Deep Grey Matter Growth and Neurodevelopmental Outcomes in Very Preterm Children

by

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Abstract

Definition of neurodevelopmental outcome from early brain imaging remains a priority for survivors of very preterm (VPT) birth given their persistently high rates of cognitive and motor difficulties. Volumes of the deep grey matter (DGM) structures were measured longitudinally using magnetic resonance imaging from 96 VPT infants studied within 2 weeks of birth and 70 at term-equivalent age. At 4 years of age, 36 children returned for neuropsychological assessments evaluating IQ, language function, and visual motor integration. Multiple hierarchical regressions examined associations of DGM growth with neuropsychological measures. Overall DGM growth, primarily attributed to the caudate and thalamus, predicted Full Scale IQ, core language and VMI scores after controlling for sex and total brain volume. Thalamic growth was additionally associated with measures of neonatal clinical severity, bronchopulmonary dysplasia, and white matter lesions. Longitudinal growth of the DGM, particularly the caudate and thalamus were established as early markers of long-term outcomes.
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Chapter 1
Introduction

1.1 Preterm birth and developmental consequences

A recent report estimated 15 million babies across the world were born preterm in 2010, ranging from 5% to 18% of all live births in developed and developing countries (Blencowe et al., 2012). Of those, babies born very preterm (VPT) at less than 32 weeks gestation comprised about 1% with rising incidences (CIHI, 2009). Improvements in health care interventions in developed countries for VPT born infants have vastly improved survival rates, although comorbid medical and neurodevelopmental difficulties persist long after birth (Marlow, 2004; Saigal & Doyle, 2008). As such, consequences of preterm birth are serious public health issues, especially for those born VPT. Understanding the underlying cortical correlates of long-term neurodevelopmental impairment is vital for improving the quality of life of this vulnerable population. Emerging studies investigating cerebral pathologies such as injury and dysmaturation serve as promising explanations of long-term developmental impairments (Hart, Whitby, Griffiths, & Smith, 2008). Conclusive findings characterizing early brain development and long-term outcome in VPT infants, however, have yet to be determined.

Long-term adverse effects of VPT birth have been widely recognized. Incidences of cerebral palsy as a function of birth weight occurs in 8-15% of these children (Hack et al., 2005; Marlow, 2004) while developmental and cognitive impairment occurs in about 20-50% (Woodward et al., 2009). Beginning at 2 years of life, impaired language, mental, and motor abilities start to emerge (Foster-Cohen, Edgin, Champion, & Woodward, 2007; Hack et al., 2005). Repeated studies of cognitive ability following 2 years of age have found that initial assessments had poor predictive ability, stressing the need for long-term follow-up well beyond
the first years of life (Hack et al., 2005; Leversen et al., 2012). VPT children ages 5 to 8 years scored consistently lower on parent reports and standardized assessments of cognitive, behavioural, language, and motor performance than their term-born counterparts, although not always below normal levels of standardized classifications (Aylward, Pfeiffer, Wright, & Verhulst, 1989; Barre, Morgan, Doyle, & Anderson, 2011; Böhm et al., 2002; Delobel-Ayoub et al., 2009; Marlow, Hennessy, Bracewell, & Wolke, 2007; Mikkola et al., 2005; Wolke & Meyer, 1999; Woodward et al., 2009). Adolescents and young adults born VPT continue to experience persisting cognitive, language, and executive function impairments (Allin et al., 2008; Casey, Whiteside-Mansell, Barrett, Bradley, & Gargus, 2006; Nosarti et al., 2007; Taylor, Minich, Klein, & Hack, 2004). Hack et al. (2002) tracked 242 very low birth weight (VLBW) infants to 20 years of age and compared education, cognitive and academic achievement to normal birth weight infants and found that VLBW born adults were less likely to graduate from high school, enroll in post secondary school, and more likely to experience lower academic achievement. As impaired academic achievement persists into adulthood (Aarnoudse-Moens, Weisglas-Kuperus, Van Goudoever, & Oosterlaan, 2009), the need for understanding the early underlying biological causes of these deficits is important to be able to alter the long-term developmental trajectories of those born VPT.

1.2 Early brain development and brain injury

In the first weeks following VPT birth until term-equivalent age, the premature brain undergoes a dramatic change in grey and white cerebral development (Huppi et al., 1998). Rapid synchronized changes occur such as synaptogenesis, neuronal migration, apoptosis, myelination, dendritic, and axonal arborization (Lenroot & Giedd, 2006). The most important network to form during 24 to 32 weeks of life involves the creation and early consolidation of thalamocortical
connections (Stiles & Jernigan, 2010). Afferents from the thalamus begin to project into the cortex via the internal capsule and subplate. The subplate, which is about four times larger than the cortical plate during this time, acts as a waiting area where thalamocortical projections pass before entering the cortical plate. The thalamocortical axons that reach the cortical plate create permanent sensory connections with the frontal, somatosensory, visual, and auditory system for the very first time (Kostović & Jovanov-Milosević, 2006; Lodygensky, Vasung, Sizonenko, & Hüppi, 2010). Thalamocortical inputs to the cortex following initial synaptic contacts are likely to impact the formation of foundational connections, especially as they relay information received from the basal ganglia and mediate flow between cortical circuits throughout differential regions of the cortex (McFarland & Haber, 2002). Structures that depend upon this network such as the subplate neurons, projection neurons from the thalamus, and oligodendrocytes precursors supporting axons between the subcortex and neocortex, are consequently the most vulnerable following VPT birth, especially when infants are critically ill (Ferriero & Miller, 2010).

