# Brain growth in the NICU: critical periods of tissue-specific expansion

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**OBJECTIVE:** To examine, using serial magnetic resonance imaging (MRI), total and tissue-specific brain growth in very-preterm (VPT) infants during the period that coincides with the early and late stages of the third trimester.

**METHODS:** Structural MRI scans were collected from two prospective cohorts of VPT infants (≤30 weeks of gestation). A total of 51 MRI scans from 18 VPT subjects were available for volumetric analysis. Brain tissue was classified into cerebrospinal fluid, cortical gray matter, myelinated and unmyelinated white matter, deep nuclear gray matter, and cerebellum. Nine infants had sufficient serial scans to allow comparison of tissue growth during the periods corresponding to the early and late stages of the third trimester.

**RESULTS:** Tissue-specific differences in *ex utero* brain growth trajectories were observed in the period corresponding to the third trimester. Most notably, there was a marked increase in cortical gray matter expansion from 34 to 40 weeks of postmenstrual age, emphasizing this critical period of brain development.

**CONCLUSION:** Utilizing serial MRI to document early brain development in VPT infants, this study documents regional differences in brain growth trajectories *ex utero* during the period corresponding to the first and second half of the third trimester, providing novel insight into the maturational vulnerability of the rapidly expanding cortical gray matter in the NICU.

The fetal brain undergoes rapid growth from the second trimester onward, with a 20-fold increase in brain volume occurring between 20 weeks of gestation and term (38–40 weeks of gestation) (1). Importantly, rates of brain growth are not consistent across this period, with cross-sectional fetal magnetic resonance imaging (MRI) studies demonstrating that the greatest period of expansion occurs during the third trimester (1). For very-preterm (VPT; born at <30 weeks of gestation) infants, this critical period of brain development will occur in the *ex utero* environment, with growing concern that environmental factors in the neonatal intensive care unit

(NICU) may deleteriously have an impact on infant brain development, along with associated implications for neurodevelopmental outcomes (2).

A growing body of literature demonstrates that preterm birth alters the typical trajectory of brain growth and development (3). MRI studies in preterm infants have shown reduced brain volumes associated with intraventricular hemorrhage, bronchopulmonary dysplasia, and postnatal dexamethasone exposure (4–6). Even among preterm infants without clear clinical risk factors, reductions in tissue volumes and brain growth have been demonstrated (7–9), some of which may be related to the rapid brain development occurring *ex utero* during the period corresponding to the third trimester (10,11). Despite providing valuable insight into brain growth trajectories in preterm infants, the majority of these studies have been cross-sectional MRI investigations at term-equivalent postmenstrual age (PMA).

Although term-equivalent MRI adds to our understanding about the impact of brain injury and altered growth on neurodevelopmental outcomes (12), longitudinal studies assessing brain development across gestational ages are crucial for identifying the onset and progression of structural changes (7). Importantly, longitudinal MRI data can provide insight into critical time points of brain maturation and tissue-specific vulnerability, helping to contextualize trajectories of brain development in relation to clinical and environmental exposures (13). Studies of infants born at varying gestational ages have shown marked linear increases in global and regional brain volumes from 25 to 40 weeks of gestation (14,15). However, few studies have examined these changes using serial observations of the same infants over time, with existing investigations largely limited to two assessments (16–19). Although one group reported growth trajectories using additional serial observations (20,21), these were limited to measures of cortical surface area and total brain growth.

The goal of this exploratory study was to utilize serial structural MRI to examine total and tissue-specific brain growth in a cohort of VPT infants during early development.

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Specifically, we aimed to (i) explore brain growth trajectories in VPT infants from birth to term equivalent, and (ii) describe tissue-specific differences in brain growth during the time that coincides with the early and late stages of the third trimester.

