This study was approved by the local institutional review board of the first author’s affiliation. The parents of the neonates were informed regarding the goals and risks of the MRI scan, and requested for the written consent.

***Subjects***

This study recruited 22 full-term neonates (13 males and 9 females; gestational age range: 37-42 weeks) without any MRI abnormalities or evidences of any clinical episodes that might cause cerebral damages.

***MRI data acquisition***

All data were acquired on a 3.0 Tesla scanner (Signa HDxt, General Electric Medical System, Milwaukee, WI, USA) with an 8-channel phase array radio-frequency head coil. To reduce the head movement and complete the MRI procedure, the subjects were sedated with a relatively low dose of oral chloral hydrate (25-50 mg/kg). The potential risks of the chloral hydrate were fully considered. The selection, monitoring, and management of subjects were strictly performed following the guidelines [31]. Neonates were laid in a supine position and snugly swaddled in blankets. A pediatrician was present during the MRI scan. Micro earplugs were inserted into the external auditory canal for hearing protection. Heads of the subjects were immobilized by molded foam, which was placed around the head. The temperature, heart rate, and oxygen saturation were monitored throughout the procedure.

Three-dimensional fast spoiled gradient-recalled echo (3D-FSPGR) T1-Weighted magnetic resonance images were acquired with the parameters: repetition time/echo time = 10.28 ms/4.62 ms, inversion time = 400 ms, field of view = 240 mm, voxel size = 0.94×0.94×1 mm3.

***Construction of brain structural network***

Figure 6 provided the workflow for constructing the neonatal brain structural network. The three steps for the workflow were detailed as follows.

***Data preprocessing.*** To investigate the impacts of data preprocessing on network construction, three preprocessing workflows were performed by BET, iBEAT and iBEAT with manual correction.

BET workflow: non-brain tissues in each T1WI image were automatically removed by BET. iBEAT workflow: three automatic preprocessing steps, including brain contrast enhancement and skull stripping were sequentially performed. iBEAT with manual correction: (1) manually align the AC-PC line; (2) strip the skull by using iBEAT; (3) identify the remaining non-brain tissues by the boundaries of brain gray matter and manually remove these tissues. The manual correction was performed by two pediatric radiologists with 5 years of experience and differences in identifying the remaining non-brain tissues were resolved by consensus.

***Calculations of brain region volume.*** To calculate the volume of each brain region, the preprocessed data were firstly registered to a standard 3D-T1WI-based template (Johns Hopkins University) by linear (rigid transformation) and nonlinear (affine transformation) registrations. And then the volume of each brain region can be estimated by Eq.(1):



where, *Vi* is the brain volume of the *i*th region of individual subjects, *Vt* represents the corresponding area in the template to accumulates. is the determinant of 3×3 sub-matrix in upper left corner of rigid transformation matrix, and is the determinant of 3×3 sub-matrix in upper left corner of affine transformation matrix. *JF* is Jacobian, for linear transformation, *JF* is a constant which equal to the inverse of the determinant of the 3×3 sub-matrix in the upper left corner of the transformation matrix; for non-linear transformation, *JF* is a three-dimensional function.

***Construction of brain structural network.*** By using the graph theoretic approaches, the cortical and subcortical regions were used as nodes to construct the brain networks, with connections between nodes defined as correlations between regional brain volumes. Here, 64 brain regions that mainly involved the gray matters and several important subcortical regions (thalamus, hippocampus and cerebellum) were selected as network nodes (Table 1). GRETNA (www.nitrc.org/projects/gretna/) was used to construct the network. Partial correlations between all nodes’ volumes were firstly estimated as edges of the network, and then network was constructed by binary connective matrices. The network properties, such as clustering coefficient (*Cp*), characteristic path length (*Lp*), global (E*global*) and local efficiency (E*local*) were calculated by the following equations (2-5).

The clustering coefficient of a node *i* (C(*i*)) is defined as the likelihood that the neighborhoods of a given node *i* are connected to each other.

 (2)

where *ki* represents the number of edges connected to the node *i*, and is equal to the weight between node *i* and *j*. The clustering coefficient, *Cp*, of a network is the average of the clustering coefficient over all nodes.

 (3)

where N is the number of nodes in the network, and *Lij* is the shortest path length between nodes *i* and *j* in a network G. *Lp*is the average of the shortest path length between all pairs of nodes in the network.

 (4)

where *Lij* is the shortest path length between node *i* and node *j* in G, and N represents all nodes in the network.

 (5)

where *Eglob* (*Gi*) is the global efficiency of *Gi*, the subgraph of the neighbors of node *i*.

The C*p* of a network is defined by the average of the clustering coefficients across nodes, where the C*p* of a node is the ratio of the number of actually connection nearest neighbors of this node to the maximum number of possible connection [32]. C*p* quantifies the local interconnectivity of a graph. The L*p* of a graph is the average of the shortest path length between all pairs of nodes in the network, and it is an indicator of overall routing efficiency of a graph [33]. The E*local* of a network is the average of the local efficiency over all nodes. It measures the mean local efficiency of the network. The E*global* of a network is defined by the mean shortest path length [34]. It measures the extent of information propagation through the whole network. Typically, a small-world network should fulfill the following conditions: C*p*/C*rand* > 1 and L*p*/L*rand* ≈1.

***Statistical analysis***

Regarding the manual corrections for anterior commissure-posterior commissure (AC-PC) alignment and skull stripping, the repeatability and consistency of brain volume calculations between two repeated measurements were evaluated by the Bland-Altman graph and intraclass correlation coefficient (ICC). Analysis of variance (ANOVA) was used to compare the differences in the volumes of 64 brain regions between the three workflows.

All the segmentation, calculation of brain region volume and network parameters, and statistical analysis were performed by using the MATLAB R2016b (Mathworks Inc, Natick, MA, USA).