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Early development of structural networks and the impact of prematurity on brain connectivity

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ABSTRACT

Preterm infants are at high risk of neurodevelopmental impairment, which may be due to altered development of brain connectivity. We aimed to (i) assess structural brain development from 25 to 45 weeks gestational age (GA) using graph theoretical approaches and (ii) test the hypothesis that preterm birth results in altered white matter network topology. Sixty-five infants underwent MRI between 25^{+3} and 45^{+6} weeks GA. Structural networks were constructed using constrained spherical deconvolution tractography and were weighted by measures of white matter microstructure (fractional anisotropy, neurite density and orientation dispersion index). We observed regional differences in brain maturation, with connections to and from deep grey matter showing most rapid developmental changes during this period. Intra-frontal, frontal to cingulate, frontal to caudate and inter-hemispheric connections matured more slowly. We demonstrated a core of key connections that was not affected by GA at birth. However, local connectivity involving thalamus, cerebellum, superior frontal lobe, cingulate gyrus and short range cortico-cortical connections was related to the degree of prematurity and contributed to altered global topology of the structural brain network. The relative preservation of core connections at the expense of local connections may support more effective use of impaired white matter reserve following preterm birth.

Introduction

The third trimester of pregnancy is associated with rapid brain development including differentiation and maturation of pre-oligodendrocytes, formation of synapses between thalamo-cortical afferents and subplate neurons, axonal growth and cortical gyrification. Infants who are born preterm have a high prevalence of motor, cognitive and behavioural deficits which are evident in childhood (Bhutta et al., 2002; Saigal and Doyle, 2008) and an increased risk of developing psychiatric disorders in adulthood (Nosarti et al., 2012). The wide spectrum of disability associated with preterm birth is consistent with pervasive abnormalities in brain growth and connectivity (Back, 2015; Volpe, 2009).

By studying both brain growth and connectivity, magnetic resonance imaging (MRI) has been used extensively to improve our understanding of the neural substrate underlying neurodevelopmental impairments in this population. MR imaging studies of preterm infants have identified: reduced cortical and subcortical grey matter (Padilla et al., 2015), diminished cerebellar volumes (Limperopoulos et al., 2010) and alterations in thalamo-cortical development at term-equivalent age (Ball et al., 2013; Ball et al., 2012); changes in structural brain network topology in young children (Pandit et al., 2014) and at school-age (Fischi-Gomez et al., 2014; Kim et al., 2014); and alterations in white matter (WM) and grey matter (GM) volumes in adolescence (Nosarti et al., 2008).

Diffusion MRI (dMRI) has demonstrated altered white matter development in preterm infants without focal lesions (Anjari et al., 2007; Huppi et al., 1998), which is related to neurodevelopmental performance in early childhood (Ball et al., 2015; Counsell et al.,

Abbreviations: ACT, anatomically-constrained tractography; CSD, constrained spherical deconvolution; CSF, cerebrospinal fluid; FA, fractional anisotropy; DGM, deep grey matter; dMRI, diffusion MRI; DTI, diffusion tensor imaging; FDR, false discovery rate; FOD, fibre orientation distribution; FS, fraction of streamlines; GA, gestational age; GM, grey matter; MRI, Magnetic resonance imaging; NDI, neurite density index; NODDI, neurite orientation dispersion and density imaging; ODI, orientation dispersion index; PMA, post menstrual age; rFA, relative fractional anisotropy; rFS, relative fraction of streamlines; rNDI, relative neurite density index; rODI, relative orientation density index; ROI, region of interest; SGA, small for gestational age; SIFT, spherical-deconvolution informed filtering of tractograms; WM, white matter

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2008; Thompson et al., 2014) and adolescence (Groeschel et al., 2014; Northam et al., 2012a; Northam et al., 2012b). Recent studies have used dMRI to assess macrostructural connectivity *in vivo* during early development (Brown et al., 2014; van den Heuvel et al., 2015) and, using dMRI, the rich-club organisation of structural brain networks during the preterm period has been characterised, demonstrating a relative preservation of core connections at term equivalent age (Ball et al., 2014). Similar findings have been reported in preterm-born children at school-age (Fischi-Gomez et al., 2016) and in adulthood (Karolis et al., 2016). However, the impact of prematurity on weighted brain network topology prior to term equivalent age is not known, largely because it is technically challenging to obtain high quality dMRI data in the neonatal period.

Typically, connectivity strength has been derived from basic measures of the amount (percentage, or density) of streamlines connecting two regions, or alternatively, by measures of directivity such as fractional anisotropy (FA). Powerful new dMRI methods are now available, which are able to provide fibre counts that are consistent with the apparent fibre density (Pestilli et al., 2014; Smith et al., 2013, 2015), and a realistic estimation of neurite architecture *in vivo* (Jespersen et al., 2007; Jespersen et al., 2012; Zhang et al., 2012). For example, neurite orientation dispersion and density imaging (NODDI) (Zhang et al., 2012) is a multi-compartment model which provides quantitative measures that correlate to tissue microstructure with greater specificity than established imaging techniques, such as diffusion tensor imaging (DTI). NODDI has been used previously to characterise WM (Kunz et al., 2014) and GM (Eaton-Rosen et al., 2015) tissue characteristics during early development, and is a promising biologically interpretable (Colgan et al., 2016) alternative to anisotropy measures to weight brain connectivity (Lemkaddem et al., 2014).