## METHODS

### Subjects

Structural MRI scans were collected from two prospective longitudinal cohort studies of VPT infants born at ≤30 weeks of gestational age and admitted to the NICU at St. Louis Children's Hospital between 2007 and 2010. The details of these cohorts have been previously published (11,22). Infants whose data included term-equivalent and serial scans were selected for inclusion in this study. Briefly, of the total 137 eligible infants, 99 had term-equivalent scans, of which 81 had two or more scans. Of these, 10 infants were not suitable for analysis because of severe injury (defined as grade 3 or 4 intraventricular hemorrhage or cystic periventricular leukomalacia) (23), one due to severe ventricular dilatation without distinct supratentorial injury, eight due to motion artifact, and a further three due to failed automated segmentation. Of the remaining subjects, 18 VPT infants were available for volumetric analysis at the time of evaluation. Written, informed consent was obtained from parents or guardians before enrollment, and institutional review boards approved all procedures.

### Image Acquisition

All preterm infants were scanned without sedation, and serial MRI scans for each infant were collected approximately every 4–6 weeks based upon clinical status (<30, 30–32, 33–36, and >36 weeks of PMA). Before scanning, infants were fed, wrapped securely in warm blankets, outfitted with ear protection, and secured in a papoose bag (Contour Fabrications; CFI Medical Solutions, Fenton, MI). Images were collected on a Siemens Magnetom Trio 3-T scanner using a magnetization-prepared rapid gradient echo $T_1$-weighted sequence (repetition time/echo time 1,500/3 ms, voxel size $1 \times 0.7 \times 1$ mm$^3$) and turbo spin echo $T_2$-weighted sequence (repetition time/echo time 8,600/160 ms; voxel size 1 mm$^3$; echo train length 17). Images were interpreted by certified pediatric neuroradiologists (Joshua

Shimony and Robert McKinstry) and a neonatologist (T.E.I.).

### Image Analysis

A previously established segmentation protocol (19,24,25) comprising sequential image-processing algorithms classified brain tissue into cerebrospinal fluid (CSF), cortical gray matter (GM), and unmyelinated white matter (WM). Briefly, these algorithms are designed to reduce image noise and allow classification of tissue according to joint signal intensities in aligned $T_1$- and $T_2$-weighted images and anatomic localization using representative voxels selected as training points (4). Using this technique, anatomic structures with similar image-acquisition characteristics can be correctly classified. Segmentations were subsequently manually edited to classify deep nuclear GM (DNGM; i.e., basal ganglia/thalamus), myelinated WM, and cerebellum. The sum of all tissues (unmyelinated and myelinated WM, cortical GM and DNGM, and cerebellum) was computed, generating the total tissue volume. The sum of all tissues plus CSF was further computed, generating the total intracranial volume (ICV).

### Statistical Analysis

Statistical analysis was performed using STATA 13.0 (StataCorp, TX). Absolute and relative brain tissue growth rates occurring between the earliest MRI scan available and the scan at 33–34 weeks of gestation (Δ1), and between the scan at 33–34 weeks of gestation and the term-equivalent MRI scan (Δ2) were compared using paired *t*-tests. These time points were chosen as they represent approximately the first and second half of the third trimester. *Absolute tissue growth rates* (cm$^3$/week) for the periods corresponding to Δ1 and Δ2 were defined as brain tissue growth divided by the number of weeks elapsed between scans. *Relative tissue growth rates* (%/week) were similarly calculated, but using tissue volumes that were first normalized by the total brain tissue volume (excluding CSF), to allow identification of specific tissue types undergoing rapid or slow growth. Absolute tissue growth for Δ1 and Δ2 was further computed as a percentage of ICV growth over the corresponding period, to determine the percentage of the intracranial cavity occupied by each tissue, thereby accounting for variations in head size.

## RESULTS

A total of 51 MRI scans from a total of 18 VPT subjects (gestation range 23–29 weeks, mean $26.6 \pm 1.4$ weeks) were available for analysis. Participant characteristics for these subjects are summarized in **Table 1**. Individual patient-level growth trajectories for total tissue, unmyelinated and myelinated WM, cortical GM, cerebellum, and DNGM were constructed from analysis of these 51 MRI scans (**Figure 1**).