Common forms of brain injury in preterm infants include periventricular white matter injury (WMI) and intraventricular hemorrhage (Back & Rivkees, 2004; Volpe, 2009). WMI, in the extreme form of periventricular leukomalacia (PVL) or cerebral white matter lesions, has been widely studied as impacting cortical, subcortical structures and cognitive deficits (Volpe, 2009). Compelling postmortem evidence of preterm babies found neuronal loss in the thalamus and globus pallidus as well as gliosis in all of the DGM structures unique to PVL cases unlike those with only diffuse white matter gliosis or neither condition (Pierson et al., 2007). Thalamic damage was also found in 59% of infants who died early in life with PVL compared to 19% of infants without PVL (Ligam et al., 2009). These postmortem studies indicate the DGM as particularly vulnerable to brain injury, especially WMI.
1.3 MRI studies in preterms

Magnetic resonance imaging (MRI) studies of preterm infants with PVL exhibited decreased cerebral cortical grey and white matter volumes at term age compared to those without (Inder et al., 1999). The thalamus is the most vulnerable to WMI and reduced in size in babies with PVL (Lin et al., 2001; Nagasunder et al., 2011; Volpe, 2009; Zubiaurre-Elorza et al., 2012). Subsequent MRI studies exploring the neuroanatomical and neurodevelopmental impact of WMI report volume reductions in the thalamus, globus pallidus, and white matter as well as impaired neurodevelopmental abilities (Boardman et al., 2010; Woodward, Anderson, Austin, Howard, & Inder, 2006; Woodward, Clark, Bora, & Inder, 2012; Zubiaurre-Elorza et al., 2012). The subcortical structures, particularly the thalamus, are highly susceptible to brain injury, impacting downstream cognition, motor, and language function.

Preterm born infants without brain injury also experience alterations in brain structure persisting through childhood. At term-equivalent age, VPT and extremely preterm born infants have reduced grey matter volume (Inder, Warfield, Wang, Hüppi, & Volpe, 2005), surface area (Ajayi-Obe, Saeed, Cowan, & Rutherford, 2000), thalamic and lentiform volumes (Boardman et al., 2006; Srinivasan et al., 2007). Ball et al. (2012) found that reduced thalamic volumes were also predictive of reduced cortical, frontal, temporal, and hippocampal volumes and reduced fractional anisotropy (FA) within corticospinal tracts and the corpus callosum of preterm infants at term-equivalent age. In school age children between 7 and 12 years, preterm children experienced reduced grey matter volumes, white matter volume gain (Ment, Hirtz, & Hüppi, 2009) overall brain volume, surface area, cortical thickness, and ratios between basal ganglia and thalamus volumes with total brain volumes (Lax et al., 2012).
1.4 MRI studies and neurodevelopmental outcomes

Identifying predictors of neurodevelopmental outcome and maturational differences in cerebral structures of VPT children from typical children is an important goal as very few MRI studies have identified such associations. In the early postnatal period, smaller cerebellar and white matter volumes (Lind et al., 2011; Peterson et al., 2003) as well as cortical surface area and volume growth (Kapellou et al., 2006; Rathbone et al., 2011) were found to be associated with later outcome. More specifically, cortical surface area growth of preterm infants was proportional to neurodevelopmental impairment at 2 years of age and developmental quotients at 6 years of age (Kapellou et al., 2006; Rathbone et al., 2011).

Studies of VPT children in childhood and adolescence have reported structural differences using voxel-based morphometry with cognitive abilities. Grey matter volume decreases in the thalamus were correlated with verbal fluency (Giménez et al., 2006). Frontal and temporal lobes were correlated with declining verbal IQs as well as occipital and temporal lobes with declining performance IQs (Isaacs et al., 2004). Nosarti et al. (2008) also found widespread grey and white matter differences in VPT versus term-born adolescents associated with gestational age, which mediated neurodevelopmental impairment.

Volumetric studies showed similar associations with neurodevelopmental outcomes. Cerebellar white matter, hippocampus, and thalamus grey matter were associated with cognitive, perceptual, and visual motor functions in VLBW preterm adolescents (Martinussen et al., 2009), sensorimotor and mid-temporal cortical volumes were associated with verbal and performance IQ in late childhood (Peterson et al., 2000), and grey matter volume in the middle temporal regions and post-central gyri were associated with Full Scale IQ (Soria-Pastor et al., 2009). Many of these studies have looked at long-term outcome, but do not have earlier longitudinal
brain imaging data that would increase our understanding of how these abnormalities evolve. Few studies report relations of early brain maturation and neurodevelopmental outcome, underlining a tremendous gap in the knowledge of this association.

1.5 Study Rationale

This present unique longitudinal study captures the dynamic subcortical growth and neurodevelopmental outcomes of children born VPT beginning at birth through 4 years of life. As VPT born children are at a disadvantage, it is important to identify the long-term implications of early insults and maturational differences as soon as possible. The DGM structures are targets of dysmaturation within the vulnerable preterm period; therefore, we examined the predictive ability of detailed longitudinal DGM growth from 24 to 46 weeks with neurodevelopmental outcome at 4 years of age. Exploratory analyses of perinatal clinical factors and maternal education with DGM development and outcome measures were also investigated in separate analyses. We hypothesized that maturation of DGM structures within the preterm period would predict neurodevelopmental scores at 4 years of age, and the early weeks of DGM maturation would prove to be a critical developmental window influencing long-term neurodevelopmental outcomes.
Chapter 2
Methods

2.1 Participants

One hundred and five VPT neonates (median age at birth in weeks: 28.6; range: 24.43 - 32.86) 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 VPT neonate underwent an MRI within 2 weeks of birth while swaddled and lying flat during natural sleep. Following the first scan, five neonates passed away in the hospital or after discharge and four had gross motion artifact 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). Around four years of age, 36 children returned (median age in years: 4.2; range: 4.02 – 4.85) for a comprehensive neuropsychological assessment.

2.2 MRI Data

MRI scans were performed on a 1.5T 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: 1x1x1 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 (identified as abnormal foci of T1 hyperintensities without simultaneous T2 hypointensity). Numbers of incidences 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 (Miller et al., 2003) by an expert neurologist.

