP onsets have more severe, complicated, and adverse course of bipolar illness than the adult ones, there is relatively less investigation on pediatric BP than that on adults. Commissural tracts of BP children are rare. We measured FA difference after TBSS registration and core white matter projection to detect the structural changes of detailed CC segments and AC of BP children. To the best of our knowledge, the abnormality of AC has not been reported in pediatric BP case. Compared to the integrity change of adult CC [1], disruption of CC in children is more clustered in the anterior part. It implies that the damage of CC may follow anterior-to-posterior pattern from childhood to adult. Data acquisition of more BP-I children and age-matched controls is under way.

References: [1] Wang, F et al (2008) Biol Psychiatry 64: 730; [2] Barnea-Goraly, N et al (2009) Biol Psychiatry (in press). [3] Pavuluri MN et al (2009) Biol Psychiatry 65: 586.
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