There was a range in the frequency of scans for the individual cases, with three infants being scanned four times, nine scanned three times, and six scanned twice. Sufficient serial data at the appropriate PMA were available for nine infants before and after the 33–34-week cutoff (Δ1 and Δ2) to allow the *a priori*-defined calculation of tissue growth. Changes in absolute and relative tissue growth were observed between the periods corresponding to the first (i.e., up to 33–34 weeks) and second (i.e., from 33 to 34 weeks to term equivalent) half of the third trimester (**Table 2**). Specifically, increases were observed in absolute growth over the latter period for total tissue volume ((mean difference (95% confidence interval, CI) 4.98 cm$^3$/week (2.51, 7.45), $P = 0.002$), cortical GM (0.07 cm$^3$/week (−0.04, 0.17), $P = 0.0002$), cerebellum (0.35 cm$^3$/week (0.13, 0.57), $P = 0.006$), and total ICV (3.71 cm$^3$/week (0.55, 6.86),

**Table 1.** Participant characteristics

| | VPT ($n = 18$) |
|---|---|
| Gestation at birth, mean (SD), weeks | 26.6 (1.4) |
| Birth weight, mean (SD), g | 966 (214) |
| SGA, *n* (%) | 2 (11) |
| PMA at term-equivalent MRI[a], mean (SD), weeks | 37.9 (1.5) |
| Weight at term-equivalent scan, mean (SD), g | 2,562 (288) |
| Female, *n* (%) | 7 (39) |
| Antenatal steroids, *n* (%) | 14 (78) |
| Oxygen at 36 weeks, *n* (%) | 6 (39) |
| Postnatal dexamethasone, *n* (%) | 1 (6) |
| Treated PDA[b], *n* (%) | 5 (28) |
| Necrotizing enterocolitis, *n* (%) | 2 (11) |
| Culture-positive sepsis, *n* (%) | 4 (22) |
| Brain injury[c], *n* (%) | 2 (11) |

