Brain functional connectivity reveals abnormal brain development in high risk bipolar infants

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Introduction

Bipolar disorder (BD) is a common psychiatric illness affecting ~1% to 2% of the population (1). BD is commonly associated with adult onset but recent data suggests an upsurge of pediatric BD incidence (1). Although overdiagnosis in pediatric population is one of the reasons for such increase, its existence in youth is indisputable and suggests an association with abnormal early brain development. Therefore, better understanding of this disease early in life might provide new insight into its neuropathology and potentially leads to a more accurate diagnosis, particularly in pediatric subjects.

Given the high heritability of this disease (2), the study of the offspring of BD parents (i.e., high-risk children) may provide an excellent model to delineate its pathophysiology during early development. In this study, 46 high-risk children aged at ~3wks, 1yr, and 2yrs were recruited to undergo a resting-state functional magnetic-resonance imaging (rs-fMRI) scan and graph theory analysis was employed to delineate potential abnormal functional connectivity development, particularly the global (GE) and local wiring efficiency (LE) for information transfer in the brain. Without any explicit symptoms at such young ages, the existence of functional connectivity abnormality, if successfully detected, could greatly improve our understanding of the underlying neurophysiology of BD and might serve as more objective early diagnosis measures.

Methods

Informed consent was obtained from the parents and the experimental protocols were approved by the institutional review board. 46 high risk children of BD, including 20 neonates (11M, 21 ± 19 days (SD)), 16 1yr olds (9M, 13 ± 1 mon), and 10 2yr olds (8M, 25 ± 1 mon) were included in this study. In addition, 147 age-matched normal subjects including 51 neonates (20M, 23 ± 12 days (SD)), 50 1yr olds (21M, 13 ± 1 mon), and 46 2yr olds (24M, 24 ± 1 mon) were also recruited for comparison. All pediatric subjects were imaged at sleep without sedation. For the rs-fMRI study, a T2*-weighted EPI sequence was used with TR = 2sec, TE = 32 ms; 33 slices; and voxel size = 4x4x4 mm^3. 150 volume data were acquired. Anatomical images using a 3D MP-RAGE sequence were acquired with TR = 1820ms; TE = 4.38 ms; inversion time = 1100ms; 144 slices; and voxel size = 1x1x1mm^3.

Preprocessing of rs-fMRI data included time shifts, rigid body correction for head movement, spatial smoothing and low pass filtering (<0.08Hz). A longitudinal data set with images acquired from a subject at 2wk, 1yr- and 2yrs-old is available at our institution, which was normalized to the MNI template to obtain 90 ROIs covering both cortical and subcortical regions of the whole brain. Subsequently, images of the study cohorts were normalized to this longitudinal data set at the corresponding time point so as to extracting the BOLD signal of each ROI from each subject. The mean time series of each ROI was then used to construct a 90*90 correlation matrix for each individual subject. To calculate GE and LE, individual matrices were thresholded (based on the magnitude of the connectivity strength) and binarized to construct sparse connectivity matrices at a series of cost (defined as ratio of the number of included connections over the number of all possible connections) ranging from 1%~50%. Based on the non-parametric rank-sum test, the GE and LE at different costs were compared between high risk and normal children at both whole brain and regional level to detect potential abnormalities. Subsequently, receiver operating curve (ROC) analysis was conducted to evaluate the potential of such graph-based measures to classify the high risk children.

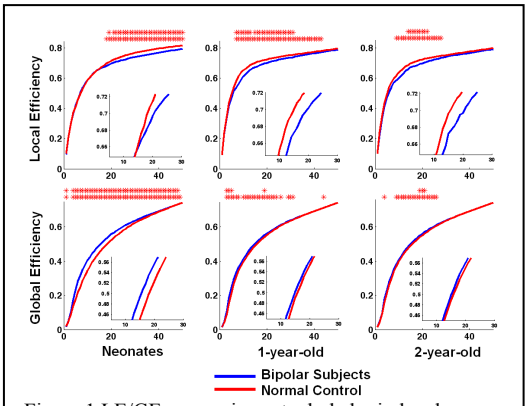

Figure.1 LE/GE comparison at whole brain level.

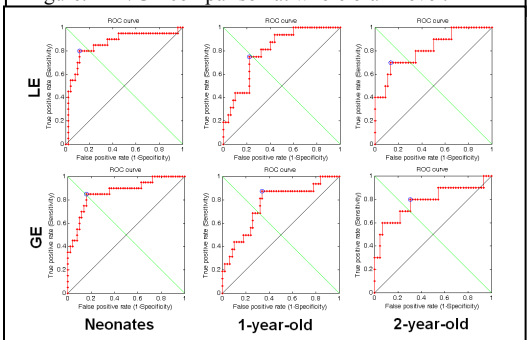

Figure.2 ROC analysis based on whole brain LE/GE.

Results

The whole brain GE/LE curves for both high risk (blue) and normal children (red) at different ages are presented in Fig.1, where significant differences at $p<0.05$ and $p<0.01$ evel (uncorrected) between the two groups at a given cost are represented by single/double red asterisks at the top of each plot. It is immediately clear that high risk children exhibit a lower LE and a higher GE compared with normal children across a wide range of costs in all three age groups, although the difference seems to become less apparent as age grows. The significant regional differences at cost 20% (where significant whole brain differences are detected for both LE/GE across all age groups) are listed in Table.1. Based on whole brain LE/GE, ROC analysis was conducted at each cost and the curves associated with the best performance are presented in Fig. 2. Generally, all measures yield reasonably good classification power, particularly for neonates, where a true positive rate of >80% can be achieved with a false positive rate around 10% (for both LE/GE).

	Neonates	1-year-old	2-year-old
LE	superior orbital frontal (r); middle frontal (r/l); middle orbital frontal (l); olfactory (l); superior medial orbital frontal (r); anterior cingulate (r); cuneus (l); inferior occipital (r); fusiform (l); angular (r); putamen (r); middle temporal (l); inferior temporal (l).	superior frontal (l); middle frontal (l); middle orbital frontal (l); inferior orbital frontal (r); inferior occipital (r).	Superior frontal (l); middle frontal (l); superior medial frontal (r); amygdala (l); middle temporal pole (r).
GE	Middle frontal (r); supplementary motor area (l); rectus (r); postcentral (r); paracentral robule (r/l); heschl (l).	amygdala (r); superior parietal (l); inferior parietal (l); superior temporal pole (l); inferior temporal (l);	cuneus (l); superior orbital frontal (l);

Table.1 Significant regional changes of LE/GE at different age groups. Blue: high risk children < normal subjects; red: high risk children > normal subjects ($p<0.01$, uncorrected).

Discussion

In this study, significant differences of brain's efficiency property (both LE/GE) were detected between high risk BD subjects and normal controls. At a whole brain level, the lower LE and higher GE observed in high risk subjects might indicate the formation of abnormal, long-range connections that is not observed in normal controls. This is consistent with one of the well documented features associated with BD-hyperconnectivity among normally disassociated regions (3). Moreover, the observed regional abnormalities (Table.1) seem to focus on prefrontal, temporal, as well as amygdala regions, which is highly consistent with the typically reported anterior limbic network disruption associated with BD (1). Finally, the high classification power (Fig.2) suggests the great potential of graph-theory based measures (i.e., LE/GE) in early diagnosis of BD.

References

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