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Structural connectivity asymmetry in the neonatal brain

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ABSTRACT

Asymmetry of the neonatal brain is not yet understood at the level of structural connectivity. We utilized DTI deterministic tractography and structural network analysis based on graph theory to determine the pattern of structural connectivity asymmetry in 124 normal neonates. We tracted white matter axonal pathways characterizing interregional connections among brain regions and inferred asymmetry in left and right anatomical network properties. Our findings revealed that in neonates, small-world characteristics were exhibited, but did not differ between the two hemispheres, suggesting that neighboring brain regions connect tightly with each other, and that one region is only a few paths away from any other region within each hemisphere. Moreover, the neonatal brain showed greater structural efficiency in the left hemisphere than that in the right. In neonates, brain regions involved in motor, language, and memory functions play crucial roles in efficient communication in the left hemisphere, while brain regions involved in emotional processes play crucial roles in efficient communication in the right hemisphere. These findings suggest that even at birth, the topology of each cerebral hemisphere is organized in an efficient and compact manner that maps onto asymmetric functional specializations seen in adults, implying lateralized brain functions in infancy.

Introduction

The human brain exhibits structural asymmetries to support its specific lateralized functions, such as language and motor control. Such asymmetry in structure is apparent even in early life. But these structural asymmetries at the neonatal period may or may not persist through life. Moreover it is unclear whether structural asymmetry is reflected in differences in connectivity.

In healthy neonates, the left cerebral hemisphere is larger than the right (Gilmore et al., 2007). However, the normal pattern of fronto-occipital asymmetry described in older children and adults, notably larger right than left frontal lobe and larger left than right occipital lobe (Chapple et al., 2004; LeMay, 1976; Sharma et al., 1999; Weinberger et al., 1982) is not present in neonates (Gilmore et al., 2007). Beyond the whole brain level, Witelson and Pallie (1973) revealed a neonatal leftward asymmetry of the planum, a region known to be of significance for language function. Additional support is derived from a diffusion tensor imaging (DTI) technique that characterizes axonal organization of the brain white matter. Structural asymmetries in language- and motor-related fibers (e.g., the parieto-temporal part of the superior longitudinal fasciculus, the corticospinal tract, the superior thalamic radiations) are present in healthy (Dubois et al., 2009) as well as preterm infants (Liu et al., 2010). These findings are similar to the pattern seen in adults, suggesting that the observed neonatal anatomical asymmetry provides a structural basis for the adult pattern of the lateralization of language functions.

Our understanding of the structural asymmetry of the neonatal brain is still largely limited to the level of individual structures. Nevertheless, widespread brain areas are wired in a compact and economic manner and hence can easily transfer information in short and long distances to adapt to cognitive demands (Bullmore and Sporns, 2012). Recent advanced modern neuroimaging techniques allow for non-invasive investigation of the brain connectivity. Using DTI tractography and structural

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network techniques, the cortical network in adults was identified with small-worldness topology, suggesting that the cortex is highly interconnected and thus has a highly efficient topological organization (Gong et al., 2009b; Yan et al., 2011). Only recently, Iturria-Medina et al. (2011) employed the same techniques and showed that in adults the left cerebral hemisphere is significantly less efficient and interconnected than the right. Furthermore, the left hemisphere presents more central or indispensable regions for the whole-brain structural network than the right hemisphere. However, it is unclear whether this asymmetric pattern can be traced to the perinatal period. To examine this, we utilized DTI deterministic tractography and structural network analysis based on graph theory to determine the pattern of structural connectivity asymmetry in 124 normal neonates (born at 36 to 42 gestation weeks). We aimed to tract white matter axonal pathways characterizing interregional connections among cortical and subcortical regions and to infer left and right anatomical network properties. In parallel to the adults' study (Iturria-Medina et al., 2011), we specially focused on graph measures of small-worldness, efficiency, and centrality of brain regions to 1) examine whether the information flow in both hemispheres of the neonatal brain is similar to that in adults; and 2) identify brain regions that play crucial roles in efficient communication in each cerebral hemisphere. To our knowledge, this is the first report on a normative reference on asymmetry of the neonatal brain structural connectivity. As the early life after birth may not only be a period of developmental vulnerability, but also a period in which therapeutic interventions have the greatest positive effects, our study provides potential insights on brain-based disorders that may originate from preexisting disruptions of anatomical connections at birth.