2.3 MRI Segmentation

Ninety-six T2-weighted images acquired shortly after preterm birth and 70 T2-weighted images acquired at term-equivalent age were co-registered by using MICe-build-model (https://wiki.mouseimaging.ca/display/MICePub/MICe-build-model; Lerch, Sled, & Henkelman, 2011). This existing software was adapted for groupwise non-linear alignment to address the complexity of analyzing a large number of pathological and normal appearing images. A composite image was then constructed for each age group. Manual segmentation of the DGM including the caudate, putamen, globus pallidus, internal capsule, and thalamus was performed on the axial slices of the composite images with the aid of a brain atlas (Harsberger et al., 2006) and expert opinion (Figure 1A and 1B). DGM and total brain masks excluding cerebral spinal fluid were manually segmented by one primary rater (JY). Two independent raters also manually segmented the DGM of the first group. Intraclass correlations were calculated and averaged for the DGM between the primary rater and two independent raters to validate the accuracy of the segmentation (caudate: 0.88, putamen: 0.99, globus pallidus: 0.85, thalamus: 0.99). Deep grey and total brain masks were warped back to each infant’s scan in an unbiased manner using the inverse transformations calculated by MICe-build-model to obtain individual segmentations and
volumes for each structure and total brain (Figure 2). Each individual’s segmentation was visually inspected for accuracy.

2.4 Perinatal Data

Perinatal data obtained at birth are shown in Table 1 for infants with both preterm and term-equivalent scans. Measures of illness severity were calculated including Apgar scores at 5 minutes and the Clinical Risk Index for Babies (CRIB-II). Medical interventions were also noted such as the use of resuscitation (CPR), antenatal steroids, and oxygen administration days.

2.5 Neuropsychological Assessments

At four years of age, children who were due for follow-up underwent a neurodevelopmental assessment. Intelligence quotients (IQ) were determined by the Wechsler Preschool and Primary Scales of Intelligence – Third Edition (WPPSI-III; Weschler, 2002) using Canadian norms. Four different indices of cognitive abilities were obtained: Verbal IQ (VIQ), Performance IQ (PIQ), Processing Speed (PSQ) and Global Language (GL). The comprehensive indices of these subtests comprise the Full Scale IQ (FSIQ). Overall language ability was determined by the Clinical Evaluation of Language Fundamentals – Preschool, Second Edition(CELF-Pre-2; Semel, Wigg, & Secord, 2004), which measures receptive and expressive language, language content and structure, and yields a core language summary score. Visual-motor integration was assessed by the Beery-Buktenica Test of Visual Motor Integration (VMI; Beery & Beery, 2010). Supplemental VMI tests of visual perception and motor coordination were also administered. Performance on these measures is shown in Table 2.
2.6 Maternal Education

Highest levels of maternal education were obtained for children with 4-year neuropsychological assessments. Levels of maternal education were ranked on a scale from 1-5 beginning with grade school (2.9%), high school (14.3%), college and post-secondary school (31.4%), university (40%), and post-graduate education (11.4%).

2.7 Statistical Analyses

All statistical analyses were conducted using SPSS version 20.0 (SPSS Inc, Chicago, IL.). Linear regressions were performed between summed left and right DGM structures and age at scan across preterm and term-equivalent ages to determine developmental trends. Growth rates of each structure used in subsequent analyses were calculated as the difference in volume divided by the difference in ages at preterm and term-equivalent scans. Associations between subtests within each neuropsychological assessment (WPPSI-III, CELF-Pre-2, VMI) were performed using Pearson correlations.

Our primary hypothesis was tested using a multiple hierarchical regression model. Neuropsychological measures were entered as dependent variables and all growth rates of the caudate, thalamus, globus pallidus, and putamen were entered as independent variables after controlling for sex and total brain volume measured from preterm scans. Post-hoc analyses using the same multiple hierarchical regression model determined the predictive ability of individual structures. Significance values of p < 0.05 were considered significant.

Exploratory analyses of DGM growth rates and neuropsychological measures with perinatal clinical measures shown in Table 1 and highest maternal education level were performed. Pearson correlations, Spearman Rank Order correlations, and non-parametric Mann-
Whitney U tests were used for continuous, scaled and non-normally distributed, and dichotomous measures respectively. Post-hoc tests of white matter lesion severity were also performed. To help correct for multiple comparisons, significance values of $p < 0.01$ were considered significant for the exploratory analyses.
Chapter 3
Results

3.1 Deep grey matter is associated with age at scan

Dynamic linear growth of the DGM was apparent between preterm and term-equivalent ages, representative of the gross changes in brain development experienced during this time. The caudate ($R^2 = 0.862, p < 0.001$), putamen ($R^2 = 0.896, p < 0.001$), globus pallidus ($R^2 = 0.943, p < 0.001$), and thalamus ($R^2 = 0.917, p < 0.001$) were all highly associated with age at scan (Figure 3). Growth measures of the DGM structures were obtained from 65 infants with both preterm and term-equivalent scans. Average (SD) growth of the caudate was 116.13 (21.52) mm$^3$/week, the putamen 206.93 (30.99) mm$^3$/week, the globus pallidus 70.99 (13.05) mm$^3$/week, and the thalamus 418.59 (71.04) mm$^3$/week.

