Whole-brain patterns of structural connectivity predict neurodevelopmental outcome in premature infants

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Background: The mapping of structural connectivity in the human brain is essential for better understanding of its function and dysfunction. To date, several models of structural connectivity have been reported which attempt to map the brain's architecture using inference of white-matter (WM) fiber pathways from diffusion MR data[1]. We use a modified probabilistic tractography approach that generates whole-brain connectivity data and accounts for both connection probability and strength[2]. This protocol has been successfully applied to characterise connectivity changes during ageing[3]. Here, we combine the above protocol with novel multivariate statistical techniques in order to identify WM connectivity patterns in the early infant population. The aim of this feasibility study is to identify the structural connectivity patterns, which are most predictive of functional outcome in two-year old preterm born infants.

Methods: 34 two year olds were imaged with a mean corrected age at scan of 26.5 months [range 24-27.5] and a mean gestational age at birth of 29.3 weeks [range 25.71-34.71]. Subjects were included if T1, T2 and DTI-32d data were all present. Subjects were excluded if major pathology was present. Diffusion imaging was carried out using a Philips 3T MRI scanner. Whole-brain probabilistic tractography followed a protocol as described previously[3] and is summarized in Fig.1. The Bayley's Scales of Infant and Toddler Development, third edition subscales were used to assess neurodevelopmental performance. The outcome measure of this study: developmental quotient (DQ) was calculated by combining cognitive, motor and language subscales into a composite score.

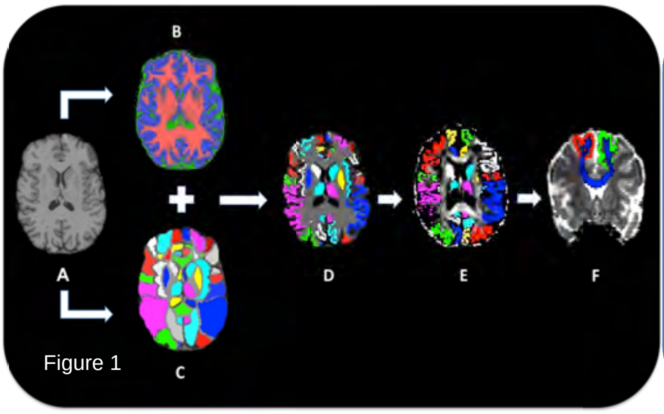

Figure 1

A: Initial raw data acquired = T1, T2, 32d DTI
B: Probabilistic tissue segmentations obtained from T1 images using SPM 8 (www.fil.ion.ucl.ac.uk/spm) separating CSF, grey and white matter
C: Segmentation of T1 images into 83 anatomical regions of interest (ROIs) using a combination of label propagation from multiple brain atlases followed by subsequent classifier fusion[4,5]
D: Merging of anatomical and tissue segmentations to generate cortical ROIs at the white-grey matter boundary with subcortical regions intact
E: Registration of T1→B0 space image via a T2 intermediate
F: Modified probabilistic tractography performed between ROIs

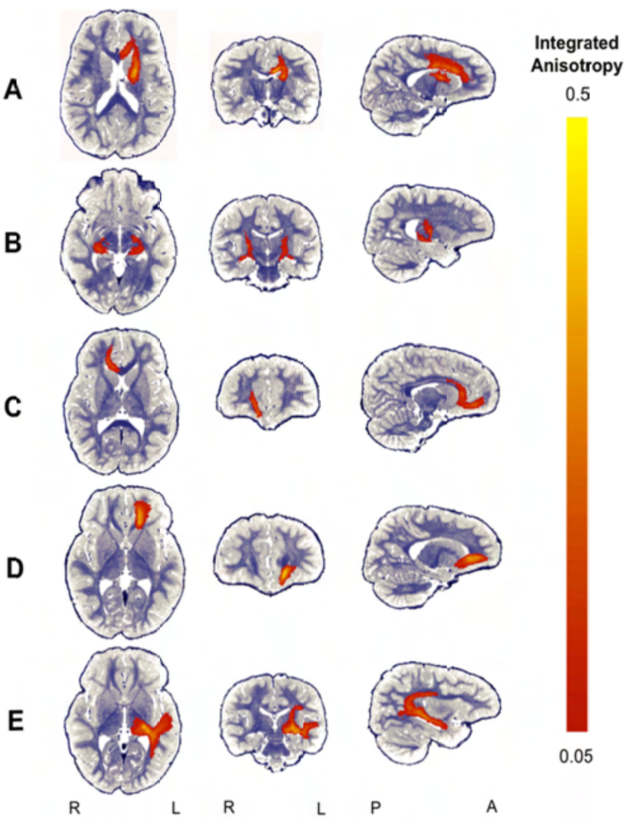

Figure 2. Probabilistic connections predictive of DQ following ENet regression. All tracts are shown in axial, coronal and sagittal sections. Colour bar indicates the level of integrated anisotropy (connectivity strength). β-coefficients: A=37.1699, B=18.6283(right); 15.0047(left), C=16.1262, D=14.6455, E=12.7566

Data analysis involved generation of a connectivity matrix for each subject in which each element corresponded to the integrated anisotropy of a probabilistic WM tract between two brain regions (Fig.1: F). After controlling for confounding variables: gestational age at birth and age at scan, Elastic Net (E-net) regression was applied to the residual data as a feature selection step in order to identify elements that were most predictive of developmental quotient (DQ). E-net is a penalized least-squares regression method, which aims to generate a subset of pertinent predictor variables by reducing to zero the coefficients of variables that have little or no apparent effect on outcome[6]. It has significant advantages over ordinary LASSO regression in that the algorithm adds a penalty term when predictor variables are highly correlated[7]. The regression parameters were optimized following 10-fold cross validation to determine the optimal mixing value and number of predictor variables.

Results

Probabilistic connections with the highest E-Net β-coefficients (with respect to the outcome variable DQ) were selected. These are presented in Figure 2. This set included WM tracts following the anterior cingulum (A,C), tracts involving the frontal (A,C,D) and temporal lobes (E), and tracts which engage the hippocampus (B) and thalamus (B,E).

Conclusion

This preliminary study supports a novel approach in which a characterisation of whole-brain connectivity can be derived and used to forecast functional outcome in a premature infant population. It also represents the first time that penalised regression methods have been applied to such neuroimaging data in this age group. The findings of this work agree, at least in part with the results of previous studies, which suggest that the connectivity of these highlighted tracts are responsible for effective neurological function[8]. Further work will seek to carry out a more detailed analysis of these predictive tracts.

References

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