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Examination of the Pattern of Growth of Cerebral Tissue Volumes From Hospital Discharge to Early Childhood in Very Preterm Infants

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IMPORTANCE Smaller cerebral volumes at hospital discharge in very preterm (VPT) infants are associated with poor neurobehavioral outcomes. Brain growth from the newborn period to middle childhood has not been explored because longitudinal data have been lacking.

OBJECTIVES To examine the pattern of growth of cerebral tissue volumes from hospital discharge to childhood in VPT infants and to determine perinatal risk factors for impaired brain growth and associations with neurobehavioral outcomes at 7 years.

DESIGN, SETTING, AND PARTICIPANTS Prospective cohort study of VPT infants (<30 weeks' gestation or <1250 g) born between April 11, 2001, and April 26, 2004, and followed up at 7 years' corrected age. The setting was The Royal Women's Hospital and The Royal Children's Hospital, Melbourne, Australia. Of 224 VPT infants and 46 full-term (FT) infants, usable magnetic resonance imaging data at either infancy or 7 years were collected for 214 VPT children (95.5%) and 46 FT children (100%), while 126 VPT children (56.3%) and 31 FT children (67.4%) had usable magnetic resonance imaging data at both time points. Follow-up was conducted from April 28, 2008, to August 9, 2011. Our final analysis was on March 3, 2016.

EXPOSURE Prematurity.

MAIN OUTCOMES AND MEASURES Absolute tissue growth, defined as change in absolute tissue volume, between infancy and 7 years was calculated for cortical gray matter volume (GMV), white matter volume (WMV), and subcortical GMV. IQ, language, and motor function were measured at 7 years.

RESULTS The study cohort comprised 260 participants. Their mean (SD) age was 7.5 (0.2) years, and 49.2% (128 of 260) were female. Early GMV deficits in VPT infants were magnified by 7 years, with less growth than FT controls. Growth differences were 31.4 (95% CI, 14.8-48.1) cm^3 for cortical GMV and 1.7 (95% CI, 0.5-2.8) cm^3 for subcortical GMV. Within the VPT group, greater growth was observed in boys for cortical GMV (31.9; 95% CI, 16.8-46.9 cm^3), WMV (31.7; 95% CI, 19.7-43.7 cm^3), and subcortical GMV (1.8; 95% CI, 0.8-2.8 cm^3). After controlling for sex and maternal education, all tissue volumes in infancy correlated with IQ ($r \geq 0.35$, $P < .05$) and language ($r \geq 0.29$, $P < .05$). Seven-year volumes correlated with IQ ($r = 0.28$, $P = .04$ for cortical GMV), language ($r = 0.29$, $P = .04$ for cortical GMV), and motor functioning ($r \geq 0.29$, $P < .05$ for all tissues). There was no evidence of any association between brain growth during childhood and outcomes in VPT infants.

CONCLUSIONS AND RELEVANCE Low brain volumes observed in VPT infants are exaggerated at 7 years. Low brain volume in infancy is associated with long-term functional outcomes, emphasizing the persisting influence of early brain development on subsequent growth and outcomes.

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Very preterm (VPT) birth, defined as less than 30 weeks' gestational age (GA), affects brain development because VPT infants are vulnerable to a range of medical complications that can cause brain injury during a crucial stage of development or alter brain development.[1] Magnetic resonance imaging (MRI) studies have assisted in the evaluation of the effect of preterm birth on structural brain development by measuring brain volumes of individuals born VPT.[2] Compared with full-term (FT) infants, VPT infants at term-equivalent age (TEA) exhibit reductions in gray matter volume (GMV) and white matter volume (WMV), with some regional variation.[3-8] Evidence suggests that perinatal complications associated with VPT birth, including white matter injury (WMI), intrauterine growth restriction, and bronchopulmonary dysplasia (BPD), can predict such volumetric reductions.[4,6,9] Moreover, these volumetric deficits at TEA have been associated with poor neurodevelopmental outcomes later in childhood and adolescence.[7,9]

Reduced cerebral volumes for VPT children, including decreased GMV and WMV compared with FT controls, have also been reported in childhood[10-13] and adolescence.[14-18] These structural abnormalities have likewise been associated with cognitive and behavioral deficits.[9-12,14-18] However, longitudinal analyses are sparse, limiting our understanding of how VPT birth affects brain growth from infancy to childhood.

