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Neurodevelopmental Outcomes following Intrauterine Growth Restriction and Very Preterm Birth

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Objectives To evaluate whether intrauterine growth restriction (IUGR) adds further neurodevelopmental risk to that posed by very preterm birth alone in terms of alterations in brain growth and poorer toddlerhood outcomes.

Study design Participants were 314 infants of very preterm birth enrolled in the Evaluation of Preterm Imaging Study (e-Prime) who were subsequently followed up in toddlerhood. IUGR was identified postnatally from discharge records (n = 49) and defined according to prenatal evaluation of growth restriction confirmed by birth weight <10th percentile for gestational age and/or alterations in fetal Doppler. Appropriate for gestational age (AGA; n = 265) was defined as birth weight >10th percentile for gestational age at delivery. Infants underwent magnetic resonance imaging at term-equivalent age (median = 42 weeks); T2-weighted images were obtained for voxelwise gray matter volumes. Follow-up assessments were conducted at corrected median age of 22 months using the Bayley Scales of Infant and Toddler Development III and the Modified-Checklist for Autism in Toddlers.

Results Infants of very preterm birth with IUGR displayed a relative volumetric decrease in gray matter in limbic regions and a relative increase in frontoinsular, temporal-parietal, and frontal areas compared with peers of very preterm birth who were AGA. At follow-up, toddlers born very preterm with IUGR had significantly lower cognitive (effect size = 0.42) and motor (effect size = 0.41) scores and were more likely to have a positive Modified-Checklist for Autism in Toddlers screening for autism (OR = 2.12) compared with peers of very preterm birth who were AGA.

Conclusions IUGR might confer a neurodevelopmental risk that is greater than that posed by very preterm alone, in terms of both alterations in brain growth and poorer toddlerhood outcomes. *(J Pediatr 2021; ■:1-10)*.

In 2015, the Global Burden of Disease Study estimated that preterm birth (<37 weeks of gestation) was the most common cause of death and disability in children younger than the age of 5 years.[1] Live preterm births are increasing, with rates currently estimated by the World Health Organization as ranging between 5% and 18% of all births. With the increase of survival to 23-24 weeks of gestation, individuals born preterm often display neurologic, behavioral, and cognitive comorbidities throughout their life. The umbrella term "preterm phenotype" has been proposed to encompass cognitive impairments, attention deficits, socioemotional difficulties, and internalizing problems associated with preterm birth.[2] However, the developmental trajectories of children born preterm are heterogeneous, hence the need to understand both the antenatal and postnatal risks for adverse outcomes before their phenotypical presentation, to devise and implement targeted interventions.[3] In particular, antenatal growth adversities have been associated with long-lasting effects on brain organization, neurodevelopment, and health outcomes,[4] although it is not clear whether these effects add further risk to that posed by very preterm birth alone.

An adverse intrauterine course, most obviously shown by intrauterine growth restriction (IUGR), is associated with perinatal mortality[5] and with 26% and

AGA	Appropriate for gestational age
BW	Birth weight
CP	Cerebral palsy
IMD	Index of multiple deprivation
IUGR	Intrauterine growth restriction
MANOVA	Multivariate analysis of variance
M-CHAT	Modified Checklist for Autism in Toddlers
MRI	Magnetic resonance imaging
PCA	Principal component analysis
SGA	Small for gestational age

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53% of preterm and term-born stillbirths, respectively.[6] IUGR frequently is accompanied by placental insufficiency and a response to reduced placental blood flow, hypoxemia, and undernutrition.[7] Such adverse environmental conditions may result in fundamental neural changes, with consequences for the developing brain.[8] Infants who survive IUGR display a range of long-lasting neurodevelopmental problems, encompassing cognitive, socioemotional, and behavioral domains.[9]

Fetuses with IUGR display altered patterns of brain volumetric growth, including smaller temporal lobes and cerebellum.[10] We previously identified a distinct pattern of neuroanatomical variation in infants born very preterm with IUGR at term-equivalent age that was characterized by global brain growth failure, with alterations in the cerebellum and brainstem, which differed from those imaging markers associated with gestational age at delivery.[11] Other studies in newborns of preterm birth with IUGR show significant reduction in intracranial volume and in cerebral cortical gray matter,[12] smaller thalamic, basal ganglia and hippocampal volumes,[13] and altered cortical gyrification and cortical thickness compared with peers who were appropriate for gestational age (AGA) and born preterm.[14] Structural brain changes have further been documented at 12 months, with findings including reduced gray matter volumes in temporal, parietal, frontal, and insular regions.[15] However, existing studies often lack precise characterization of antenatal adversity, simply relying on birth weight (BW) to define IUGR. Many also have small sample sizes, do not use a whole-brain approach, or fail to define brain–behavior associations.

