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Deep grey matter growth predicts neurodevelopmental outcomes in very preterm children

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ABSTRACT

We evaluated whether the volume and growth rate of critical brain structures measured by MRI in the first weeks of life following very preterm (<32/40 weeks) birth could predict subsequent neurodevelopmental outcomes at 4 years of age. A significant proportion of children born very prematurely have cognitive deficits, but these problems are often only detected at early school age. Structural T2-weighted magnetic resonance images were acquired in 96 very preterm neonates scanned within 2 weeks of birth and 70 of these at term-equivalent age. An automated 3D image analysis procedure was used to measure the volume of selected brain structures across all scans and time points. At 4 years of age, 53 children returned for neuropsychological assessments evaluating IQ, language and visual motor integration. Associations with maternal education and perinatal measures were also explored. Multiple regression analyses revealed that growth of the caudate and globus pallidus between preterm birth and term-equivalent age predicted visual motor integration scores after controlling for sex and gestational age. Further associations were found between caudate and putamen growth with IQ and language scores. Analyses at either preterm or term-equivalent age only found associations between normalized deep grey matter growth and visual motor integration scores at term-equivalent age. Maternal education levels were associated with measures of IQ and language, but not visual motor integration. Thalamic growth was additionally linked with perinatal measures and presence of white matter lesions. These results highlight deep grey matter growth rates as promising biomarkers of long-term outcomes following very preterm birth, and contribute to our understanding of the brain–behaviour relations in these children.

Introduction

An estimated 15 million preterm births occurred worldwide in 2010, with about 10% at less than 32 weeks gestation (Blencowe et al., 2012). These infants are born during the third trimester of human gestation, a period of accelerated brain growth that coincides with a critical window when dendritic and axonal arborization, synaptogenesis and myelination occur (Lenroot and Giedd, 2006). Foundational thalamocortical networks are consolidated that further establish cortical and basal ganglia connectivity with widespread cerebral networks (Kostović and Jovanov-Milosević, 2006). Neural components key to these networks, such as cortical and deep grey matter projection neurons, subplate neurons and oligodendrocyte precursors, are potentially the most vulnerable during this period, especially if very preterm birth is associated with white matter injury (WMI) and illness (Back et al., 2001; Ferriero and Miller, 2010; McQuillen et al., 2003). As deep grey matter structures are implicated in a wide range of cognitive functions (Arsalidou et al., 2013), their development is fundamental to normal cognition.

Modern health care interventions have greatly improved survival rates of very preterm-born infants in developed countries, yet the rates of subsequent comorbid neurodevelopmental impairments have not improved; while 40–50% are indistinguishable at school-age from term-born children, at least 50% of very preterm-born children experience cognitive, language and/or motor skill deficits (Marlow, 2004; Saigal and Doyle, 2008). Perinatal clinical measures alone have failed to explain long-term developmental outcomes (Hart et al., 2008), and current explanations include a role for interacting environmental factors such as maternal education and biological factors such as WMI

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and cortical dysmaturation detected by magnetic resonance imaging (MRI). Longitudinal study designs provide more potential to understand developmental outcomes in contrast to cross-sectional designs. For example, serial imaging of abnormal maturation of white matter microstructure and metabolism within the basal nuclei in conjunction with WMI beginning in the neonatal period is associated with adverse outcomes in very preterm-born infants (Chau et al., 2013). Dynamic changes in cortical thickness and growth in preterm and typically developing children and adolescents have also demonstrated connections with cognitive ability (Kapellou et al., 2006; Rathbone et al., 2011; Shaw et al., 2006; Sowell et al., 2004). The relation between longitudinal, neonatal structural brain maturation, however, has not been established.

Previous cross-sectional MRI studies of deep grey matter structural development in preterms are limited and vary by analysis technique. The thalamus and lentiform nucleus at term-equivalent age display reduced growth, exacerbated by the presence of WMI (Ball et al., 2012; Boardman et al., 2006; Lin et al., 2001; Srinivasan et al., 2007). Whole-brain analyses similarly found reductions of the deep grey matter directly associated with disability and developmental outcome at infancy, yet only indirectly associated with cognitive function in later childhood and adolescence (Boardman et al., 2010; Inder et al., 2005; Kesler et al., 2004; Nosarti et al., 2008; Peterson et al., 2000). Specific examination of the thalamus, caudate and hippocampi in later childhood and adolescence of very preterm-born infants, however, found correlations between thalamic and caudate volumes with verbal fluency and intelligence (Giménez et al., 2006; Abernethy et al., 2004). While these cross-sectional studies have investigated aspects of deep grey matter volumes in relation to neurodevelopmental abilities, there remains a gap in our understanding of how these associations evolve from birth in very preterm-born infants.