In this study, we aimed to examine the growth of cerebral tissue volumes (cortical GMV, WMV, and subcortical GMV) in VPT infants from infancy to childhood relative to their FT peers. We hypothesized that VPT birth would have a negative effect on brain growth. We also examined perinatal factors associated with poor brain growth in VPT children, hypothesizing that sex, birth GA, WMI, infection, BPD, and being born small for GA would negatively affect brain growth. Finally, we assessed the association between brain tissue volumes (in both infancy and childhood) and neurodevelopmental outcomes at 7 years, as well as the association between brain tissue growth from TEA to 7 years and neurodevelopmental outcomes. We also hypothesized that smaller brain tissue volumes and poor brain tissue growth would result in poorer neurodevelopmental outcomes for VPT children.

Key Points

Question Do brain volumes of very preterm infants, which are small at birth compared with controls, show catch-up growth, and do they correlate with neurodevelopmental outcomes?

Findings In this cohort study, brain volumes (cortical gray matter, white matter, and subcortical gray matter) were measured at the time of discharge from the hospital and at 7 years. Low brain volumes observed in preterm infants were exaggerated at 7 years, and low brain volume in infancy was associated with worse long-term functional outcomes.

Meaning Brain growth in the preterm infant during the critical early period before hospital discharge is essential to normal neurodevelopmental outcomes.

Methods

Participants

The participants were part of a prospective, longitudinal, observational cohort study conducted at The Royal Women's Hospital in Melbourne, Australia, and were born between April 11, 2001, and April 26, 2004. Magnetic resonance imaging brain studies were conducted in 224 VPT infants (GA <30 weeks or birth weight <1250 g) and a concurrent control group of 46 infants born FT (37-42 weeks' GA) and of normal birth weight (≥2500 g). Eligible VPT infants were those who were born without congenital abnormalities that would impair neurological function and who survived the neonatal period. The families of FT infants were recruited before or shortly after birth from postnatal wards or via response to advertisements. Magnetic resonance imaging was performed without sedation. The target window for imaging was 38 to 42 weeks' postmenstrual age (PMA).

Usable TEA tissue volumes were generated for 206 VPT infants and 44 FT infants (**Figure 1**). At 7-year follow-up, 134 VPT children and 33 FT children had usable MRI data. Usable MRI data at either infancy or 7 years were collected for 214 VPT children (95.5%) and 46 FT children (100%).

Parental written informed consent was obtained for all participants. The study was approved by the human research ethics committees at The Royal Women's Hospital and The Royal Children's Hospital, Melbourne, Australia. Follow-up was conducted from April 28, 2008, to August 9, 2011. Our final analysis was on March 3, 2016.

