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Structural network analysis of brain development in young preterm neonates

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ABSTRACT

Preterm infants develop differently than those born at term and are at higher risk of brain pathology. Thus, an understanding of their development is of particular importance. Diffusion tensor imaging (DTI) of preterm infants offers a window into brain development at a very early age, an age at which that development is not yet fully understood. Recent works have used DTI to analyze structural connectome of the brain scans using network analysis. These studies have shown that, even from infancy, the brain exhibits small-world properties. Here we examine a cohort of 47 normal preterm neonates (i.e., without brain injury and with normal neurodevelopment at 18 months of age) scanned between 27 and 45 weeks post-menstrual age to further the understanding of how the structural connectome develops. We use full-brain tractography to find white matter tracts between the 90 cortical and sub-cortical regions defined in the University of North Carolina Chapel Hill neonatal atlas. We then analyze the resulting connectomes and explore the differences between weighting edges by tract count versus fractional anisotropy. We observe that the brain networks in preterm infants, much like infants born at term, show high efficiency and clustering measures across a range of network scales. Further, the development of many individual region-pair connections, particularly in the frontal and occipital lobes, is significantly correlated with age. Finally, we observe that the preterm infant connectome remains highly efficient yet becomes more clustered across this age range, leading to a significant increase in its small-world structure.

Introduction

The early configuration and development of the brain's structural network is not yet well understood. In vivo analysis of white matter connections typically requires a diffusion magnetic resonance (dMR) image of the brain which, for in utero subjects, presents significant challenges (Jiang et al., 2007). Preterm neonatal subjects provide an opportunity to study the early connectome without the difficulties associated with in utero imaging. Understanding the connectomes of these infants is doubly important due to the risk factors associated with preterm birth, including white matter injury and abnormal neurodevelopment (Dudink et al., 2008). Here, we examine a normative cohort of preterm neonatal infants scanned between 27 and 45 weeks post-menstrual age (PMA) and identify consistent topological and developmental trends in their structural brain networks. Our goal is to develop a better understanding of early brain configuration and growth which will enable future studies to better characterize abnormal development and injury.

Previous works have examined white matter development in young infants. Many early studies focused on voxel-wise measures of fractional anisotropy (FA) and mean diffusivity (MD) (Bonifacio et al., 2010; Hüppi et al., 1998; Neil et al., 1998). These works discussed the effects of myelination and reduction in brain water over time on increasing FA and decreasing MD (Dudink et al., 2008; Gao et al., 2009a).

Many other studies have looked at functional network development in young infants (Fransson et al., 2007, 2011; Gao et al., 2009b; Wang et al., 2008). Fransson et al., in particular, examined the resting-state functional network architecture of very young preterm infants (25 weeks mean gestational age) and found that only half of the number of resting-state sub-networks found in healthy adults were present at the preterm stage (Fransson et al., 2007). Recently, van der Heuvel et al. found that functional networks in preterm infants agreed well with the underlying anatomical structure (van den Heuvel et al., 2014). In general, the relationship between functional networks and structural networks is complex

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and still not fully understood and there is still much work being done trying to explain causal relationships between the two (Betzel et al., 2013; Supekar et al., 2010).

Some other recent works have focused on the examination of the structural connectome of young infants by performing tractography between numerous anatomical regions in the brain (Ball et al., 2013; Pandit et al., 2013; Takahashi et al., 2012; Tymofiyeva et al., 2012, 2013; Yap et al., 2011; van den Heuvel et al., 2014). Takahashi et al. examined results of full-brain tractography qualitatively and described trends across postmortem infants between 17 and 40 weeks (Takahashi et al., 2012). In order to quantify and organize tractography results, many studies abstract the connections in the brain as a network, where nodes typically represent anatomical regions and edges represent some measure of connectivity between those regions. Ball et al. examined connections in the thalamocortical network of preterm infants and showed that early birth correlated with reduced connectivity (Ball et al., 2013). Pandit et al. studied the change in connection strengths across scan age and birth age on a cohort of preterm infants scanned as early as 47 weeks post-conception (Pandit et al., 2013). They reported that the frontal lobe showed a higher rate of development than other regions across their age group. They further noted that babies born prematurely showed lower overall cortical and sub-cortical connectivity than infants born at term.

Other preterm infant studies have looked into summarizing structural connectomes using network measures. Yap et al. examined the development of connectomes in young children, across a range of ages between 2 weeks and 2 years, using measures of network integration and segregation (Yap et al., 2011). Tymofiyeva et al. used an atlas-free approach to analyze connectome development in preterm infants, children and adults, also employing network measures to capture topological changes (Tymofiyeva et al., 2012, 2013). Very recently, Ball et al. studied a specific network measure known as *rich-club organization* in a cohort of preterm infants (Ball et al., 2014). They found that this rich-club structure, known to be present in adult brain networks, emerges as early as 30 weeks PMA.