In this study we used high angular resolution multi-shell dMRI to assess connectivity between brain regions using connectivity metrics obtained from the diffusion tensor (fractional anisotropy, FA) as well as streamline measures obtained using constrained spherical deconvolution (CSD) with the spherical-deconvolution informed filtering of tractograms (SIFT) algorithm (Smith et al., 2013, 2015) and NODDI model characteristics: neurite density index (NDI) and orientation dispersion index (ODI). We applied these technical advances for the first time in a neonatal dataset in order to assess brain development from 25 to 45 weeks gestational age (GA) using graph theory measures of structural brain networks weighted with microstructural features (NDI and ODI) and to assess the impact of prematurity on network organisation. We complemented typical network features with the assessment of core and local average connectivity characteristics, and connection-wise correlations with normal development and degree of prematurity (GA at birth), allowing us to investigate in detail the topological changes we observed.

Methods

In order to investigate brain development prior to the time of normal birth and to assess the impact of prematurity on brain network organisation we performed CSD based tractography (*Tractography*), extracted network measures (*Network extraction, Network measures and Network normalisation*), determined the development of core versus non-core connections (*The development of core versus non-core connections*) and examined edge-wise correlations (*Edge-wise association in the minimum grid of connectivity*). We assessed the association between these graph theory features and edge-wise connections with age at MRI and GA at birth (*Statistical analysis*). See Fig. 1 for a scheme of the methodology used to extract brain networks and Fig. 2 for the different normalisation approaches used.

Participants and MRI acquisition

Research Ethics Committee approval for MR imaging was granted (12/LO/1247) and written parental consent was obtained prior to MRI. The inclusion criteria for this study were MR imaging without motion artefacts, performed ≤46 weeks post-menstrual age (PMA). We studied an initial sample of 80 datasets, corresponding to 72 subjects scanned one or two times. Based on exclusion criteria of congenital malformations or evidence of focal lesions on MRI, 7 subjects were excluded, leading to a final cohort of 65 neonates with a median (range) GA at birth of 33^{+2}, (range 24^{+2}–41^{+1}) weeks, and median PMA at scan of 36^{+2}, (25^{+3}–45^{+6}) weeks. Of those, 8 subjects were scanned twice (median 6^{+6}, range 3^{+3}–8^{+5} weeks after the first scan). See Table 1 for details of perinatal clinical characteristics of the infants.

MR imaging was performed on a 3 T Philips Achieva system (Best, The Netherlands) sited on the neonatal intensive care unit using a 32-channel head coil. 3D MPRAGE (repetition time (TR)=17 ms, echo time (TE)=4.6 ms, flip angle 13°, voxel size: 0.82×0.82×0.8 mm) and T2 weighted fast spin echo (TR=8670 ms, TE=160 ms, flip angle 90°, slice thickness 2 mm with 1 mm overlapping slices, in-plane resolution 1.14×1.14 mm) were acquired. dMRI data were acquired at 2 mm isotropic resolution and SENSE factor of 2 in 2 shells; 64 non-collinear directions with a *b*-value of 2500 s/mm², 4 non-diffusion weighted images (*b*=0) with TR 9000 ms and TE 62 ms; and 32 non-collinear directions with a *b*-value of 750 s/mm², 1 non-diffusion weighted image (*b*=0) with TR 9000 ms and TE 49 ms.

A paediatrician experienced in MRI procedures supervised all examinations, and pulse oximetry, temperature and electrocardiography data were monitored. Earplugs moulded from a silicone-based putty (President Putty, Coltene, Whaldent, Mahwah, NJ, USA) placed in the external auditory meatus and neonatal earmuffs (MiniMuffs, Natus Medical Inc., San Carlos, CA, USA) were used for auditory protection. Term controls and preterm infants < 37 weeks PMA at scanning were imaged during natural sleep without sedation. However, preterm infants at term equivalent age were sedated with oral chloral hydrate (25–50 mg/kg) prior to scanning.

Pre-processing

T2-weighted brain volumes were bias corrected (Tustison et al., 2010), skull striped and tissue segmented into WM, GM, deep grey matter (DGM), cerebrospinal fluid (CSF) and cerebellum using a neonatal-specific segmentation algorithm (Makropoulos et al., 2014). Parcellation into cortical and subcortical regions was performed with a block matching non-linear registration (Tristan-Vega and Arribas, 2007) of a version of the standard anatomical automatic labelling (AAL) atlas (Tzourio-Mazoyer et al., 2002) which has been specifically adapted to the neonatal brain (Shi et al., 2011). Parcellation of the atlas was propagated into each subject's native space following the non-linear registration previously calculated and a nearest neighbour propagation. All AAL cerebellar regions were merged into one, producing a total of 91 regions in each subjects' native space, which constituted the nodes used in the network analyses (Supplementary Table 1).

dMRI volumes were first visually inspected in order to detect data with motion artefacts, and exclude them from further analysis. All subjects included in the study had at most 8 (median 4, range 0–8) gradient directions excluded from the higher shell, and at most 6 (median 2, range 0–6) gradient directions excluded from the lower shell. Volumes were first corrected for EPI phase encoding distortions, eddy-induced distortions and subject movements by means of FSL5.0 topup-eddy algorithm (Andersson et al., 2003; Andersson and Sotiropoulos, 2015), using T2 volume rigidly registered to b0 maps and assuming a bandwidth of zero (no phase-encoding). This process was performed separately for the two acquired shells and their corresponding *b*=0 volumes, and then the lower shell was rigidly