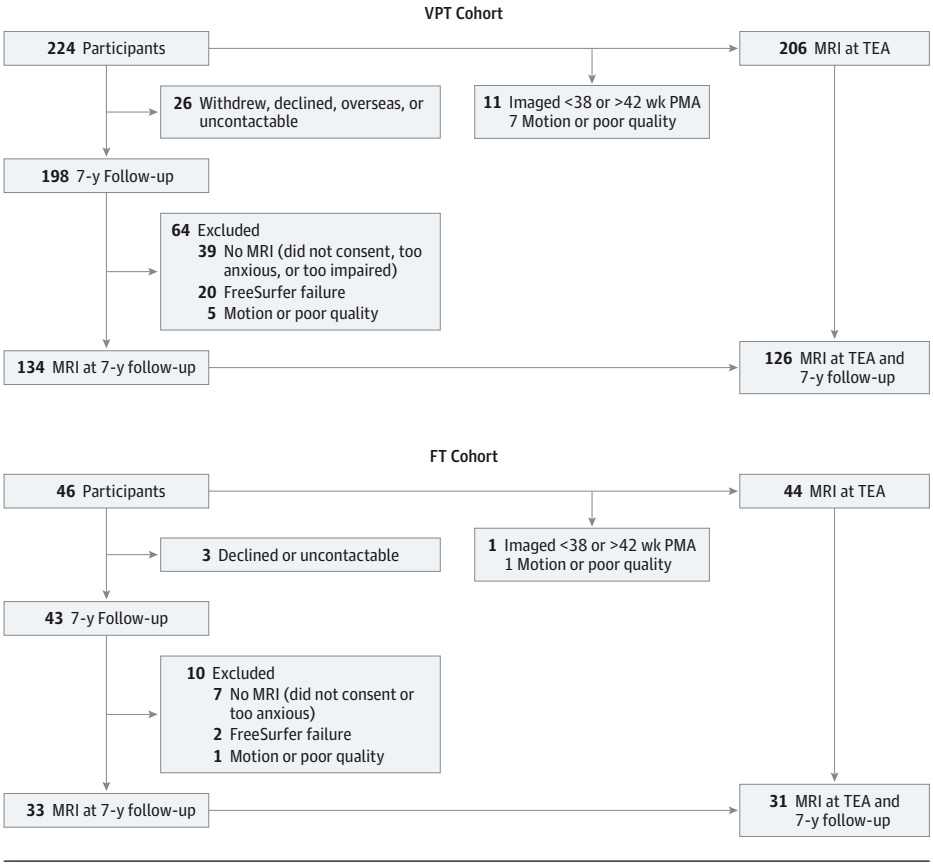
Perinatal Data

Perinatal data were obtained by medical record review and included sex, birth GA, birth weight, infection (defined as ≥1 episode of sepsis or necrotizing enterocolitis), BPD (defined as oxygen dependency at 36 weeks' corrected age), and being born small for GA (defined as birth weight >2 SD below the mean for GA). Total WMI was assessed using an established scoring system.[19]

MRI Data Acquisition and Processing

Participants underwent imaging at The Royal Children's Hospital. Neonatal MRI data were acquired at TEA (38-42 weeks' GA) using a 1.5-T imaging system (Signa LX Echospeed System; General Electric) as previously described.[6] Coronal T2-weighted, dual-echo, fast spin-echo images with interleaved acquisition were collected at a section thickness of 1.7 to 3 mm. The repetition time was 4000 milliseconds, echo times were 60 milliseconds (first echo) and 160 milliseconds (second echo), and the field of view was 22 × 16 cm^2, with a 256 × 192–pixel matrix interpolated to a 512 × 512–pixel matrix. Volumes were obtained from the T2-weighted structural image at TEA using an in-house method of automated Morphologically Adaptive Neonatal Tissue Segmentation (MANTiS), which classifies the brain into WM, cortical GM, cerebrospinal fluid, subcortical GM (including deep nuclear GM, hippocampus, and amygdala), brainstem, and cerebellum. MANTiS extends the unified segmentation approach to tissue classification implemented in statistical parametric mapping software to infant brain scans and

Figure 1. Flowchart of Participants in the Study



Magnetic resonance imaging (MRI) numbers reflect usable images suitable for this analysis. FT indicates full term; PMA, postmenstrual age; TEA, term-equivalent age; and VPT, very preterm. FreeSurfer is version 4.4.0 (http://surfer.nmr.mgh.harvard.edu).

performs well in the presence of brain abnormalities common in preterm infants.[20]