MRI, magnetic resonance imaging; PDA, patent ductus arteriosus; PMA, postmenstrual age; SGA, small for gestational age; VPT, very preterm.
[a]$n = 15$ infants with term-equivalent tissue volumes.
[b]Medical or surgical.
[c]One infant with Grade II intraventricular hemorrhage, one infant with Grade 3 noncystic periventricular leukomalacia (23).
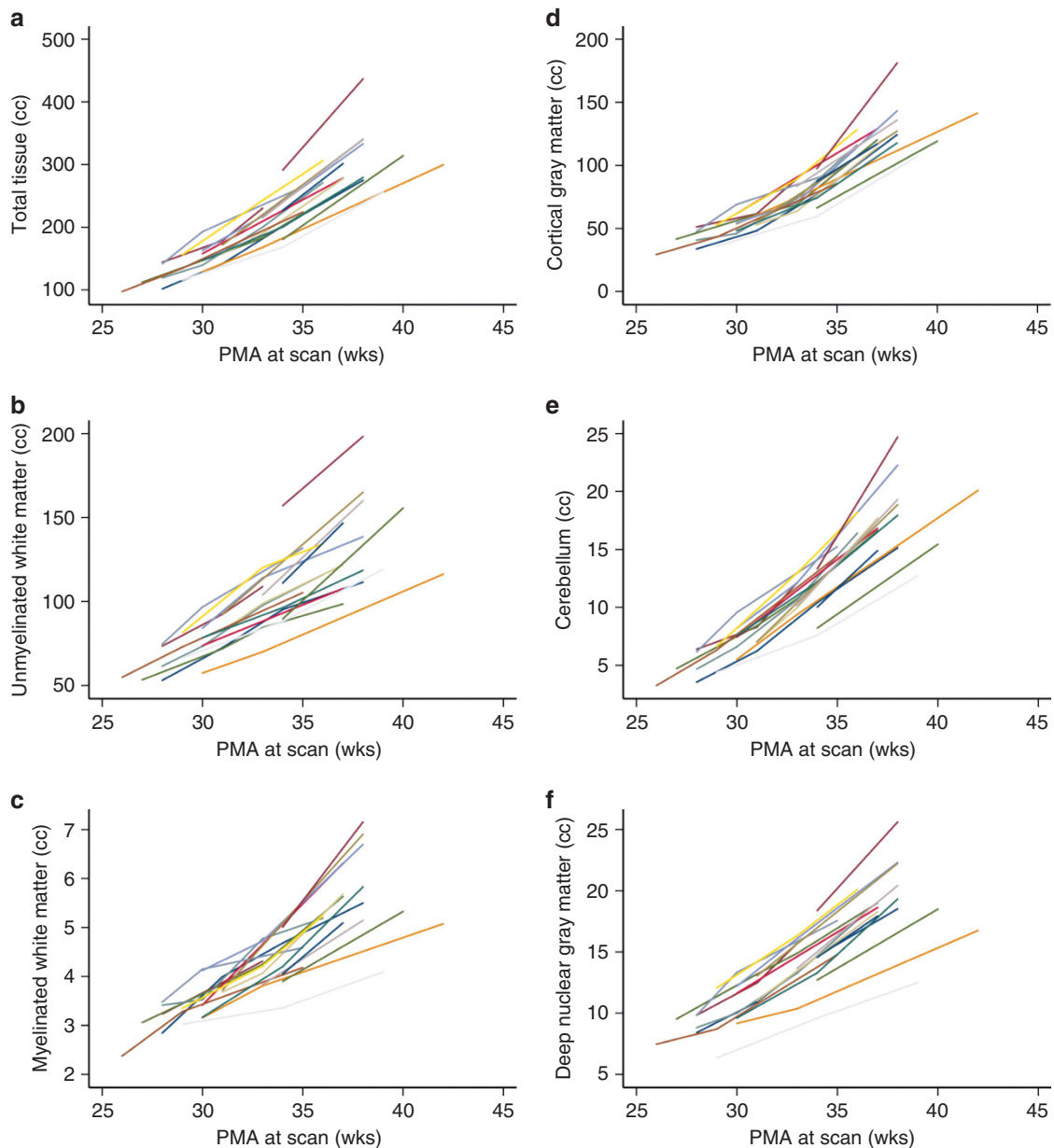
**Figure 1.** Longitudinal growth trajectories for total tissue, unmyelinated white matter, myelinated white matter, cortical gray matter, cerebellum, and deep nuclear gray matter in preterm infants from 26 weeks of gestation to term-equivalent age. cc, cubic centimeters; PMA, postmenstrual age; wk, week.

$P = 0.027$). WM, CSF, and DNGM maintained consistent absolute growth rates over both periods.

The increased growth rate observed for cortical GM remained significant even after accounting for variations in head size, with the percentage of ICV occupied by cortical GM increasing from 29.4% in the period before 33–34 weeks to 47.2% in the period after 33–34 weeks (95% CI (10.4, 25.3), $P = 0.001$; **Table 3**). Unmyelinated WM occupied 20.6% of ICV after 33–34 weeks vs. an initial 30.6% (95% CI (−19.00, −1.05), $P = 0.033$). The percentage of ICV occupied by cerebellum increased slightly from 5.5 to 6.1%, although this did not reach significance (95% CI (−0.12, 1.21), $P = 0.093$). The percentage occupied by myelinated WM and DNGM

remained largely unchanged over this period (mean difference (95% CI), myelinated WM 0.11% (−0.27, 0.49), $P = 0.516$, and DNGM −1.61% (−5.68, 2.46), $P = 0.389$)). The percentage of ICV occupied by CSF decreased by 16% over this period, but did not reach statistical significance (95% CI (−37.87, 5.13), $P = 0.117$).

