Functional Connectivity Reveals Abnormal Affective, Executive and Sensorimotor Resting State Networks in Psychotropic Naïve Patients with Pediatric Mania
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Introduction
Pediatric bipolar disorder (PBD) is a complex cyclical illness with episodes of mania and depression, chronic inter-episodic symptoms of mood disturbance due to partial recovery, neurocognitive dysfunction, and a high prevalence of comorbid attention deficit hyperactivity disorder (ADHD) [1]. We examined the functional connectivity of previously-identified resting state networks to investigate intrinsic network abnormalities that may represent PBD pathophysiology.

Materials and Methods
This is a cross-sectional study of psychotropic-naïve patients with pediatric mania and HC. Seventy-four subjects participated in this study: 34 PBD patients (age 13.88 ± 2.29 years (mean ± SD), 17M/17F IQ = 104.09 ± 9.59, YMRS = 22.79 ±7.59, BRIEF =166.10 ± 60.79) and 40 HC. age 14.85 ± 2.69 years (mean ± SD), 18M/22F IQ = 108.48 ± 11.18, YMRS = 2.35 ± 3.32, BRIEF = 80.27 ± 17.38). 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 subjects.

Subjects were scanned on a 3.0 Tesla GE Signa HDx scanner (General Electric Health Care, Waukesha, Wisconsin) using an 8-channel head coil. Resting state fMRI images sensitive to BOLD contrast were acquired: 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). Anatomic images also were acquired in the axial plane (three-dimensional spoiled gradient recalled [SPGR], 1.5-mm-thick contiguous slices) for co-registration with the functional data.

The first 5 scans from each dataset were discarded to allow longitudinal magnetization to stabilize. The remaining 195 scans per subject were preprocessed in SPM for motion correction, slice timing correction, co-registration, normalization and smoothed (isotropic Gaussian kernel FWHM=6mm) into the MNI template space. The data were then subsequently bandpass filtered using a bandpass filter of 0.01 to 0.1 Hz to extract the low-frequency resting-state BOLD signal.

Group ICA MELODIC coupled with a dual regression step implemented in FSL is used to identify group-level independent components and to reconstruct subject-level components [2]. Voxel-wise comparison of the subject-level independent components is performed to identify group differences in resting state connectivity. Permutation testing (randomize, FSL) with a thresholded component-specific mask (threshold p > 0.5) and 5000 permutations was used to correct for multiple comparisons at a corrected p < 0.05

Results and Discussion
Twenty-one independent spatial components were automatically detected by the group ICA, including the consistently-identified resting state networks previously documented in pediatric [3] and adult [4] populations. Three resting state networks that differentiated the patients from HC included the affective, executive, and sensorimotor networks. These results align with the task-elicited affective and cognitive circuitry abnormalities in PBD studies published to date [5][6]. The abnormal task-relevant neural activity observed in these studies may have been influenced by these regions heightened readiness to respond as indexed by their hyper-connectivity in the resting state. The intrinsic abnormalities in these three resting state networks complement the findings from previous task-based fMRI studies as well as the few existing resting state connectivity studies in adult and pediatric samples with BD, and future studies of resting and conventional MRI studies in the same sample can directly elucidate such dynamic interplay.

The amygdala hyperconnectivity in the resting state affective network is associated with better daily functioning (parent-reported BRIEF score and subscores in executive, affective and behavior, p < 0.03 to 0.01) as well as less intense manic symptoms (the elevated mood item in YMRS) (p < 0.04). Greater connectivity of amygdala within the affective network at rest may be a compensatory mechanism to modulate daily function in patients with PBD.

References