The 7-year MRI data were acquired using a 3-T imaging system (Magnetom Tim Trio; Siemens). Acquired data included sagittal, 3-dimensional, rapid gradient-echo T1-weighted images at a section thickness of 0.8 mm. The repetition time was 1900 milliseconds, the echo time was 2.27 milliseconds, and the field of view was 210 × 210 mm, with a 256 × 256–pixel matrix. Volumes were obtained from T1-weighted images using an automated segmentation procedure (FreeSurfer, version 4.4.0; http://surfer.nmr.mgh.harvard.edu[21]) with manual editing, including cortical GMV, WMV, and subcortical GMV. Subcortical GMV included the thalamus, caudate nucleus, putamen, pallidum, nucleus accumbens, hippocampus, and amygdala. Absolute tissue growth, defined as change in absolute tissue volume, was calculated for cortical GMV, WMV, and subcortical GMV for each participant by subtracting the volume at TEA (adjusted for PMA at the time of imaging) from the volume measured at 7 years. Percentage increase from TEA was also calculated.

7-Year Data

At 7 years' corrected age, children underwent an extensive battery of neuropsychological assessments. Selected measures for this study were used to assess general intellectual ability (IQ), language ability, and motor functioning. Performance was based on the child's age corrected for prematurity because such correction has been shown to be important for longitudinal studies.[22]

IQ was estimated with the 4-subtest version of the Wechsler Abbreviated Scale of Intelligence,[23] which yields the full-scale IQ, age standardized with a mean score of 100 points and SD of 15 points. Verbal IQ and performance IQ were also calculated and reported.

Language ability was assessed with the Core Language Scale Index from the Clinical Evaluation of Language Fundamentals Fourth Edition, Australian Standardised Edition,[24] age standardized with a mean (SD) of 100 (15). In addition, the following 4 language subdomains were assessed: auditory comprehension using the Receptive Language Index, language production using the Expressive Language Index, semantics using the Language Content Index, and grammar using the Language Structure Index. All results are reported using scaled scores, with a mean (SD) of 100 (15).

Motor functioning was assessed using the second edition of the Movement Assessment Battery for Children.[25] The battery provides a standardized assessment of both gross and fine-motor development, with a mean (SD) of 10 (3).

Analysis

All TEA volumes, including intracranial volume (ICV), were first adjusted for PMA at the time of imaging because regression analyses confirmed the expected strong associations between

Table 1. Sample Characteristics for the Perinatal and 7-Year Periods[a]

Variable	VPT Cohort (n = 214)	FT Cohort (n = 46)	*P* Value
Perinatal data			
Birth gestational age, mean (SD), wk	27.5 (1.9)	38.9 (1.2)	<.001
Birth weight, mean (SD), g	966 (223)	3304 (480)	<.001
PMA at imaging, mean (SD), wk	40.1 (1.1)	40.6 (1.0)	.03
Male sex, No. (%)	107 (50.0)	25 (54.3)	.59
Singleton, No. (%)	122 (57.0)	44 (95.7)	<.001
Being born small for gestational age, No. (%)	20 (9.3)	1 (2.2)	.11
Infection, No. (%)	76 (35.5)	1 (2.2)	<.001
Bronchopulmonary dysplasia, No. (%)	69 (32.2)	0	<.001
Moderate to severe white matter injury, No. (%)	42 (19.6)	0	.001
cGMV, least squares mean (SE), cm^3	150.4 (2.6)	159.9 (5.4)	.68
WMV, least squares mean (SE), cm^3	143.3 (2.3)	157.5 (4.7)	.04
scGMV, least squares mean (SE), cm^3	27.8 (0.3)	29.7 (0.5)	.008
7-y Data			
Height, mean (SD), cm	124 (6)	128 (6)	<.001
Weight, mean (SD), kg	24.6 (4.9)	26.6 (4.5)	.01
Age at imaging, mean (SD), y	7.5 (0.2)	7.6 (0.2)	.17
IQ, full scale, mean (SD)	97.2 (13.7)	109.2 (12.4)	<.001
Language, CELF-IV, mean (SD)	92.3 (17.5)	107.4 (14.2)	<.001
Motor functioning, MABC-2, mean (SD)	8.6 (3.4)	10.8 (2.7)	<.001
cGMV, least squares mean (SE) cm^3	568.4 (3.1)	617.5 (6.1)	<.001
WMV, least squares mean (SE), cm^3	403.4 (2.7)	446.4 (5.3)	<.001
scGMV, least squares mean (SE), cm^3	47.9 (0.3)	51.6 (0.6)	<.001

Abbreviations: CELF-IV, Clinical Evaluation of Language Fundamentals Fourth Edition, Australian Standardised Edition; cGMV, cortical gray matter volume; FT, full-term; MABC-2, second edition of the Movement Assessment Battery for Children; PMA, postmenstrual age; scGMV, subcortical gray matter volume; VPT, very preterm; WMV, white matter volume.