Normalizing individual tissue volumes by total tissue volume (**Table 2**) revealed differential patterns of relative tissue growth between the periods corresponding to the first and second half of the third trimester. Notably, an accelerated increase in relative cortical GM growth rate was observed after 33–34 weeks (1.6%/week) compared with an earlier increase of 0.5%/week (95% CI (0.35, 1.85), $P = 0.010$). In

**Table 2.** Brain tissue growth in VPT infants before and after 33–34 weeks of gestation

| Tissue type | Delta | Mean (SD; n = 9) | Mean difference (95% CI) | P value |
|---|---|---|---|---|
| *Absolute tissue growth (cm³/week)* | | | | |
| Total tissue | 1 | 15.59 (3.63) | 4.98 (2.51, 7.45) | 0.002 |
| | 2 | 20.56 (2.25) | | |
| CSF | 1 | 8.60 (8.17) | − 3.05 (−9.08, 2.97) | 0.276 |
| | 2 | 5.55 (2.87) | | |
| Unmyelinated WM | 1 | 6.69 (2.26) | − 1.60 (−3.55, 0.36) | 0.096 |
| | 2 | 5.10 (0.91) | | |
| Myelinated WM | 1 | 0.21 (0.07) | 0.07 (−0.04, 0.17) | 0.174 |
| | 2 | 0.28 (0.12) | | |
| Cortical GM | 1 | 6.27 (1.43) | 5.61 (3.56, 7.66) | 0.0002 |
| | 2 | 11.88 (2.26) | | |
| DNGM | 1 | 1.38 (1.51) | − 0.28 (−1.40, 0.85) | 0.584 |
| | 2 | 1.10 (0.31) | | |
| Cerebellum | 1 | 1.20 (0.27) | 0.35 (0.13, 0.57) | 0.006 |
| | 2 | 1.55 (0.37) | | |
| ICV | 1 | 21.75 (4.00) | 3.71 (0.55, 6.86) | 0.027 |
| | 2 | 25.46 (5.40) | | |
| *Relative tissue growth (%/week)* | | | | |
| Unmyelinated WM | 1 | − 0.62 (0.48) | − 1.02 (−1.77, − 0.27) | 0.014 |
| | 2 | − 1.64 (0.59) | | |
| Myelinated WM | 1 | − 0.08 (0.03) | 0.03 (−0.01, 0.07) | 0.105 |
| | 2 | − 0.04 (0.05) | | |
| Cortical GM | 1 | 0.52 (0.49) | 1.10 (0.35, 1.85) | 0.010 |
| | 2 | 1.62 (0.58) | | |
| DNGM | 1 | 0.18 (0.87) | − 0.28 (−0.96, 0.40) | 0.377 |
| | 2 | − 0.10 (0.08) | | |
| Cerebellum | 1 | 0.28 (0.09) | − 0.11 (−0.19, − 0.03) | 0.013 |
| | 2 | 0.16 (0.08) | | |

Delta 1: ≤ 33–34 weeks; delta 2: ≥ 33–34 weeks.
CI, confidence interval; CSF, cerebrospinal fluid; DNGM, deep nuclear gray matter; GM, gray matter; ICV, intracranial volume; VPT, very preterm; WM, white matter.

contrast, the unmyelinated WM growth rate demonstrated a greater relative decrease after 33–34 weeks, from − 0.6% to − 1.6%/week (95% CI (−1.77, − 0.27), $P = 0.014$). Cerebellar growth showed a reduction in relative increase after 33–34 weeks, from 0.3% to 0.2%/week (95% CI (−0.19, − 0.03), $P = 0.013$)).