The present longitudinal study examined whether growth of the caudate, putamen, globus pallidus, thalamus, and total brain during the crucial third trimester of rapid brain growth predicted neurodevelopmental outcomes at 4 years of age. The contribution of perinatal clinical factors and maternal education with deep grey matter development and outcome measures was also investigated. We hypothesized that the maturation of the deep grey matter structures over the preterm period would predict cognitive outcomes at 4 years of age, and that these early weeks of maturation would prove to be a critical developmental window influencing cognitive outcomes in very preterm born children.

Materials and Methods

Participants

One hundred and five very preterm neonates (median age at birth in weeks: 28.6; range: 24.43–32.86; 55 males and 50 females) were recruited from the neonatal intensive care unit at the Hospital for Sick Children in Toronto. Neonates with any known chromosomal or major congenital abnormalities were excluded from recruitment. All families signed an informed consent agreeing to MRI scans, access to medical records and follow-up participation. The study protocol was approved by the Hospital for Sick Children research ethics board.

Each very preterm neonate underwent an MRI within 2 weeks of birth (median age in weeks: 30.14, range: 25.1–34.86) while swaddled and lying flat during natural sleep. Following the first scan, five neonates died before term-equivalent age and four had gross motion artefact and anatomical abnormalities and were excluded from subsequent analyses. At term-equivalent age, 70 infants were scanned again (median age in weeks: 42; range: 36.57–46.43). At four years of age, 53 children returned (median age in years: 4.2; range: 4.02–4.91; median gestational age: 28.86; range: 26.29–31.14; 30 males and 23 females) for a comprehensive neuropsychological assessment.

MRI data

MRI scans were performed on a 1.5 T GE Signa Excite HD Scanner (GE Medical Systems, Milwaukee, WI, USA) using an MR-compatible incubator and neonatal head coil (AIR Inc., Cleveland, OH, USA). Axial T2-weighted and T1-weighted images were acquired (repetition time/echo time: 4000/145 and 23/4 ms; field of view: 128 and 128 mm; resolution: 1 × 1 × 1 mm; 90 and 110 slices; scan time: 4.16 and 5.39 min).

Two paediatric neuroradiologists with extensive experience in neonatal imaging evaluated clinical images of each neonate's first scan independently. Images were evaluated for the grade of germinal matrix haemorrhage (GMH) and non-cystic white matter lesions. Incidence numbers are reported in Table 1 for infants with both preterm and term-equivalent scans. White matter lesions were further graded for mild to moderate and severe levels of injury by an expert neurologist (Miller et al., 2003). Two neonates had white matter injury consistent with periventricular leukomalacia (PVL).

MRI segmentation

Manual segmentation of the whole caudate, putamen, globus pallidus, internal capsule and thalamus was performed on two 3D average images by one primary rater (JY) with the aid of a brain atlas (Harsberger et al., 2006) as shown in Figs. 1A–B. Two independent raters, a neuroradiologist and neurosurgeon, also manually segmented the selected structures. Intraclass correlations were calculated and averaged between the primary rater and two independent raters to assess the accuracy of the segmentation (caudate: 0.88, putamen: 0.99, globus pallidus: 0.85, thalamus: 0.99). The reference segmentation created by the primary rater was then used to automatically segment and compute the volume of the brain structures on each MRI using the previously derived spatial transformations (Fig. 2). These segmentations were inspected visually for accuracy. Only two caudate and one thalamus segmentation at the preterm time point were determined to be unreliable and excluded from further analysis. Total brain volume, including the cerebellum and excluding ventricles, was also manually drawn on the average images and propagated back to individual scans using the same method previously described. For those with enlarged ventricles, additional manual editing was performed to ensure that only brain regions were included to acquire total brain volume measures.

Table 1
Perinatal characteristics at very preterm birth.

Characteristic	Mean (SD) or number (%)
Gestational age (weeks)	28.84 (1.78)
Antenatal steroids	49 (75%)
Intrauterine growth restriction	12 (19%)
Caesarean-section delivery	39 (60%)
Multiple births	10 (7%)
Males	35 (54%)
Birth Weight (g)	1162.5 (263.5)
Head circumference (cm)	25.9 (2.0)
Apgar score at 5 min	7.3 (1.8)
Resuscitation required (CPR)	7 (11%)
CRIB II	6.6 (2.5)
Endotracheal tube days	12.7 (16.5)
Oxygen administration days	19.6 (28.3)
Patent ductus arteriosus (treated)	16 (25%)
Sepsis (culture positive)	23 (35%)
Meningitis	5 (8%)
Necrotizing enterocolitis (stages 2 & 3)	7 (11%)
Bronchopulmonary dysplasia	15 (23%)
GMH (grades 1–2)	13(20%)
GMH (grades 3–4)	13 (20%)
White matter lesions	22 (34%)

Characteristics are reported for 65 infants with longitudinal scans. CRIB II — Clinical Risk Index for Babies; GMH — germinal matrix haemorrhage.