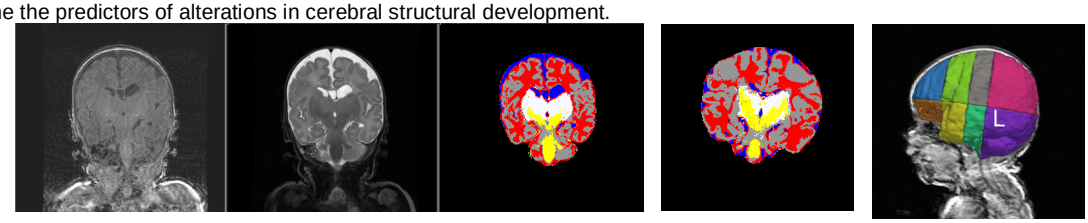
Application of advanced MRI to assess factors contributing to total and regional cerebral tissue volumes in the preterm brain

D. K. Thompson[1], M. Pavlovic[1], H. X. Wang[1], L. W. Doyle[2], S. K. Warfield[3], G. F. Egan[1], T. E. Inder[2,4]

[1]Howard Florey Institute, Melbourne, Victoria, Australia, [2]Royal Womens Hospital, Melbourne, Victoria, Australia, [3]Brigham & Women's Hospital, Harvard Medical School, Boston, USA, Boston, MA, United States, [4]Royal Childrens Hospital, Melbourne, Victoria, Australia

Introduction: Impairment in neurobehavioral outcome is prevalent in extremely preterm infants (<32 weeks' gestation) with significant educational, social and economic ramifications. Advanced post-acquisition MR imaging techniques such as quantitative volumetric analysis of structural MR images can improve our understanding of the neuroanatomical differences between the term and preterm infant brain. Furthermore, a better understanding of the perinatal factors that contribute to altered neuroanatomical development in preterm infants can be examined. Alterations in cerebral tissue volumes may at least partially explain later cognitive and motor deficits in preterm infants, including cerebral palsy.

Method: Full-term and preterm infants (<32 weeks or <1250 grams) delivered at the Royal Women's Hospital, Melbourne were included in the study. All infants were scanned at term or term equivalent (40wks) in a 1.5 Tesla General Electric MRI scanner. Two imaging sequences were used: T1 spoiled gradient recalled acquisition (SPGR) (1.5mm coronal slices; flip angle(FA) 45°; TR 35ms; TE 9ms; FOV 18cm; matrix= 256 x 256) and dual-echo (proton density (PD) and T2-weighted) spin echo sequences (3mm coronal; TR= 4000msec; TE 60 / 160msec; FOV 18cm; matrix= 512 x 512, interleaved acquisition) (Figure 1a,b). The t2w and pdw images were registered to the spgr image using a rigid body transformation algorithm, followed by a model-based segmentation. The segmentation method uses a spatially varying statistical classification in which a classified 40-week infant brain image is used as an anatomical template to estimate each subject's tissue classification[1] (Figure 1c,d). Average cerebral tissue volumes were calculated for cortical gray matter (CGM), unmyelinated white matter (unMWM), myelinated white matter (myelin), basal ganglia (BG or subcortical gray matter) and cerebrospinal fluid (CSF). In addition to the whole brain volume, regional comparisons were made by dividing the brain into hemispheres. Each hemisphere was further divided into eight anatomical sectors (dorsal prefrontal, orbitofrontal, premotor, subgenual, sensorimotor, midtemporal, parieto-occipital and inferior occipital with cerebellum)[2], using the axial plane encompassing the anterior commissure - posterior commissure (AC-PC) line and 3 limiting coronal planes. The first coronal plane was positioned at the genu of the corpus callosum, the second passed through the anterior border of the AC, and the third through the PC (Figure 1e). Statistical analyses were undertaken using SPSS12.0, analyzing the contribution of demographic factors such as gestational age at birth, gender, multiple birth, white matter injury, intraventricular hemorrhage, cardio-respiratory treatments, antenatal and postnatal steroids, patent ductus arteriosus, sepsis, growth and nutrition. Multiple perinatal factors were further analysed in a multivariate model to determine the predictors of alterations in cerebral structural development.



(a) (b) (c) (d) (e)

Figure 1: (a) Spgr and (b) T2 weighted images. Segmented image of (c) a WMI preterm infant and (d) full term infant. Tissue types: cortical GM (gray); unmyelinated WM (red); CSF (blue); myelinated WM (yellow); and basal ganglia (white). (e) Parcellated infant brain volume.