3.2 Neuropsychological Assessments

Composite scores of the neuropsychological assessments obtained in 36 four-year olds were highly correlated with individual subtests. The FSIQ of the WPPSI-III was correlated with VIQ, PIQ, and PSQ ($p < 0.001$) as well as GL ($p = 0.003$). The core language component of the CELF-Pre-2 was also correlated with receptive language, expressive language, language content, and language structure subtests (all $p < 0.001$). The VMI of the Beery-Buktenica test was correlated with visual perception ($p = 0.003$) and motor coordination ($p = 0.001$) subtests. Therefore, only the most representative composite scores of each assessment, the FSIQ, core language, and VMI were used in subsequent analyses.
3.3 Deep grey matter is associated with 4-year outcomes

Longitudinal DGM growth and 4-year neuropsychological measures were recorded in 31 children. Growth of all the DGM structures significantly predicted measures of FSIQ (p = 0.019), core language (p = 0.047), and VMI (p = 0.01) after controlling for sex and preterm total brain volume. Post-hoc analyses as shown in Table 3 revealed caudate and thalamic growth to be significant individual predictors of FSIQ, core language, and VMI. Globus pallidus growth was a significant predictor of only VMI. Putamen growth was not a significant predictor of any neuropsychological measure. (Figure 4, A-F).

3.4 Associations with clinical factors and maternal education

Thalamic growth was most correlated to perinatal clinical variables compared to all other structures as shown in Table 4. Thalamic growth was significantly reduced with the CRIB II, bronchopulmonary dysplasia, and presence of white matter lesions. Post-hoc Mann-Whitney U Tests determined that 15 infants with moderate and severe white matter lesions drove the association (U = 166, Z = -2.7, p = 0.007) (Figure 5. A-B). No other structures were associated with white matter lesions. Intrauterine growth restriction was also significantly associated with putamen growth. Only caudate and thalamic growth showed a trend of association with maternal education (p = 0.018 and p = 0.034). All other perinatal clinical and radiological measures were not significantly associated with any DGM growth.

Core language scores were significantly associated with birth weight and the CRIB II while gestational age showed a trend of association. Full Scale IQ also showed a trend of association with white matter lesions (p = 0.029). Maternal education was highly correlated with FSIQ ($r_p = 0.490$, p = 0.003), core language ($r_p = 0.54$, p = 0.001), and VMI ($r_p = 0.453$, p =
0.006). No other perinatal clinical and radiological measures were associated with neuropsychological measures as shown in Table 5.
Chapter 4
Discussion

4.1 Longitudinal deep grey matter growth

Longitudinal growth of the DGM structures between preterm and term-equivalent age in children who are born VPT was demonstrated to have a role in long-term developmental outcomes. These dramatic age-related volumetric changes represent the extensive maturational transformations of the neuronal components within the DGM during this time. Our study determined that DGM growth, particularly of the caudate and thalamus is closely related to comprehensive measures of intelligence, language, and visual-motor integration in childhood. Thus, consideration of changes in brain structure beginning at birth is valuable for informing our understanding of what specific cortical regions may be responsible for neurodevelopmental outcomes.

The present study distinctively focused on structural growth rather than absolute volumes of structures, such as many cross-sectional studies with comparison term-born infants. The literature suggests that the thalamus and basal ganglia are reduced in size in preterm born infants at term-equivalent age (Boardman et al., 2006), childhood (Peterson et al., 2000), and adolescence (Nosarti et al., 2008). As such, the beginning of DGM dysmaturation likely occurs during the preterm period and before term-equivalent age, as reduced volumes have already been reported by that time. What is not evident is when the divergence from typical growth transpires during the preterm period. We found greater variability in volumes at term-equivalent age compared to the preterm age (see Figure 3), implying that there may be more evidence of dysmaturation at the latter time point as a result of developmental change between preterm and term-equivalent age. Thus, by capturing the variability of DGM growth over this critical period, we were able to identify an association between growth and neurodevelopmental outcome, where
those with poorer outcomes experienced greater dysmaturation as characterized by slower growth of the caudate, thalamus, and globus pallidus. From this finding, we argue that studying the longitudinal changes of cortical growth immediately following birth may provide more predictive information of neurodevelopmental trajectories than cross-sectional studies.

Few studies have examined longitudinal cortical growth in VPT infants beginning at birth over the preterm period as a biomarker of developmental outcomes; however, none have assessed the deep grey matter structures in this manner. In extremely preterm infants serially imaged until term-equivalent age, cortical surface area expansion was related to cerebral volume growth by an allometric scaling law and proportional to neurodevelopmental impairment at 2 years of age assessed by the Griffiths Developmental Quotient (Kapellou et al., 2006). Follow-up of this cohort at 6 years of age also resulted in cortical growth to be proportional to the FSIQ of the WPPSI-R and the NEPSY summary score measuring verbal, performance, attention, language, memory, attention abilities but not motor measures (Rathbone et al., 2011). In typically developing populations, longitudinal designs have proven to be key in assessing the development of intelligence, as dynamic cortical maturation has better characterized intelligence over absolute measures (Shaw et al., 2006). Therefore, the present study provides a rare and important account of detailed longitudinal deep grey matter growth in relation to neurodevelopmental outcomes in VPT infants.

4.2 Deep grey matter and neuropsychological measures

Caudate growth was found to be a strong predictor of FSIQ, language, and VMI outcomes, indicating that it serves a widespread role in overall cognitive function. Only a few studies have investigated similar relations in adolescents and adults. Two studies found that caudate volumes correlated with IQ and hyperactivity at 7 and 14 years in VPT born children and adolescents
Others revealed relations between functional activation in the caudate with visuo-perceptual learning and executive function in VPT born adolescents and young adults (Narberhaus et al., 2009; Nosarti et al., 2009). The association found between caudate growth and VMI was most expected in our study, as the caudate is typically known for its role in sensorimotor coordination and pathological role in Parkinson’s disease (Grahn, Parkinson, & Owen, 2008). Less known functions of the caudate in typically developing populations include executive function, goal-directed behavior (Grahn, Parkinson, & Owen, 2009) and auditory language perception (Kotz, Schwartze, & Schmidt-Kassow, 2009). Our novel findings of caudate growth with FSIQ and language in the developing brain support emerging non-motor related caudate functions, and highlight its importance for predicting outcomes in VPT infants.