[a] Least squares means (SE) were obtained from a linear mixed-effects model.

PMA at imaging and tissue volumes ($P < .01$ for all tissues). Because no such associations existed at 7 years ($P > .30$ for all tissues), 7-year volumes were not adjusted for age at 7-year imaging. All analyses involving absolute tissue growth were also adjusted for corresponding tissue volumes at baseline.

Group differences in absolute tissue volumes between TEA and 7 years were assessed using 3-level linear mixed-effects models. Each model included a random intercept at level 3 to capture the correlations within participants at the 2 time points and a random intercept at level 2 for the nesting of twins. Although 126 VPT children (56.3%) and 31 FT children (67.4%) had usable MRI data at both time points, all participants with usable MRI data at either TEA or 7 years were included in this analysis, which yields unbiased estimates under an ignorable and missing-at-random assumption to account for missing data.[26] Separate models were used for each tissue. Models were tested for an interaction between group and time point to assess whether growth trajectories differed between groups. Effect sizes for group differences in volumes were calculated using Cohen *d*.

Group differences in growth measures were assessed for only the subset of participants who had longitudinal data at both time points. Differences in absolute tissue growth were evaluated using linear regression (controlling for corresponding tissue volumes at baseline), while differences in percentage increase were evaluated using *t* tests.

Associations between perinatal factors and absolute tissue growth were evaluated using multiple linear regression for only the VPT group in the longitudinal subset. Partial correlations (controlling for sex and maternal education) between absolute tissue growth, volumes at TEA and 7 years, and neurodevelopmental outcomes were also tested for the VPT group in the longitudinal subset. Partial correlation analyses controlling for sex were used because sex effects have been observed in neurobehavioral outcomes in VPT children.[10] In a secondary analysis, partial correlations between tissue volumes and outcomes were further adjusted for the corresponding ICV.

Mixed-model analyses were performed using statistical software (SAS, version 9.4; SAS Institute Inc), while linear regressions, *t* tests, and correlations were performed using other software programs (SPSS, version 22; IBM and R; R Foundation for Statistical Computing). For multiple comparisons, *P* values were adjusted using the false discovery rate criteria[27] (for the partial correlation analyses) and Bonferroni correction (for all other analyses).

Additional sensitivity analyses were performed using the Markov chain Monte Carlo multiple imputation method with single chain[28,29] to impute missing data (1.5% [4 of 260] of cases for TEA MRI, 35.8% [93 of 260] of cases for 7-year MRI, and 15.4% [40 of 260] of cases for 7-year outcomes). The imputation model consisted of all covariates, behavioral measures, and MRI outcomes (at both time points) used in the above complete-case analyses.

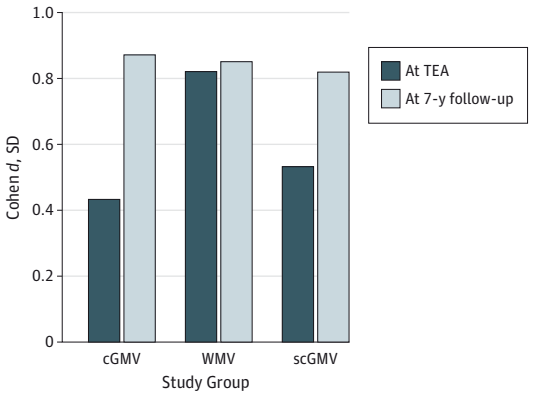
Results

Sample characteristics for each group are summarized in **Table 1** for subjects with MRI at either time point (VPT, n=214; FT,

n=46). Of all recruited VPT infants (n=224), there was a higher proportion of WMI in infants without MRI at 7 years (n = 90) than in infants with MRI at 7 years (n = 134). There were no other differences in clinical characteristics between those with MRI and those without.