Materials and methods

Subjects

Neonates scanned for this study were part of a larger ongoing birth cohort study of Growing Up in Singapore Towards Healthy Outcomes (GUSTO). This birth cohort consists of pregnant Asian women aged 18 years and above attending the first trimester antenatal ultrasound scan clinic at the National University Hospital (NUH) and KK Women's and Children's Hospital (KKH) in Singapore. Both parents were Singapore citizens or Permanent Residents of Chinese, Malay or Indian ethnic background. Mothers on chemotherapy, psychotropic drugs, including antidepressant or anxiolytic medications, or with Type I Diabetes Mellitus were excluded. The study was approved by the Centralized Institutional Review Boards of the Singapore Health Services and the Domain Specific Review Board (DSRB) of the National Health Care Group. One hundred eighty-nine eligible mothers agreed to participate in the brain imaging study and provided written consent.

Among 189 subjects, we excluded 65 subjects with incomplete demographic information, or birth weight less than 2000 g, or APGAR score less than 9, or absence of large motion artifacts with DTI. Hence, the present study included 124 subjects (58 females, gestational age: 40.2 ± 1.3 weeks; range: 36.9–42.7 weeks; and 66 males, gestational age: 39.9 ± 1.3 weeks; range: 36.6–42.1 weeks). All brain scans were reviewed by a radiologist (M.V.F.).

MRI data acquisition

At 5 to 17 days of life, neonates underwent single-shot echo-planar diffusion weighted (DW) MRI scans (TR = 7000 ms; TE = 56 ms; flip angle = 90°, FOV = 200 mm × 200 mm; matrix size = 256 × 256; 40 to 50 axial slices with 3.0 mm thickness; 19 diffusion directions with b = 600 s/mm^2; 1 baseline image with b = 0 s/mm^2) using a 1.5-Tesla GE scanner at the Department of Diagnostic and Interventional Imaging of the KKH. The scans were acquired when subjects were sleeping in the scanner. No sedation was used and precautions were taken to reduce exposure to the MRI scanner noise. A neonatologist was present during each scan. A pulse oximeter was used to monitor heart rate and oxygen saturation throughout the entire scans.

The construction of the neonatal brain networks

Fig. 1 illustrates the data analysis for constructing the anatomical networks of the two cerebral hemispheres. For each subject, DWIs were first corrected for motion and eddy current distortions using affine transformation to the image without diffusion weighting. Using multivariate least-square fitting, six elements of the diffusion tensor were determined from which fractional anisotropy (FA) was calculated. The FA image and the image without diffusion weighting were then simultaneously aligned via affine and nonlinear large deformation diffeomorphic metric mapping (LDDMM) transformations (Du et al., 2011) to those of the neonatal brain DTI atlas that was proposed by Oishi et al. (2011) with manually labeled 32 cortical and subcortical structures per hemisphere (Table 1). We then employed the reorientation scheme of diffusion tensor using the preservation of principal direction (PPD) method, in which the reoriented tensor keeps its eigenvalues, yet its principal vector is transformed (Cao et al., 2005), to transform subjects' DTI to the atlas.

Whole-brain fiber tractography was subsequently performed in the neonatal DTI atlas space using the fiber assignment by continuous tracking (FACT) (Mori et al., 1999) algorithm. The algorithm computes fiber trajectories starting from the deep white matter regions and ending at a voxel with FA value less than 0.1 or the turning angle between adjacent voxels was greater than 70°.

Two matrices with 32 × 32 elements were constructed based on the whole brain tractography to represent the anatomical networks among each intra-hemispheric regions. The $(i,j)^{th}$ element in the matrix was computed as the number of fiber tracts connecting regions i and j normalized by the mean volume of the two regions and thus represents the connectivity strength between regions i and j. To eliminate brain connections due to possible noise effects on the whole brain tractography, non-parametric one-tailed sign test was performed on each element of the matrices among all the subjects to determine the existence of the connection between any two regions, and thus determine whether the number of fiber tracts going through regions i and j is equal to zero at a significance level of 0.05. We now consider each of the matrices representing one network with the anatomical regions (listed in Table 1) as its nodes and the $(i,j)^{th}$ element of the matrix as its edge with weight information. The path length between any two nodes is the sum of the inverse weights of edges that must be traversed to go from one node to another.

Network analysis

Small-worldness, global efficiency and local efficiency were computed to characterize the potential ease with which information can be transferred concurrently across a network and locally communicated within neighborhood. At a regional level, betweenness centrality was calculated to identify nodes of a network that play crucial roles in efficient communication.

Small-worldness

A “Small-world” network model was originally proposed by Watts and Strogatz (1998), relating network clustering coefficient and characteristic path length. The clustering coefficient (C) was defined as the ratio of the number of existing edges between neighbors to the number of all possible connections between neighbors (Onnela et al., 2005). A network with a high value of the clustering coefficient has tightly connected local clusters and hence the loss of an individual node has an impact on the structure of the network. The characteristic path length (L) was defined by the average shortest path length in a network (Watts and Strogatz, 1998), suggesting how far apart any two nodes are linked in the network. A real network is considered small-world if it