The remaining structures of the basal ganglia that comprise the lentiform nucleus, globus pallidus and putamen, had marginal associations with the neuropsychological measures. Both structures, in contrast to the caudate, are primarily involved in motor function as opposed to cognitive function (Grahn et al., 2008). Growth of the putamen did not result in any relationship with outcomes while the globus pallidus growth only demonstrated a robust association with VMI. Therefore, growth of the globus pallidus and putamen may not be very informative for the purpose of predicting long-term cognitive function.

Thalamic growth was highly associated with the neurodevelopmental measures, although more strongly with FSIQ and language than VMI function. This finding is consistent with the literature, which has shown relations between thalamic reductions and impaired cognitive skills in preterm born children and adolescents, although often presented in conjunction with WMI. The cognitive abilities assessed in these studies included overall developmental quotients,
working memory and IQ, semantic and phonetic language fluency, and VMI (Boardman et al., 2010; Giménez et al., 2006; Martinussen et al., 2009; Zubiaurre-Elorza et al., 2012). Similarly, studies of typically developing children through young adulthood from various neuroimaging techniques also found strong correlations of the thalamus with FSIQ, VIQ, and syntactic and semantic language (Frangou, Chitins, & Williams, 2004; Wahl et al., 2008; Xie, Chen, & Bellis, 2012). Importantly, none of these studies have linked thalamic growth shortly after birth in VPT infants with later cognitive functioning, when thalamocortical connections are beginning to form.

The relation between the caudate and thalamus with neurodevelopmental outcome reinforces the critical timing of cortical connections forming between these structures in early development. The caudate, as a part of the striatum, is an integral structure within cortico-striatal connections, where topographical projections from the cortex are received and projected back through the globus pallidus, substantia nigra, and thalamus (Grahn et al., 2008). The thalamus is a complex structure, containing abundant nuclei with specific functions. Its initial neurons develop in the second trimester, although recent research has found evidence of a second later surge of generated neurons in the dorsal region of the thalamus (Letinic & Rakic, 2001). The vulnerability of the dorsal medial nucleus of the thalamus from preterm birth and diffuse WMI may be due to a disruption of this event (Volpe, 2009). Furthermore, the connections between the dorsomedial nucleus of the thalamus with afferents from the striatum, basal ganglia, limbic system and projections to the frontal cortex and anterior cingulate are likely to be largely responsible for cognitive impairment in VPT born infants (Boardman et al., 2010). Less known factors influencing thalamo-cortical connections such as pre-oligodendrocytes and subplate neurons likely serve just as an important role in cognitive function and needs to be better understood in conjunction with its neuronal DGM components.
4.3 Deep grey matter and perinatal data

As expected, we found that thalamic growth was affected by the presence of WMI as an entire group. This finding is widely supported in the literature (Volpe, 2009) in WMI ranging from focal and diffuse injury to PVL. In our study, WMI was further classified as moderate or severe if the initial scan contained three or more areas of T1 signal abnormalities or areas greater than 2 mm and 5% of the hemisphere. The mild classification included those with three or fewer signal abnormalities less than 2 mm (Miller et al., 2003). After considering the impact of WMI severity on DGM growth, it was apparent that moderate and severe white matter injury impacted thalamic growth the most in comparison to mild WMI. Interestingly, none of the other DGM structures, such as the caudate, globus pallidus, and putamen were significantly affected by WMI in our cohort. This finding may be due to the majority of infants having focal and diffuse non-cystic white matter lesions as opposed to more severe PVL. Riddle and colleagues (submitted manuscript) modeled fetal sheep models of ischemia, which caused WMI and impaired grey matter growth. Importantly, they found reduced caudate growth as well as abnormal dendritic arborization and dendritic spines within the caudate as a result of induced ischemia. In contrast to the thalamus, more severe forms of WMI such as PVL as opposed to less severe forms of WMI may affect the basal ganglia, especially the caudate.

Overall, perinatal clinical measures did not have a robust effect on the growth of all the DGM structures. The thalamus was the only structure most affected by showing associations with the CRIB II and BPD in addition to WMI. The putamen, on the other hand, was the only structure affected by IUGR. The CRIBII is an index of illness severity consisting of a combination of measures such as gestational age, birth weight, sex, temperature at admission, and maximum base excess over 12 hours (Parry, Tucker, & Tarnow-Mordi, 2003) while BPD is defined as prolonged oxygen required. Both of these measures have been found to reduce
cortical growth over the preterm period (Kaukola et al., 2009). Thompson et al. (2007) reported that WMI, IUGR, and BPD were the only perinatal clinical measures specifically involved in regions of cortical dysmaturation at term-equivalent age, although not within the DGM as reliable segmentations were unavailable. The mechanisms of BPD and IUGR on cortical dysmaturation remain unclear, although they may serve as an important contributor towards neurodevelopmental outcomes. In our cohort, we did not find correlations between perinatal clinical measures and outcomes measures apart from birth weight and CRIB II measures with language scores, perhaps, due to the relatively small sample of children who have underwent neurodevelopmental assessments at four years of age in comparison to the number of DGM growth measures in our cohort.