**Table 3.** Brain tissue growth in VPT infants before and after 33–34 weeks of gestation as a percentage of ICV

| Tissue type | Delta | Mean (SD; n = 9) | Mean difference (95% CI) | P value |
|---|---|---|---|---|
| *Tissue growth (% ICV)* | | | | |
| Total tissue | 1 | 70.84 (13.62) | 8.50 (−2.14, 19.13) | 0.103 |
| | 2 | 79.33 (7.43) | | |
| CSF | 1 | 37.04 (28.56) | − 16.37 (−37.87, 5.13) | 0.117 |
| | 2 | 20.67 (7.43) | | |
| Unmyelinated WM | 1 | 30.62 (8.03) | − 10.02 (−19.00, − 1.05) | 0.033 |
| | 2 | 20.60 (4.92) | | |
| Myelinated WM | 1 | 0.99 (0.32) | 0.11 (−0.27, 0.49) | 0.516 |
| | 2 | 1.10 (0.40) | | |
| Cortical GM | 1 | 29.42 (7.31) | 17.82 (10.39, 25.25) | 0.001 |
| | 2 | 47.24 (7.48) | | |
| DNGM | 1 | 5.92 (5.23) | − 1.61 (−5.68, 2.46) | 0.389 |
| | 2 | 4.31 (0.77) | | |
| Cerebellum | 1 | 5.53 (1.11) | 0.55 (−0.12, 1.21) | 0.093 |
| | 2 | 6.08 (0.70) | | |

Delta 1: ≤ 33–34 weeks; Delta 2: ≥ 33–34 weeks. CI, confidence interval; CSF, cerebrospinal fluid; DNGM, deep nuclear gray matter; GM, gray matter; ICV, intracranial volume; VPT, very preterm; WM, white matter.

## DISCUSSION

We report for the first time tissue-specific differences in *ex utero* brain growth trajectories during the period corresponding to the first and second half of the third trimester. Specifically, we observed a marked increase in cortical GM, occupying nearly half of the intracranial cavity after 33–34 weeks of gestation, with a greater than threefold increase in relative tissue growth rate over this period. Notably, this was mirrored by an almost threefold decrease in relative unmyelinated WM growth rate, and a 10% decrease in the proportion of ICV occupied by unmyelinated WM beyond 33–34 weeks. Cerebellar growth rates also differed over this period, with a slightly higher relative growth rate observed before 33–34 weeks of gestation. Together, these findings demonstrate that cortical GM undergoes rapid growth during the latter half of the third trimester, whereas unmyelinated WM and cerebellum undergo faster relative growth during the first half of the third trimester.

The contrasting relative cortical GM and WM trajectories observed here are consistent with cross-sectional observations in preterm infants documenting brain tissue growth between 27 and 45 weeks (26,27). Importantly, our results provide novel evidence for differential *ex utero* brain growth development taking place in the NICU environment, specifically, the rapid expansion of cortical GM from 33 to 34 weeks to term equivalent. We postulate that the latter half of the third trimester represents a potentially critical period of tissue-specific developmental vulnerability. This hypothesis is corroborated by recent reports of rapid fetal cortical GM growth in the third trimester compared with WM (28), as well as evidence of marked increases in fetal cortical GM growth

along with decreases in fetal WM and cerebellar growth during the third trimester (28–39 weeks) compared with the second trimester (18–27 weeks) (1). In their study, Andescavage *et al.* demonstrated fetal WM as the primary initial contributor to cerebral development peaking between 29 and 30 weeks of gestation, at which point relative cortical GM volume begins to rapidly increase (1). For infants born VPT, this period of accelerated growth taking place *ex utero* is susceptible to disruption by exposures and stressors in the NICU (2,29), and our previous work suggests that regions of rapid cortical expansion are likely to be more sensitive to postnatal experience and insult (30). Importantly, disruptions to normal cortical maturational trajectories during the late third trimester have been postulated to underpin the neurodevelopmental impairments seen in preterm infants (20,21,31). Related to this, we have reported in the larger cohort the potential adverse effects of varying amounts of environmental sound and language exposure in the NICU, namely reduction in normal hemispheric asymmetry and lower language scores at the age of 2 years in infants from private rooms (11). Although the current study included VPT infants from both private room and open-ward environments, we were unable to assess the associated potential differences in brain developmental trajectories because of our small sample size.