Separate mixed-effects models revealed significant main effects of group and time point for all tissues ($P < .001$), with significant interactions between group and time point for all tissues ($P < .01$). The subcortical GMV model showed significant twin-level correlation ($P = .002$ by likelihood ratio test). To illustrate the effect of the group and time point interactions for the longitudinal subset, we calculated effect size (Cohen *d*) for each tissue at both time points (**Figure 2**). Because VPT volumes were smaller than FT volumes, Cohen *d* can be interpreted as the magnitude of VPT volume deviation from the FT volume mean. Effect sizes for group differences in cortical and subcortical GMV increased at 7 years by approximately 100% and 50%, respectively, relative to effect sizes at TEA. White matter volume showed little difference in effect size, but effect sizes were large at both time points (approximately 0.8 SD). While both groups showed similar percentage increase in volumes, absolute cortical and subcortical GMV growth differed significantly between groups (**Table 2**).

Figure 2. Effect Size Calculations for Differences in Volume at Both Time Points for the Longitudinal Cohort



cGMV indicates cortical gray matter volume; scGMV, subcortical gray matter volume; TEA, term-equivalent age; and WMV, white matter volume.

Within the VPT group, greater growth was observed in boys for cortical GMV (31.9; 95% CI, 16.8-46.9 cm^3), WMV (31.7; 95% CI, 19.7-43.7 cm^3), and subcortical GMV (1.8; 95% CI, 0.8-2.8 cm^3). Boys in the VPT group had significantly larger cortical GMV, WMV, and subcortical GMV at 7 years (eFigure in the Supplement). There was no evidence of associations with other perinatal variables.

Within the VPT group, all volumes at TEA were positively associated with several neurodevelopmental outcomes, including IQ, language, and motor functioning, after controlling for sex and maternal education (**Table 3**). All tissue volumes in infancy correlated with IQ ($r \geq 0.35$, $P < .05$) and language ($r \geq 0.29$, $P < .05$). Seven-year volumes correlated with IQ ($r = 0.28$, $P = .04$ for cortical GMV), language ($r = 0.29$, $P = .04$ for cortical GMV), and motor functioning ($r \geq 0.29$, $P < .05$ for all tissues). There was no significant association between absolute tissue growth and any neurodevelopmental outcomes at 7 years. All significant associations were weakened after further adjustment for ICV.

Results after multiple imputation were similar to the complete-case analyses with the exception of an increase in significant correlations between volumes and behavioral outcomes (eTable 1 and eTable 2 in the Supplement). These findings remained significant for TEA WMV (language and motor functioning) and subcortical GMV (motor functioning) after adjustment for ICV.

Discussion

Brain growth in VPT infants has been previously assessed longitudinally during the neonatal period,[5,30-32] with cortical and subcortical GMV growth during this window being associated with later neurodevelopmental outcomes.[31,32] Brain growth between 8 and 12 years has also been shown to increase for WMV and decrease for GMV in both VPT and FT children,[33] as expected with dendritic pruning,[34,35] but the magnitude of change for both WMV and GMV was substantially larger for FT children. The main objective of this study was to determine the pattern of brain growth in VPT survivors between infancy and middle childhood. To our knowledge, this investigation represents the first report of cortical GMV, WMV, and subcortical GMV growth between TEA and middle childhood using longitudinal MRI data from a VPT cohort.