Results: Thirty-six term-born (T) controls and 202 preterm (PT) infants were analyzed. Significant structural differences were observed between the term and preterm infants. Preterm infants had 25cc less total cerebral tissue than term controls (mean ± SD: PT 395 ± 64cc; T 420 ± 50cc; p=0.011), including less CGM (PT 159 ± 42cc; T 173 ± 32cc; p=0.059) and significantly less BG (PT 13.5 ± 3.9cc; T 15.5 ± 2.5cc; p<0.0005), with a corresponding increase in CSF (PT 46.0 ± 26.0cc; T 26.3 ± 11.0cc; p<0.0005). These findings were confirmed by correcting for % total intracranial volume for CGM (PT 35.8 ± 5.6%; T 38.6 ± 5.3%; p=0.005), BG (PT 3.1 ± 0.8%; T 3.5 ± 0.5%; p<0.0005) and CSF (PT 10.2 ± 4.9%; T 5.8 ± 2.1%; p<0.0005). A major predictor of preterm tissue volumes was the presence and severity of cerebral white matter injury (WMI). The presence of moderate-severe WMI amongst preterm infants resulted in a significant reduction in CGM (WMI 33.0 ± 5.0%; noWMI 36.3± 5.6%; p<0.002) and BG (WMI 2.7 ± 0.7%; noWMI 3.2 ± 0.8%; p<0.0005) when compared to preterm infants with no or mild WMI. However, even when moderately to severely WM injured preterm infants were excluded from the analysis, preterm infants still exhibited less CGM (PT 36.3 ± 5.6%; T 38.6 ± 5.3%; p=0.024) and BG (PT 3.2 ± 0.8%; T 3.5 ± 0.6%; p=0.002), and more CSF (PT 9.4% ± 4.1%; T 5.8% ± 2.1%; p<0.0005) than term-born controls. In preterm infants the perinatal factors contributing to reduced total brain tissue volume included number of days on total parenteral nutrition (p=0.02) and intrauterine growth restriction (IUGR, p=0.002), while increases in CSF volumes related to gestational age (p=0.002) and WMI (p<0.0005). The main factor contributing to smaller BG was exposure to postnatal steroids (p=0.025). CGM volumes were only affected by IUGR (p=0.03). Following regional parcellation, the regions that were most significantly affected by tissue loss in preterm infants varied with the perinatal risk factor in a multivariate regressional model. The regions that were most affected for preterm infants included sensorimotor, dorsal prefrontal, parieto-occipital, and premotor. The sensorimotor region displayed the most significant changes in CGM (PT 37.7 ± 5.0%; T 40.7 ± 4.7%; p=0.001) with gestational age (p=0.024), hours on positive pressure ventilation (p=0.03), and IUGR (p=0.05) as major predictors. The dorsal prefrontal region displayed changes in CGM (PT 20.3 ± 7.0%; T 23.5 ± 8.9%; p=0.02) with IUGR as a contributor (p=0.036), and unMWM (PT 63.0 ± 9.6%; T 68.7 ± 8.8%; p=0.001) with no clear perinatal correlates. The parieto-occipital area showed significant differences between preterm and term infants for CGM (PT 40.3 ± 7.6%; T 43.4 ± 7.7%; p=0.033), again with no clear perinatal correlates. In contrast the premotor area was reduced in unMWM (PT 52.8 ± 7.6%; T 55.8 ± 7.6%; p=0.032), with the male gender as a significant perinatal contributor (p=0.031).

Conclusion: Infants born prematurely demonstrate significant alterations in macroscopic anatomical organization and regional distribution of cerebral tissue types at term equivalent compared with term born infants. Maximal tissue reduction is demonstrated in cortical and deep nuclear gray matter. Regions most at risk of alteration within the preterm brain include dorsal prefrontal, orbitofrontal, premotor and parieto-occipital. These changes are regionally related to perinatal factors including WMI, gestational age at birth, use of postnatal steroids, IUGR, and respiratory illness. Significant insights into neurodevelopmental outcomes for these infants born preterm is crucial for further investigation and implementation of neuroprotective strategies. Utilization of advanced MRI coupled with quantitative volumetric image analysis provides a unique tool for assessing alterations in brain tissue volumes and regionally specific abnormalities of premature birth.

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