From a biological perspective, our findings are consistent with the dynamically changing processes characteristic of cortical maturation during this period, namely increasing synaptic complexity and dendritic arborization (31). Notably, cortical microstructural development has been shown to be impaired in a dose-dependent manner by preterm *ex utero* exposure (31), with animal studies suggesting that these alterations may reflect dendritic retraction secondary to perinatal stress (32). More recent animal studies have proposed that neurodevelopmental disturbances in VPT survivors are attributed to cortical growth abnormalities specifically related to reduced dendritic spines and impaired expansion of the dendritic arbor, as well as overall reduced synaptic density (33,34). Relatedly, the greater variability in brain tissue volumes observed at closer to term gestation (**Figure 1**) may reflect altered growth trajectories secondary to clinical exposures, such as opiates, nutrition, and environmental influences as outlined above.

The relative increase in cerebellar growth observed before 33–34 weeks of gestation is consistent with evidence of the cerebellum's dynamic growth phase during the second and third trimesters (35), characterized by external granule cell proliferation and migration, and formation of the internal granular layer (36). Our observation of a reduction in relative increase in cerebellar growth beyond 33–34 weeks was somewhat unexpected, given previously documented linear increases in cross-sectional investigations of cerebellar volume from 28 weeks of PMA to term (37). Of note, we have previously reported in the larger cohort reductions in transverse cerebellar diameter at term-equivalent age in association with cumulative fentanyl dose (22). Although a large proportion of subjects in the current study received

fentanyl (89%), exposure was very brief, with six out of the nine infants receiving less than 2 days of fentanyl. Nonetheless, given the cerebellum's developmental vulnerability to opioid exposure (38,39), and more recent reports demonstrating associations between increased opioid exposure and impaired cerebellar growth (40), further investigations into these relationships along with longitudinal neurodevelopmental follow-up are needed to establish the clinical significance of these findings.

Despite major advancements in the application of noninvasive MRI to study early brain development in the preterm infant, existing investigations have been largely cross-sectional in nature, or have been employed in limited serial assessments. The primary strength of this study is the use of individual serial, rather than cross-sectional cohort data, allowing us to serially track the progression of brain development early in the neonatal course and identify critical periods of tissue-specific growth. However, due to the difficulties in obtaining multiple serial MRI scans on VPT infants during the period before term equivalent, this approach has resulted in a smaller sample size than some previously reported cross-sectional or longitudinal studies with fewer imaging time points. A further limitation relates to the assumption of linear tissue growth around an apparent inflection point at 33–34 weeks, and larger cohorts with multiple assessments throughout this critical developmental period are needed to enable exponential modeling of brain growth. In addition, because of the sample size of the current cohort, the population was not further stratified based on birth weight or other clinical factors that may be associated with brain growth such as nutrition or duration of ventilation. Although this may be considered as a limitation, it ensures that the data are a true representation of the general population of VPT infants seen in routine clinical practice. Nonetheless, future work in larger cohorts investigating the relationships between differential patterns of growth in brain tissue during the critical NICU period and perinatal risk factors, such as sex, infection, and WM injury, is needed to provide added insight into potential early predictors of deviations in brain development. Furthermore, exploration of brain tissue trajectories in relation to later neurodevelopmental outcomes may identify functional impairments that can be predicted by early deviations from normal brain growth and maturation.

## CONCLUSIONS
Assessment of brain tissue growth trajectories in the NICU has the potential to identify early deviations in brain development before discharge, allowing focused timely interventions such as therapeutic, nutritional, or neurodevelopmental support. This is the first report utilizing serial MRI data to document regional differences in brain tissue growth trajectories *ex utero* during the period corresponding to the first and second half of the third trimester. Importantly, this study provides novel insight into the maturational vulnerability of the rapidly expanding cortical GM in the NICU, and highlights the importance of continued research into interventions aimed at reducing or ameliorating exposure

to potentially harmful stressors during this developmentally critical period.

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