4.4 Associations with maternal education
Maternal education was highly correlated with each neurodevelopmental outcome measure at four years of age yet weakly associated with caudate and thalamic growth. Similar results between maternal education and outcomes were found in preterm born children and adolescents (Kesler et al., 2004; Luu et al., 2009), indicating that environmental factors such as maternal education play an integral role in neurodevelopmental outcomes. Lange, Froimowitz, Bigler, & Lainhart (2010) studied a large cohort of typically developing children and adolescents and found parental education to be highly correlated with verbal, performance, and full scale IQ that did not mediate effects between total brain volume and IQ measures. It was argued that parental education is associated with genetic and environmental mechanisms influencing features of brain development that are in turn, associated with IQ. This reasoning supports the notion that disturbances in cortical growth during the preterm period in addition to genetic and environmental factors are all highly inter-related in explaining the functional outcomes of VPT infants and should ideally be studied in combination with one another.
4.5 Conclusion

Our novel characterization of longitudinal DGM growth in the VPT brain has elucidated key structures of the subcortex involved in long-term neurodevelopmental outcomes. In particular, growth of the caudate may play a larger role in cognitive function than previously realized. We reinforced previous findings that the growth of the thalamus was highly impacted by adverse neonatal conditions and is essential in understanding neurodevelopmental outcomes. Early brain dysmaturation of the DGM in the context of neurodevelopmental outcomes emphasizes the preterm period as a critical window for development.
References


Canadian Institute of Health Information. (2009). *Too Early, Too Small: A Profile of Small Babies across Canada*. Ottowa, ON.


### Table 1. Clinical and radiological characteristics at VPT birth

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Mean (SD) or number (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gestational Age (weeks)</td>
<td>28.84 (1.78)</td>
</tr>
<tr>
<td>Antenatal steroids</td>
<td>49 (75.4%)</td>
</tr>
<tr>
<td>Intrauterine growth restriction</td>
<td>12 (19%)</td>
</tr>
<tr>
<td>Cesarean-section delivery</td>
<td>39 (60%)</td>
</tr>
<tr>
<td>Multiple births</td>
<td>10 (6.5%)</td>
</tr>
<tr>
<td>Males</td>
<td>35 (53.8%)</td>
</tr>
<tr>
<td>Birth Weight (g)</td>
<td>1162.5 (263.5)</td>
</tr>
<tr>
<td>Head circumference (cm)</td>
<td>25.9 (2.0)</td>
</tr>
<tr>
<td>Apgar score at 5 min</td>
<td>7.3 (1.8)</td>
</tr>
<tr>
<td>Resuscitation required (CPR)</td>
<td>7 (11%)</td>
</tr>
<tr>
<td>CRIB II</td>
<td>6.6 (2.5)</td>
</tr>
<tr>
<td>Endotracheal tube days</td>
<td>12.7 (16.5)</td>
</tr>
<tr>
<td>Oxygen administration days</td>
<td>19.6 (28.3)</td>
</tr>
<tr>
<td>Patent ductus arteriosus (treated)</td>
<td>16 (24.6%)</td>
</tr>
<tr>
<td>Sepsis (cultures positive)</td>
<td>23 (35%)</td>
</tr>
<tr>
<td>Meningitis</td>
<td>5 (7.7%)</td>
</tr>
<tr>
<td>Necrotizing entercolitis (stage 2 &amp; 3)</td>
<td>7 (10.8%)</td>
</tr>
<tr>
<td>Bronchopulmonary dysplasia</td>
<td>15 (23%)</td>
</tr>
<tr>
<td>GMH (Grade 1-2)</td>
<td>13 (20%)</td>
</tr>
<tr>
<td>GMH (Grade 3-4)</td>
<td>13 (20%)</td>
</tr>
<tr>
<td>White Matter lesions</td>
<td>22 (34%)</td>
</tr>
</tbody>
</table>

Characteristics are reported for 65 infants with longitudinal scans. CRIB II - Clinical Risk index for Babies; GMH - Germinal Matrix Hemorrhage
Table 2. Psychological assessments of VPT children at 4 years of age

<table>
<thead>
<tr>
<th>Assessment</th>
<th>Subtests</th>
<th>N</th>
<th>Mean (SD)</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>WPPSI-III</td>
<td>Full Scale IQ</td>
<td>36</td>
<td>93.8 (16.6)</td>
<td>62-123</td>
</tr>
<tr>
<td></td>
<td>Performance IQ</td>
<td>36</td>
<td>93.8 (13.2)</td>
<td>65-131</td>
</tr>
<tr>
<td></td>
<td>Processing Speed</td>
<td>34</td>
<td>90.5 (18.3)</td>
<td>63-121</td>
</tr>
<tr>
<td></td>
<td>Verbal IQ</td>
<td>36</td>
<td>98.8 (18.6)</td>
<td>62-133</td>
</tr>
<tr>
<td></td>
<td>Global Language</td>
<td>30</td>
<td>102.6 (15.1)</td>
<td>74-135</td>
</tr>
<tr>
<td>CELF-Pre-2</td>
<td>Core Language</td>
<td>34</td>
<td>93.9 (17.0)</td>
<td>57-121</td>
</tr>
<tr>
<td></td>
<td>Receptive Language</td>
<td>34</td>
<td>93.5 (16.4)</td>
<td>61-120</td>
</tr>
<tr>
<td></td>
<td>Expressive Language</td>
<td>34</td>
<td>95.4 (18.0)</td>
<td>53-123</td>
</tr>
<tr>
<td></td>
<td>Language Content</td>
<td>34</td>
<td>96.2 (16.9)</td>
<td>59-124</td>
</tr>
<tr>
<td></td>
<td>Language Structure</td>
<td>34</td>
<td>92.7 (17.7)</td>
<td>50-120</td>
</tr>
<tr>
<td>VMI</td>
<td>Visual Motor Integration</td>
<td>36</td>
<td>99.8 (11.24)</td>
<td>66-121</td>
</tr>
<tr>
<td></td>
<td>Visual Perception</td>
<td>35</td>
<td>89.6 (18.7)</td>
<td>46-115</td>
</tr>
<tr>
<td></td>
<td>Motor Coordination</td>
<td>35</td>
<td>86.4 (16.0)</td>
<td>58-126</td>
</tr>
</tbody>
</table>

