Prominent Nodal Role of Amygdala and Nucleus Accumbens and Altered Prefrontal Strength in Functional Connectivity in Pediatric Bipolar Disorder

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Introduction

Pediatric bipolar disorder (PBD) is a cyclical illness with episodes of mania and depression with affect dysregulation and poor frustration tolerance with loss of rewards[1][2]. Beyond the conventional fMRI, in this study, we combined resting state functional connectivity (rs-fcMRI) and graph theoretical analyses [3][4] to probe the system-level changes in brain organization at rest in PBD.

Materials and Methods

This is a cross-sectional study of patients with PBD and healthy controls (HC). One hundred and forty-one subjects participated in this study: 57 PBD patients (age 14.02 ± 2.24 years (mean $\pm$ SD), 34M/23F IQ = 104.63 ± 10.80) and 84 matched HC (age 14.23 ± 2.08 years (mean $\pm$ SD),44M/40F IQ = 106.01 ± 10.49). This study was approved by the University of Illinois at Chicago's Institutional Review Board (IRB). Informed consent was obtained from at least one parent, and assent was obtained from all participants.

The participants were scanned on 3.0 Tesla GE Signa HDx scanner (General Electric Health Care, Waukesha, Wisconsin) with a quadrature head coil. Axial T1-weighted image was acquired with FSPGR BRAVO: FOV = 240x240 mm^2, 512x512 matrix, 120 slices, slice thickness = 1.5mm, gap = 0mm, TR = 11.58ms, TE = 4.96ms, TI = 450ms, flip angle = 13°. Resting state images: TE = 25ms; flip angle = 90°; FOV = 20×20 cm2; matrix = 64×64; TR = 2.5s; 5-mm slice thickness with 1-mm gap, 200 time frames.

The resting state fMRI data were preprocessed in SPM for slice timing correction, motion correction and smoothed (FWHM=6mm). The data were then subsequently band-pass filtered [0.009 0.08] Hz to extract the low-frequency resting-state BOLD signal. Nuisance signals from white matter, cerebrospinal fluid (CSF), the global signals, and six motion parameters were removed by regression. Individual T1 image was parcellated into 82 cortical and subcortical regions of interest (ROI) using FreeSurfer and mapped to the fMRI space through co-registration. For each subject, regional resting state timeseries were extracted from the 82 ROIs, and were used to construct the correlation matrix M(82x82), where M(i,j) represents the timeserie correlation of regions i and j. The correlation matrix was then threholded at different cost/density (K) to generate 82-node binarized graphs for each subject. Graph theoretic metrices including small-worldness, global/local efficiency, node clustering coefficient, degree, betweenness centrality were computed and compared between groups to characterize the network topological changes in PBD.

Results and Discussion

Using this graph theory-based approach, both PBD and HC groups consistently showed a small-world architecture of functional brain networks in low-cost to medium-cost networks (0.05<cost<0.25). Fig1. A showed in the PBD group that the small-worldness decreased while global and local efficiency increased as a function of cost (K), and the cost efficiency reached its maximum at K = 0.2.
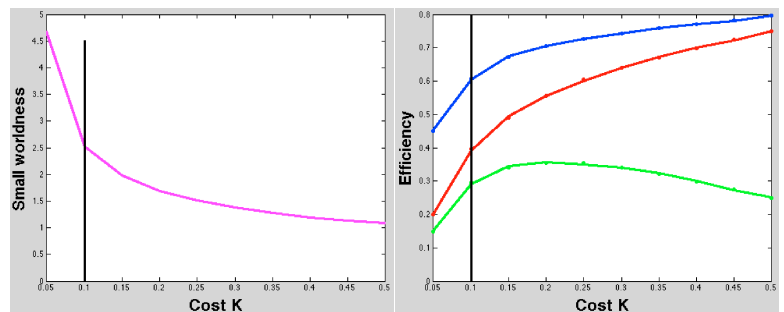

Fig. 1.A. Small-worldness (magenta). B. global efficiency (red), local efficiency(blue), and cost efficiency (green) as a function of cost K in PBD.

We have also examined the group difference (PBD vs HC) in the topology of sparse functional networks at low-cost threshold K = 0.1 (shown in Fig. 1A as the black vertical line), which preserved the top 10% of strongest resting connectivity. There is no significant group difference between PBD and HC in small-worldness, or global efficiency of the functional networks. Significant increased betweenness centrality (BC) in PBD, relative to HC, is observed in left amygdala, nucleus accumbens, precuneus, and right temporal pole (p < 0.05). Betweenness centrality measures the load placed on a given node as the number of shortest paths passing through and reflects its importance in the graph. Increased BC suggests more pronounced roles of amygdala in terms of affect regulation and accumbens in terms of reward related processing in PBD. Meanwhile, compared to HC, PBD also showed significant decreased connectivity degree in left medial OFC, and increased connectivity degree in right DLPFC, which again may reflect frontal deficits in OFC as well as the altered DLPFC engagement. Overall, the pattern of increased thoroughfare via subcortical nodes of amygdala and nucleus accumbens and altered connectivity strength of DLPFC and OFC offer strong support in favor of how affective and reward circuits are potentially interlinked and impaired in PBD. These changes in brain networks may potentially lead to the increased intensity to rewards and poor modulation of affect around rewards in PBD, which needs to be tested in a reward task-based functional connectivity analyses.

References

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