Neural Systems Affected by Preterm Birth

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Background. Neuropsychiatric impairment is common among children born preterm[1], but the neural substrates for these disorders have not yet been characterised. Diffuse white matter disease is the most common cerebral abnormality in preterm infants at term equivalent age[2], and it can be quantified by apparent diffusion coefficient (ADC) values obtained from diffusion weighted imaging (DWI)[3]. The effect of diffuse white matter disease on developing neural systems is unknown. The objective of this study was to identify evidence of abnormal neural systems associated with preterm birth, particularly with diffuse white matter disease, using computational anatomic techniques.

Method. *Subjects* (Group 1 cross-sectional study): 3D MR images were acquired from 62 preterm infants (median GA 29.71 weeks, 24-34 weeks) at term equivalent age (median GA 40.43 weeks, 37-44.57 weeks), together with 12 term born control infants (median GA 39.57 weeks, median postnatal day 4). Infants were classified as having abnormal white matter if ADC values exceeded the mean + 2sd of the control group in one or more white matter region (measured in anterior, centrum semiovale and posterior white matter). Group 2 (longitudinal study): 274 images were acquired from 113 infants born between 23 and 30 weeks gestation, and imaged serially between birth and term equivalent age. Infants with focal parenchymal lesions were excluded.

Image acquisition. Group 1: a 1.5 Tesla MR system was used to acquire high resolution T1 weighted (TR=30ms, TE=4.5ms, flip angle=30°) volume datasets in contiguous slices with a voxel size of 1.0x1.0x1.6mm in addition to conventional and DWI. Group 2: a 1.0 Tesla MR system situated on our Neonatal Intensive Care Unit at that time was used to acquire conventional images, and T2-weighted fast-spin echo images (TR=3500ms, TE_{eff}=208ms) were analysed.

Image processing. Group 1: a deformation-based morphometric (DBM) approach was used to model structural differences between sub-groups of patients. Non-rigid image registration[4] was used to precisely transform 3D images to a common space (the image of a term born control), resulting in deformation fields describing the transformation of each subject to the template space. Voxel-wise volume change was estimated from the determinant of the Jacobian operator of the deformation field and group comparisons were made using parametric tests with a correction for multiple comparisons, implemented in SPM99 (http://www.fil.ion.ucl.ac.uk/spm).

For group 2 cerebral tissue volume (v) and cortical surface area (s) were measured semi-interactively, and the scaling exponent of surface area to cerebral volume together with interaction terms to the exponent were estimated using cross-sectional time series regression analyses of the log transformed data.

Results

Structural alteration in preterm infants at term equivalent age detected using DBM. Preterm infants at term equivalent age have volume loss within lentiform and thalamic nuclei compared with term born controls (t=5.81, p<0.05) (figure 1). These changes are more severe among infants with damage to overlying white matter (t=6.43, p<0.05) (figure 2) and with increasing prematurity at birth (t=7.13, p<0.05 for infants born at less than 28 weeks' gestation). We speculated that altered deep grey matter development is secondary to a disturbance in corticothalamic circuitry mediated by injury to white matter tracts. Therefore we tested whether cortical development is also impaired following preterm birth by measuring the scaling of cerebral surface area to volume.

Reduced surface area to cerebral volume scaling. For cerebral volumes >50cm^3 cortical surface area is related to cerebral volume by a power law with a scaling exponent of 1.3 (95% CI 1.26 to 1.34, p<0.0001) (figure 3a), and gestational age at birth is a highly significant interaction term to this exponent (p<0.0001). These findings indicate that there is a dose-dependent relationship between cortical development and degree of prematurity at birth.

Conclusions

These data strongly suggest that disturbance to corticothalamic connectivity plays an important role in the neural sequelae of preterm delivery.

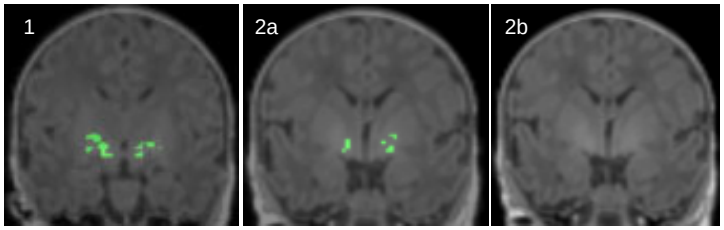

Figure 1. 2D coronal representation of the statistical parametric map (SPM) showing thalamic and lentiform volume reduction in 62 preterm infants at term equivalent age compared with 12 term controls. Figure 2a is the SPM showing deep grey matter volume loss in infants with diffuse white matter disease compared with controls, and Figure 2b is an equivalent slice of the SPM comparing preterm infants at term equivalent with normal white matter to the controls: no significant volume loss is identified.

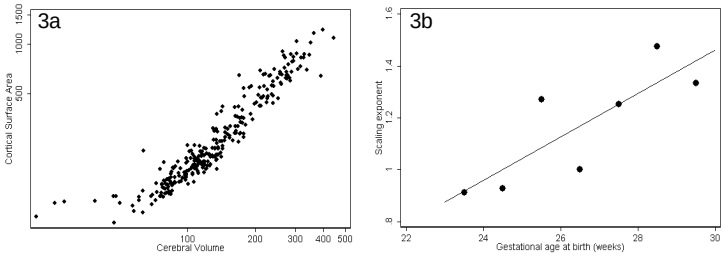

Figure 3a. Cortical surface area and cerebral volume in log coordinates. The relationship is described by $\log s = \alpha \log v + c$ where α is the scaling exponent. In figure 3b the images are grouped by gestational age at birth, showing that surface area to cerebral volume scaling decreases with prematurity at birth (p=0.024 for the slope of the linear regression line).

References. 1.Bhutta, A.T. *et al. JAMA* 288,728-737 (2002). 2. Maalouf, E.F. *et al. J.Pediatr*. 135,351-357 (1999). 3.Counsell, S.J. *et al. Pediatrics* 112,1-7 (2003). 4.Rueckert, D. *et al. IEEE Trans.Med.Imaging* 18, 712-721 (1999). **Acknowledgement**.We thank Philips medical systems, the Medical Research Council and the Engineering and Physical Sciences Research Council for research grant support.