**Table 3. Multiple hierarchical regression statistics**

<table>
<thead>
<tr>
<th>Measure</th>
<th>df</th>
<th>F</th>
<th>p-value</th>
<th>df</th>
<th>F</th>
<th>p-value</th>
<th>df</th>
<th>F</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Measures</td>
<td>4,23</td>
<td>3.648</td>
<td>0.019*</td>
<td>4,22</td>
<td>2.869</td>
<td>0.047*</td>
<td>4,23</td>
<td>4.276</td>
<td>0.010*</td>
</tr>
<tr>
<td>Caudate</td>
<td>1,26</td>
<td>6.058</td>
<td>0.021*</td>
<td>1,25</td>
<td>6.217</td>
<td>0.020*</td>
<td>1,26</td>
<td>7.429</td>
<td>0.011*</td>
</tr>
<tr>
<td>Thalamus</td>
<td>1,26</td>
<td>8.751</td>
<td>0.007*</td>
<td>1,25</td>
<td>6.151</td>
<td>0.020*</td>
<td>1,26</td>
<td>4.731</td>
<td>0.039*</td>
</tr>
<tr>
<td>Globus pallidus</td>
<td>1,27</td>
<td>4.092</td>
<td>0.053</td>
<td>1,26</td>
<td>3.67</td>
<td>0.066</td>
<td>1,27</td>
<td>9.683</td>
<td>0.004*</td>
</tr>
<tr>
<td>Putamen</td>
<td>1,27</td>
<td>2.412</td>
<td>0.132</td>
<td>1,26</td>
<td>4.05</td>
<td>0.055</td>
<td>1,27</td>
<td>2.13</td>
<td>0.156</td>
</tr>
</tbody>
</table>

Reported statistics represent the change in F statistic and significance after controlling for sex and preterm total brain volumes. All measures denote all deep grey matter growth measures entered into the model at the same time. Individual measures such as the caudate, thalamus, globus pallidus, and putamen denotes post-hoc tests performed. Degrees of freedom vary due to children who were unable to complete every assessment. *Significance values of p < 0.05 are considered statistically significant.
Table 4. Analyses of clinical and radiological characteristics with deep grey matter growth

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Thalamic Growth</th>
<th>Caudate Growth</th>
<th>Globus Pallidus Growth</th>
<th>Putamen Growth</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>rₚ, rₛ, U/Z</td>
<td>p-value</td>
<td>rₚ, rₛ, U/Z</td>
<td>p-value</td>
</tr>
<tr>
<td>Gestational Age (weeks)</td>
<td>0.172</td>
<td>0.173</td>
<td>-0.009</td>
<td>0.944</td>
</tr>
<tr>
<td>Antenatal steroids</td>
<td>331/-0.822</td>
<td>0.411</td>
<td>279/-1.532</td>
<td>0.126</td>
</tr>
<tr>
<td>Intrauterine growth restriction</td>
<td>263/-0.843</td>
<td>0.399</td>
<td>237/-1.208</td>
<td>0.227</td>
</tr>
<tr>
<td>Cesarean-section delivery</td>
<td>368/-1.722</td>
<td>0.085</td>
<td>333/-2.066</td>
<td>0.039</td>
</tr>
<tr>
<td>Birth Weight (g)</td>
<td>0.189</td>
<td>0.134</td>
<td>0.137</td>
<td>0.285</td>
</tr>
<tr>
<td>Head circumference (cm)</td>
<td>0.133</td>
<td>0.305</td>
<td>0.090</td>
<td>0.494</td>
</tr>
<tr>
<td>Apgar score at 5 min</td>
<td>0.135</td>
<td>0.301</td>
<td>0.144</td>
<td>0.274</td>
</tr>
<tr>
<td>Resuscitation required (CPR)</td>
<td>163/-0.785</td>
<td>0.447</td>
<td>162/-0.744</td>
<td>0.472</td>
</tr>
<tr>
<td>CRIB II</td>
<td>-0.382</td>
<td>0.002*</td>
<td>-0.112</td>
<td>0.387</td>
</tr>
<tr>
<td>Endotracheal tube days</td>
<td>-0.259</td>
<td>0.040</td>
<td>0.071</td>
<td>0.582</td>
</tr>
<tr>
<td>Oxygen administration days</td>
<td>-0.244</td>
<td>0.052</td>
<td>-0.080</td>
<td>0.531</td>
</tr>
<tr>
<td>Patent ductus arteriosus (treated)</td>
<td>308/-1.074</td>
<td>0.283</td>
<td>361/-0.113</td>
<td>0.910</td>
</tr>
<tr>
<td>Sepsis (cultures positive)</td>
<td>467/-0.063</td>
<td>0.950</td>
<td>449/-0.029</td>
<td>0.977</td>
</tr>
<tr>
<td>Meningitis</td>
<td>133/-0.305</td>
<td>0.777</td>
<td>132/-0.271</td>
<td>0.802</td>
</tr>
<tr>
<td>Necrotizing entercolitis (stage 2-3)</td>
<td>160/-0.656</td>
<td>0.527</td>
<td>176/-0.219</td>
<td>0.839</td>
</tr>
<tr>
<td>Bronchopulmonary dysplasia</td>
<td>159/-3.304</td>
<td>0.001*</td>
<td>271/-1.436</td>
<td>0.151</td>
</tr>
<tr>
<td>GMH (Grade 1-2)</td>
<td>194/-2.294</td>
<td>0.022</td>
<td>253/-1.223</td>
<td>0.221</td>
</tr>
<tr>
<td>GMH (Grade 3-4)</td>
<td>279/-0.568</td>
<td>0.570</td>
<td>214/-1.304</td>
<td>0.192</td>
</tr>
<tr>
<td>White matter lesions</td>
<td>265/-2.785</td>
<td>0.005*</td>
<td>368/-1.197</td>
<td>0.231</td>
</tr>
</tbody>
</table>