Table 2. Absolute Tissue Growth and Percentage Increase Comparison by Study Group[a]

Variable	cGMV	WMV	scGMV
Observed absolute tissue growth, cm^3			
VPT cohort, mean (SD) (n = 126)	417.9 (44.1)	260.2 (38.0)	20.0 (2.7)
FT cohort, mean (SD) (n = 31)	454.4 (37.5)	286.4 (39.7)	21.7 (2.6)
Difference (95% CI)	31.4 (14.8 to 48.1)	15.8 (0.8 to 30.9)	1.7 (0.5 to 2.8)
Corrected *P* value	.002	.24	.03
% Increase			
VPT cohort, mean (SD) (n = 126)	278 (43)	181 (26)	72 (12)
FT cohort, mean (SD) (n = 31)	287 (40)	184 (31)	74 (12)
Difference (95% CI)	9 (−8 to 26)	3 (−7 to 14)	2 (−3 to 7)
Corrected *P* value	>.99	>.99	>.99

Abbreviations: cGMV, cortical gray matter volume; FT, full-term; scGMV, subcortical gray matter volume; VPT, very preterm; WMV, white matter volume.

[a] Difference is based on the model adjusted for volume at baseline.

Table 3. Partial Correlation Coefficients Between Absolute Tissue Volumes, Volumetric Growth (Adjusted for Tissue Volume in Infancy), and 7-Year Outcomes for the Very Preterm Group With All Data at Both Ages, Controlling for Sex and Maternal Education

Neurodevelopmental Outcome	At TEA				At 7 y				Growth		
	cGMV	WMV	scGMV	ICV	cGMV	WMV	scGMV	ICV	cGMV	WMV	scGMV
IQ											
Verbal	0.24	0.24	0.25	0.27	0.10	0.10	0.14	0.11	−0.03	−0.06	−0.03
Performance	0.31[a]	0.34[a]	0.36[a]	0.26	0.28[a]	0.18	0.23	0.31[a]	0.15	−0.05	−0.33
Full scale	0.35[a]	0.36[a]	0.38[a]	0.33[a]	0.24	0.17	0.23	0.26	0.08	−0.07	−0.05
Language											
Core Language Scale Index	0.19	0.29[a]	0.21	0.20	0.24	0.20	0.22	0.24	0.17	0.02	0.11
Receptive Language Index	0.29[a]	0.32[a]	0.29[a]	0.28	0.24	0.28	0.24	0.29[a]	0.11	0.10	0.04
Expressive Language Index	0.16	0.28	0.19	0.16	0.24	0.18	0.22	0.23	0.19	0.00	0.14
Language Content Index	0.29[a]	0.30[a]	0.23	0.27	0.20	0.19	0.14	0.22	0.07	0.00	−0.04
Language Structure Index	0.20	0.31[a]	0.24	0.20	0.29[a]	0.26	0.29	0.29[a]	0.22	0.08	0.18
Motor functioning											
MABC-2	0.27	0.32[a]	0.33[a]	0.22	0.29[a]	0.30[a]	0.33[a]	0.30[a]	0.18	0.14	0.15

Abbreviations: cGMV, cortical gray matter volume; ICV, intracranial volume; MABC-2, second edition of the Movement Assessment Battery for Children; scGMV, subcortical gray matter volume; TEA, term-equivalent age; WMV, white matter volume.

[a] Statistically significant (corrected $P < .05$).

Cortical GMV increased by approximately 280%, WMV by approximately 180%, and subcortical GMV by approximately 70% between TEA and 7 years for both VPT and FT children. Our results demonstrate that, while VPT infants show percentage increase values similar to FT infants, their absolute cortical and subcortical GMV growth is less than that of their FT peers at 7 years. Therefore, VPT children's GMV continues to fall further behind that of their FT-born peers, with the standardized volumetric difference (ie, difference measured in SD) being greater in middle childhood than in infancy. In contrast, VPT children's WMV, which shows a large initial deficit, does not fall further behind but does not show any catch-up gains either.

