Analysis of *in vivo* microstructural features during the first weeks of life using structural brain networks

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INTRODUCTION:

A better understanding of the development of brain connectivity during the first weeks after birth is crucial in the search for meaningful imaging biomarkers to characterise neurodevelopment. In particular, graph theoretic features of structural brain networks based on diffusion MRI in infants and neonates have shown associations with altered neurodevelopmental outcomes [1, 2]. However, it is technically challenging to obtain sensitive parameters that provide a detailed characterisation of connectivity fingerprints, especially in early infancy, when several maturational neuronal processes are taking place. Neurite orientation dispersion and density imaging (NODDI) allows the assessment of micro-structural parameters of brain tissue *in vivo* using a clinically feasible acquisition scheme [3]. While streamline count (SC) and fractional anisotropy (FA) have been previously used to weight connectivity [4, 5], we hypothesise that NODDI features can provide a complementary characterisation of brain connectivity. In addition, the use of high angular resolution diffusion imaging (HARDI) and constrained spherical deconvolution (CSD) allows a detailed reconstruction of macrostructural white matter (WM) tracts, overcoming several disadvantages of other techniques [6]. In this study, we used microstructural NODDI parameters (neurite density index (NDI) and orientation dispersion index (ODI)) in combination with CSD-HARDI tractography to assess the evolution of brain connectivity during very early infancy exploiting the versatility of network analysis. We compare the results with those obtained using SC and FA as connectivity weights [4, 5].

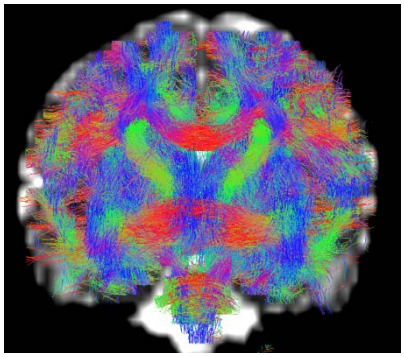

Fig. 1. CSD-HARDI tractography cropped to a slab of 6 mm in a coronal slice of interest, of an infant at 35 weeks PMA.

METHODS:

A cohort of 35 neonates (gestational age: 24^{+6}– 41^{+1} weeks) were scanned between 1 and 19 weeks after birth (post menstrual age, PMA: 29^{+1}–45 weeks) on a Philips 3-Tesla system. Image acquisition included: an MPRAGE (voxel size = 0.8 × 0.9 × 1 mm^3), a T2-weighted anatomical acquisition scan (voxel size = 1.1 × 1.1 × 2 mm^3) and 32- and 64-direction diffusion MRI with b=750 & 2500 s/mm^2 respectively (voxel size = 2 × 2 × 2 mm^3). T2-weighted brain volumes were parcellated by means of elastic registration with a neonatal specific atlas into 90 cortical and sub-cortical regions [7]. Segmentation of WM tissue was performed using a technique specially tailored for the developing brain [8]. T2 images were registered to diffusion space and parcellations and WM segmentations transformed accordingly. A maximum of 5 gradient volumes with apparent motion artefacts were excluded from each diffusion shell. FSL 5.0 was used to correct eddy currents [9]. CSD was applied to the outer diffusion shell to estimate the voxel-wise fibre orientation distribution (FOD) and tractography was performed using MRtrix [6], generating 10^6 streamlines for each subject (see Fig. 1). In addition, an FA map was also obtained based on a tensor model. The NODDI model was applied to the multi-shell diffusion MRI data to produce NDI and ODI maps for each subject. Brain networks were generated by combining the anatomical parcellation and the previously obtained tractography, assuming a connection exists between a pair of regions if at least 10 streamlines connected them. Each connection was weighted by their number of streamlines (SC) and average value of FA, NDI or ODI along all the streamlines connecting them. Graph theoretic features used to characterize brain networks were: network density, average weighted degree, weighted global efficiency (integration) and weighted local efficiency (segregation) [10]. As we populated all subject's brains with the same number of streamlines independently of size (which obviously increases with age), brain volume is a clear confounder and was regressed out of all parameters.

RESULTS:

Analysis of average weighted degree showed that only NDI-weighted average degree was significantly correlated with PMA (ρ=0.37 p=0.028). Importantly, both ODI- and NDI-weighted measures of integration and segregation (global and local efficiency) were significantly correlated with PMA (Fig 2), while SC- and FA-weighted features did not show any significant correlation.

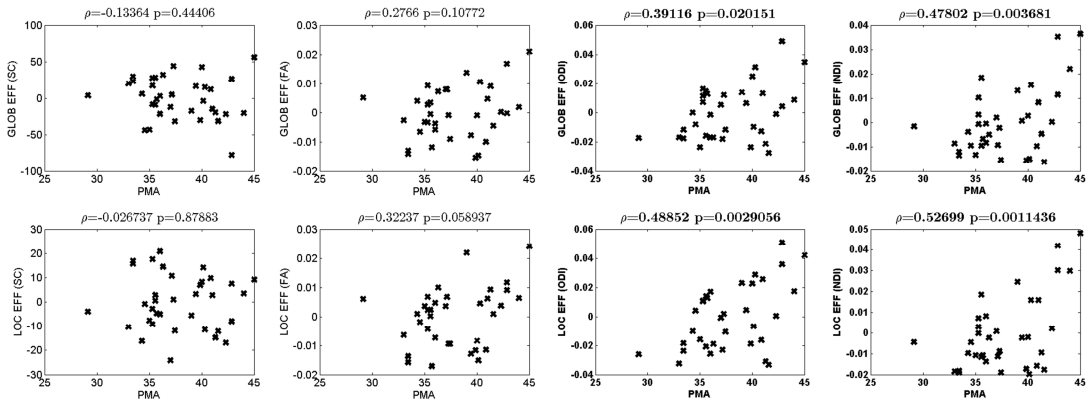

Fig. 2. Correlation of main network features with PMA (regressing out the effect of brain volume). Significant correlations (p<0.05) highlighted in bold.

DISCUSSION AND CONCLUSION:

This study demonstrates the suitability of NODDI to assess the microstructural features of brain connectivity of neonates using a brain network approach. In particular, we showed the high sensitivity of networks weighted with microstructural parameters (ODI and NDI) to assess brain maturation independently of brain volume. The correlation of NDI-weighted average degree with PMA suggests a general increase of neurite density in the connectivity pathways of the neonatal brain during the early neonatal period, independently of brain size. While this overall increase in neurite density with PMA was expected, NDI was also associated with the efficiency of the organisation of the brain network, as indicated by the significant correlation of NDI-weighted global and local efficiency. Interestingly, while ODI-weighted average degree was not associated with PMA, ODI-weighted global and local efficiency showed a positive correlation with PMA, suggesting that this measure could be linked with specific connectivity characteristics of the developing brain. The results highlight the potential of NODDI measures to capture essential characteristics of brain connectivity during maturation that were not shown with other, more traditional, connectivity features. Overall, the results confirm the potential of using *in vivo* microstructural features in brain network methodologies to capture specific aspects of brain maturation.

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