Such network measures allow high-level summaries of brain network topology which have been shown to be useful, reliable biomarkers in discriminating normal and abnormal brain networks (Lo et al., 2010; Owen et al., 2013; Shu et al., 2011). Rubinovand Sporns recently presented a comprehensive summary of such measures in relation to their use on structural and functional brain networks (Rubinov and Sporns, 2010).

To date, network analysis of the entire preterm infant connectome, particularly over anatomically defined regions, has not been done for gestational ages earlier than term equivalent age. This gap is likely because of the difficulties in acquiring a large dataset of subjects at such a young age and because, until recently, brain atlases of young infants were not available. It is possible to perform a similar analysis without an atlas, as demonstrated by Tymofiyeva et al., however, this strategy makes it difficult to identify the anatomical significance of specific connections and sub-networks.

In this work, we compute structural brain networks for a cohort of young preterm neonates and analyze both local and global longitudinal trends. In performing this analysis, we observe that the brain networks of preterm infants show high efficiency and clustering measures across a range of network scales, a result seen in analogous studies of term infants at slightly older ages. We also note that the development of individual region-pair connections is often significantly correlated with age. In particular, we find that connections in the frontal and occipital lobes show high rates of development during this period. Finally, using established brain network measures (Rubinov and Sporns, 2010), we see that the preterm infant connectome remains highly efficient and becomes more clustered across this age range, leading to a significant increase in small-worldness. As far as we are aware, this is the first connectome analysis of subjects as young as 27 weeks PMA and the first work to look at whole-brain network integration and segregation in a large, normative cohort of preterm infants.

Materials and method

Study population

To establish normative development of preterm structural brain connectivity, we selected "normal" infants from a prospective cohort described in Chau et al. (2013). This cohort consists of premature newborns born between 24 to 32 weeks post-menstrual age at the Children's & Women's Health Centre of British Columbia. Exclusion criteria included 1) congenital malformation or syndrome; 2) antenatal infection; or 3) large parenchymal hemorrhagic infarction (>2 cm) on head ultrasound scanning. This prospective study was approved by the University of British Columbia Clinical Research Ethics Board. The newborns enrolled in this cohort were evaluated with MRI scans in the neonatal period (outlined below) and had neurodevelopmental assessments at 18 months of age (corrected for prematurity) with the Bayley Scales of Infant and Toddler Development, Third Edition (BSID-III) (Bayley, 2006) and the Peabody Developmental Motor Scales, Second Edition (PDMS-II) (Folio and Fewell, 2000). The 3 composite scores (cognitive, language and motor scores) of the BSID-III have a mean of 100 and a standard deviation of 15. The PDMS-II provides a more sensitive assessment of motor function yielding gross, fine and total motor scores with a mean of 100 and a standard deviation of 15. To ensure a normative sample of preterm neonates, we included those infants without acquired brain injury on MRI (no white matter injury, no intraventricular hemorrhage) and with scores on all six composite measures of neurodevelopment within 1 standard deviation of the normal mean (>85). After removing subjects with low cognitive test scores, detectable brain injury and low image quality (described below), the final number of subjects used in this study was 47 (28 males, 19 females).

Magnetic resonance imaging

Each of the 47 preterm neonates was scanned within the first weeks of life once they were clinically stable. Twenty-three of these 47 infants were scanned again at term-equivalent age, with 2 to 15 (9.49 ± 3.45) weeks between scans. The resulting 70 structural and diffusion MRI scans cover the age range of 27 to 45 (35.8 ± 5.29) weeks PMA (Table 1).

Our MRI studies were carried out on a Siemens (Berlin, Germany) 1.5 T Avanto using VB 13A software and included the following sequences: 3D coronal volumetric T_1-weighted images (repetition time [TR], 36 ms; echo time [TE], 9.2 ms; field of view [FOV], 200 mm; slice thickness, 1 mm, no gap) and a 3D axial volumetric diffusion tensor image set (TR 4900 ms; TE 104 ms; FOV 160 mm; slice thickness, 3 mm; no gap) with 3 averages of 12 non-colinear gradient directions over 2 diffusion weightings of 600 and 700 s/mm^2 (b-value), resulting in an in-plane resolution of 0.625 mm. Each diffusion weighted image set was preprocessed using the FSL Diffusion Toolbox (FDT) pipeline[1] and tensors were fit using RESTORE (Chang et al., 2005).

An experienced neuroradiologist (K.P.) reviewed the resulting MR images for the presence of white matter injury (WMI), intraventricular hemorrhages (IVH), and poor image quality due to subject motion. The presence of WMI was identified using a system found to be predictive of adverse neurodevelopmental outcome at 12 to 18 months of age (Leonard et al., 2005). We noted IVH using the protocol of Papile et al. (1978). The 70 scans used in this study were selected so as to be of sufficient quality and be free of these pathologies.

[1] http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/FDT.