Altered small-world properties in newborns at high risk for schizophrenia

F. Shi[1], Y. Fan[1], P-T. Yap[1], W. Lin[1], J. Gilmore[2], and D. Shen[1]
[1]Department of Radiology and BRIC, University of North Carolina at Chapel Hill, Chapel Hill, NC, United States, [2]Department of Psychiatry, University of North Carolina at Chapel Hill, Chapel Hill, NC, United States

Introduction: There is growing evidence that the offspring of schizophrenic parents is at high risk for schizophrenia (SCZ). Disrupted brain connectivity has been widely observed in studies on adults with SCZ. So far, however, the brain connectivity pattern of the high risk offspring is still unclear. Brain network analysis has been employed recently for evaluating the brain connectivity properties in various imaging modalities such as MRI, EEG, MEG, fMRI, and DTI [1]. Human brain networks demonstrate so-called small-world network properties, i.e., they are densely locally clustered and highly globally integrated, with characteristics in between regular lattices and random networks. We hypothesize that the brain network of individuals of high risk for SCZ may be altered even at their early development stage. We tested this hypothesis by studying brain networks constructed from brain images of high risk newborns, and compared their network properties with those derived from age-matched healthy newborns, as well as healthy adults.

Methods: We recruited three groups of subjects in this study, including 27 high risk newborns of SCZ, 27 both age and gender matched healthy newborns, and 27 gender matched healthy adults. Their demographic information is summarized in Table 1. For each subject, T1 and T2 brain images were collected using a 3T Siemens scanner. All images were first skull-stripped, brain tissue segmented [2], and spatially normalized to a standard template space with a nonlinear image registration technique [3]. From the resulting deformation fields, tissue density maps were computed to represent the local brain volume changes relative to the selected template voxel-wise. From the tissue density maps, regional brain volume measures were obtained for 90 brain regions using an anatomically labeled brain template [4]. The effect of total brain volume size was removed by normalizing the regional brain volume measures with the intracranial volume.

Table 1. Demographics of the three groups of subjects.

	Gender	Gestation Age
High Risk Newborns	12 males /15 females	42.9±3.5 weeks
Healthy Newborns	13 males /14 females	42.9±2.2 weeks
Healthy Adults	13 males /14 females	24±3 years

Brain structural connectivity was defined as statistical association in volumes of each pair of anatomical regions, measured by the Pearson correlation coefficient across subjects. Three correlation matrices of size 90 by 90, each corresponding to a group, are shown in Fig. 1. Graph theory techniques were then used to study the topographical characteristics of brain networks derived from these correlation matrices. Specifically, for each network, we focused on its network efficiency and modularity with respect to the network cost. Network cost measured the percentage of the number of existing edges in all possible connections, while the network efficiency was used to measure the minimum path length between regions at each cost. Global efficiency describes the efficiency of parallel information transfer in the whole brain; while local efficiency describes the mean transfer efficiency in every region with its neighbors. Modularity was used to measure a network's community structure, having large value for networks with clusters of vertices that are densely connected within cluster but sparsely connected to vertices outside of the cluster. For reference, comparable regular lattices and random graphs (average of 100 times running at each cost) were also generated over the same range of network costs.

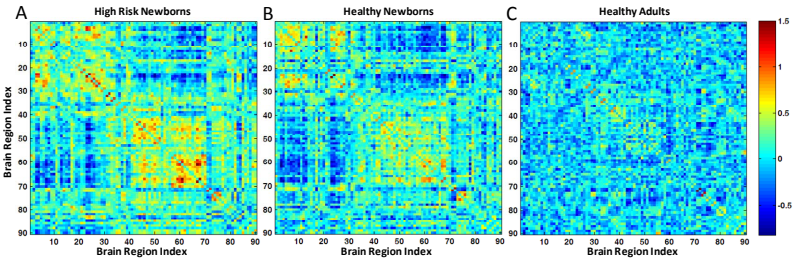

Fig. 1. Correlation matrices of three groups, from left to right: high risk newborns (A), healthy newborns (B), and healthy adults (C). Warm color indicates high correlation and cold color indicates low correlation.

Results: Fig. 1 shows the correlation matrices of three groups. As shown in Fig. 1 (A), the network of high risk newborns exhibited a locally clustered pattern, i.e., having two clusters where brain regions in each cluster have higher correlations than those outside of the cluster. Specifically, the first cluster consisted of the first 30 regions located in the frontal lobe, and the second cluster was composed of regions indexed from 43 to 70, located in the parietal-occipital lobe. However, the locally clustering pattern was not obvious in healthy newborns (Fig. 1 (B)), and not observable in healthy adults (Fig. 1 (C)). This observation was consistent with the following network properties, shown in Fig. 2. Figs. 2 (A) and (B) show the curves of global and local efficiency of three groups, which were in the range between the regular lattice and random network, indicating their small-worldness. The global efficiency of networks derived from healthy adults was higher than healthy newborns', and the local efficiency displayed a reverse order, suggesting that the brain development starts from mainly local connections towards high overall integration, consistent with a recent study which demonstrated that brain networks development follows a ''local to distributed'' organization [5]. However, high risk newborns showed a more localized pattern and lack global integration compared with healthy newborns. This indicates that a delay might have occurred during brain development of the high risk group. Modularity is shown in Fig. 2 (C). Newborns had higher modality than adults, consistent with the visual inspection of their correlation matrices.

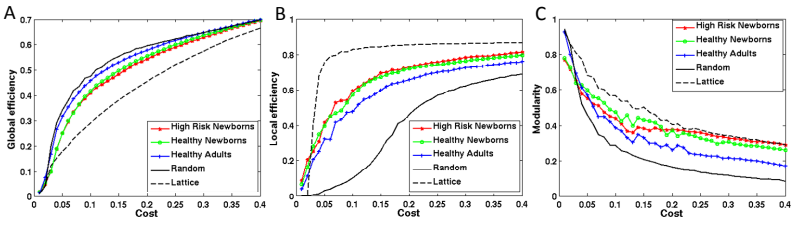

Fig. 2. Global (A), local (B) efficiency, and modularity (C) as a function of cost for brain networks. Regular lattice and random graphs with same node and edges are constructed for comparison.

Discussion: This study yielded three findings. First, the brain structural networks of all three groups had small-world properties. Second, brain networks of newborns were associated with reduced regularity and enhanced randomness compared with adults'. High risk newborns show a development delay effect with even higher regularity and lower randomness than healthy newborns. Third, modularity decreases in development from newborns to adults. In newborns, brain regions are clustered into mainly two clusters with few connections in between. In contrast, adults have a collection of specialized functional clusters and more connections between them to maintain an efficient information transfer. These findings verified our hypothesis that the network of newborns at risk of SCZ is altered and appears to suffer from a development delay effect.

References: [1]. Stam, C.J. and J.C. Reijneveld, Nonlinear Biomedical Physics, 2007. 1: 3. [2]. Shi, F., et al., in MMBIA 2009. 2009. [3]. Shen, D. and C. Davatzikos, IEEE TMI, 2002. 21(11): 1421-1439. [4]. Tzourio-Mazoyer, N., et al., Neuroimage, 2002. 15(1): 273-289. [5]. Fair, D.A., et al., PLoS Computational Biology, 2009. 5(5).