We found positive associations between cortical GMV (at both TEA and 7 years) and cognitive outcomes in VPT children, which remained after controlling for maternal education. Modest but significant associations were observed between cortical GMV (at TEA and 7 years) and language subdomains. Previous studies[10,12] in VPT children have reported positive associations between cortical GMV and cognitive outcomes, such as IQ, which were also observed here, but we know of no other study reporting such associations between cortical GMV and language. Language impairment is common in VPT children but often is not reported due to the lack of a comprehensive assessment of language in follow-up studies on children born VPT.[36]

Others have reported positive WMV associations with IQ[11,14,16,17] and motor functioning[3,17] for VPT children. We found that WMV at TEA was positively associated with IQ and motor functioning, as well as several language subdomains. This result corroborates previous findings of associations between white matter abnormality at TEA and language outcomes.[36] Subcortical GMV at TEA has been positively associated with neurodevelopmental outcomes at 12 months[4] and at 4 years.[32] We likewise found positive associations between subcortical GMV at TEA and IQ, language, and motor functioning. It is reasonable to expect the latter association given the known role of the basal ganglia in motor function.

We observed that volumes at TEA generally showed stronger association with neurobehavioral outcomes than volumes at 7 years, suggesting that the volume at TEA may be an early biomarker for later neurodevelopmental outcomes in VPT children. With our data, we are unable to conclude whether this observation is a causal relationship because it is possible that neurodevelopment is related to factors besides brain tissue volume. Nonetheless, associations remained after controlling for maternal education. While the strength of these associations is modest, they are impressive given that childhood neurodevelopment is the result of complex interactions involving neural (ie, size, shape, and connectivity), genetic, epigenetic, nutritional, social, and environmental factors. This finding confirms that brain growth in the newborn period for the preterm infant is critical to later functioning and requires greater focus on optimization during the neonatal intensive care unit stay. Associations between tissue volumes (at both TEA and 7 years) and outcomes were reduced when adjusting for ICV, with the exception of TEA WMV (language and motor functioning) and subcortical GMV (motor functioning) in the sensitivity analysis. This result is not surprising because ICV is strongly correlated with tissue volumes.

While it has been previously reported that cortical and subcortical GMV growth for VPT infants during the neonatal period is associated with cognitive abilities at 4 to 6 years,[31,32] we found little evidence of an association between tissue growth from TEA to 7 years and childhood outcomes. It is possible that tissue growth is related to other outcomes, such as attention, executive functioning, or academics.

For the VPT group, male brains grew larger by 7 years than female brains. This result corroborates previous findings showing that male brains are larger than female brains for 8-year-old children born VPT.[10,33] However, boys did not perform better on cognitive assessments, and brain growth was

not indicative of cognitive or motor performance at 7 years, even after controlling for sex. Our results suggest that the influence on brain development for well-accepted risk factors, such as birth GA, WMI, infection, and BPD, is largely restricted to the neonatal period.

Despite the unique nature of this large cohort study, several limitations should be considered. The methods of tissue segmentation at TEA and 7 years were different. Although both techniques (MANTiS and FreeSurfer) have optimized segmentation methods, misclassifications of tissues can occur, which we attempted to minimize by manual inspection. In addition, MANTiS uses tissue classifications for cortical GMV and WMV comparable to FreeSurfer.[20] We attempted to address the issue of missing data in this study using multiple approaches. While multiple imputation in part highlighted the robustness of our initial complete-case findings, the added significant correlations observed after imputation may have been due to an inflation of bias that potentially existed in the complete cases or the imputation model given the large amount of missing MRI data at 7 years.[37] Finally, limitations exist in that there may be neonatal and postnatal variables that influenced brain growth but that were not collected or examined in this cohort.

Conclusions

This investigation is the first longitudinal study to report that cortical GMV, WMV, and subcortical GMV growth does not compensate for VPT infants' volumetric deficits in infancy by 7 years. Results of our study suggest that lower brain tissue volume in the neonatal period is associated with long-term functional outcomes, including language. Furthermore, brain growth during childhood for VPT infants is influenced by sex. For the clinician caring for VPT infants, our findings emphasize that the brain development that occurs when VPT infants are in the neonatal intensive care unit is critical and will have a persisting influence on brain growth and outcomes.

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