* Significance values of p < 0.01 are considered statistically significant. Pearson Correlation: rₚ. Spearman Rank Order correlation: rₛ. U and Z score correspond to Mann-Whitney U Test.
Table 5. Analyses of clinical and radiological characteristics with neuropsychological measures

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Full Scale IQ</th>
<th>Core Language</th>
<th>VMI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>( r_{p}, r_s, U/Z )</td>
<td>( p )-value</td>
<td>( r_{p}, r_s, U/Z )</td>
</tr>
<tr>
<td>Gestational Age (weeks)</td>
<td>0.150</td>
<td>0.384</td>
<td>0.419</td>
</tr>
<tr>
<td>Antenatal steroids</td>
<td>43.5/-1.904</td>
<td>0.055</td>
<td>50/-1.006</td>
</tr>
<tr>
<td>Intrauterine growth restriction</td>
<td>40/-2.123</td>
<td>0.033</td>
<td>31/-2.021</td>
</tr>
<tr>
<td>Cesarean-section delivery</td>
<td>125.5/-1.099</td>
<td>0.276</td>
<td>92/-1.755</td>
</tr>
<tr>
<td>Birth Weight (g)</td>
<td>0.178</td>
<td>0.299</td>
<td>0.517</td>
</tr>
<tr>
<td>Head circumference (cm)</td>
<td>0.070</td>
<td>0.688</td>
<td>0.270</td>
</tr>
<tr>
<td>Apgar score at 5 min</td>
<td>-0.028</td>
<td>0.875</td>
<td>0.216</td>
</tr>
<tr>
<td>Resuscitation required (CPR)</td>
<td>34/-0.887</td>
<td>0.409</td>
<td>37.5/-0.547</td>
</tr>
<tr>
<td>CRIB II</td>
<td>-0.242</td>
<td>0.154</td>
<td>-0.556</td>
</tr>
<tr>
<td>Endotracheal tube days</td>
<td>0.089</td>
<td>0.605</td>
<td>0.073</td>
</tr>
<tr>
<td>Oxygen administration days</td>
<td>-0.137</td>
<td>0.437</td>
<td>-0.244</td>
</tr>
<tr>
<td>Patent ductus arteriosus (treated)</td>
<td>106/-0.848</td>
<td>0.413</td>
<td>90.5/-0.860</td>
</tr>
<tr>
<td>Sepsis (cultures positive)</td>
<td>154.5/-0.096</td>
<td>0.924</td>
<td>139/-0.035</td>
</tr>
<tr>
<td>Meningitis</td>
<td>32.5/-0.973</td>
<td>0.347</td>
<td>26.5/-1.216</td>
</tr>
<tr>
<td>Necrotizing enterocolitis (stage 2-3)</td>
<td>44/-1.883</td>
<td>0.062</td>
<td>53/-0.855</td>
</tr>
<tr>
<td>Bronchopulmonary dysplasia</td>
<td>84.5/-1.047</td>
<td>0.302</td>
<td>77.5/-1.078</td>
</tr>
<tr>
<td>GMH (Grade 1-2)</td>
<td>79.5/-0.446</td>
<td>0.664</td>
<td>82.4/-0.068</td>
</tr>
<tr>
<td>GMH (Grade 3-4)</td>
<td>75.5/-1.040</td>
<td>0.306</td>
<td>77/-0.747</td>
</tr>
<tr>
<td>White matter lesions</td>
<td>79/-2.182</td>
<td>0.029</td>
<td>113.5/-0.479</td>
</tr>
</tbody>
</table>

* Significance values of \( p < 0.01 \) are considered statistically significant. Pearson Correlation: \( r_{p} \), Spearman Rank Order correlation: \( r_s \). U and Z score correspond to Mann-Whitney U Test.
Figures

Figure 1. Average templates are shown with manual segmentations of the (1) caudate, (2) putamen, (3) globus pallidus, and (4) thalamus in each hemisphere. Left and right structures were summed for subsequent analyses. (A) An average of 96 VPT T2-weighted images scanned within 2 weeks of birth (left). Manual segmentations are shown in the axial and sagittal planes (top middle and right). The posterior internal capsule was segmented (anterior portion was undetectable) for the purpose of creating an anatomically accurate boundary between the thalamus and basal ganglia. (B) An average of 70 VPT T2-weighted images scanned at term-equivalent age (left). Segmentations are also shown in the axial and sagittal planes (bottom middle and right). The anterior and posterior internal capsule was segmented to provide anatomically accurate boundaries.
Figure 2. Individual subcortical segmentations at four different ages across preterm and term-equivalent age. Note: images are not to scale.
Figure 3. Cross-sectional scatter plot depicting linear growth of DGM volumes (mm$^3$) across preterm and term-equivalent ages (weeks). Included are 164 thalamus (open circles), 165 putamen (open squares), 163 caudate (open diamonds), and 165 globus pallidus (open triangles) volumetric measures of VPT infants.
Figure 4. Post-hoc multiple hierarchical regression models are represented in partial regression graphs. Residuals are plotted to illustrate the partial correlations of neuropsychological measures and structural growth (mm³/weeks) after controlling for sex and preterm total brain volume. (A, D) Association of caudate and thalamic growth with FSIQ. (B, E) Association of caudate and globus pallidus growth with VMI. (C, F) Association of caudate and thalamic growth with core language.
Figure 5. (A) Boxplot depicting differences in thalamic growth ($\text{mm}^3$/week) between groups with (present) and without (not present) white matter lesions. (B) For visual purposes, the scatterplot of cross-sectional thalamus volumes ($\text{mm}^3$) by scan age (weeks) show a gradient decline in thalamus volume with white matter lesion severity. Blue triangles represent no white matter lesions, green open squares represent mild white matter lesions, and red open circles represent moderate and severe white matter lesions. Those with moderate and severe white matter lesions have the smallest thalamus volumes by term-equivalent age.