This study aimed to investigate whether IUGR adds further risk of alterations in neurodevelopmental outcomes beyond the effect of very preterm birth. First, we compare brain volumes differences between IUGR and AGA infants of very preterm birth at term-equivalent age; second, we compare cognitive, motor, language neurodevelopmental scores, and autism screening scores outcomes between IUGR and AGA toddlers born very preterm at corrected median age of 22 months. Third, we explore the association between brain volumes at term-equivalent age and toddlers' outcomes.

Methods

This study represents secondary analysis of Evaluation of Preterm Imaging Study data (e-Prime; European Clinical Trials Database: EudraCT 2009-011602-42; NCT01049594).[16] e-Prime is a randomized control trial that investigated whether routine magnetic resonance imaging (MRI) compared with ultrasonography would improve the care and well-being of babies born preterm and their families. e-Prime participants were recruited at birth in 2010-2013 from hospitals within the North and Southwest London Perinatal Network. Infants were included in e-Prime if born before 33 weeks of gestation and their mother was older than 16 years of age and not a hospital inpatient. Exclusion criteria included the presence of major congenital malformation, metallic implants, parents unable to speak English, or if the infant was subject to child protection proceedings.

Infants underwent MRI at term-equivalent age (median = 42.40 weeks of postmenstrual age, IQR = 1.84) on a Philips 3 Tesla (Philips Medical Systems) magnetic resonance system sited within the neonatal intensive care unit using an 8-channel phased array head coil. Pulse oximetry, temperature, and electrocardiography data were monitored during MRI. Silicone-based putty (President Putty; Coltene Whaledent) and neonatal earmuffs (MiniMuffs; Natus Medical Inc) were used for ear protection. In total, 445 (87%) infants were sedated with oral chloral hydrate (25-50 mg/kg) before undergoing MRI. T2-weighted images were inspected for motion artifacts by an expert reviewer, and subjects with evidence of motion were excluded.

For this study, IUGR was identified by reviewing medical discharge records, which are completed by attending clinicians on clinical grounds. Given the difficulties in retrospectively assessing IUGR, and to ensure the presence of antenatal adverse growth, the definition of IUGR was limited to reported antenatal abnormalities on fetal scans and/or Doppler ultrasound velocimetry (N = 36) (ie, absent and/or reversed end-diastolic flow), without taking infants' weight into account, hence including those infants with BW > 10th percentile; or reported clinical evaluation of IUGR, risk factors for IUGR (ie, maternal preeclampsia, placental insufficiency, reported signs of cerebral redistribution, asymmetrical fetal growth), combined with BW < 10th percentile for gestational age (N = 13). AGA was defined as BW > 10th percentile for gestational age.

In addition to the aforementioned e-Prime exclusion criteria listed, for the current study, the following also were used: BW < 10th percentile in the absence of any aforementioned reported evidence of antenatal adversity (n = 32), as these infants were not classifiable as either IUGR nor as AGA; major lesion on term MRI (n = 153),[17] defined as cystic periventricular leukomalacia, >10 punctate white matter lesions, grade 3 or 4 germinal matrix hemorrhage, this choice being informed by the fact that major brain lesions are likely to have other causes other than IUGR[18]; and cerebral palsy (CP) at follow-up assessment, defined by a Gross Motor Function Classification System score >2[19] (IUGR: n = 0; AGA n = 8), as motor impairments may bias the assessment of other outcomes of interest (ie, cognition, language, and autism screening).[20]

The study was approved by the Hammersmith and Queen Charlotte's Research Ethics Committee (09/H0707/98) and was carried out in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki). Written informed consent was obtained for all participants.

MRI

For the current analysis, T2-weighted fast-spin echo MRI was used with the following measures: repetition time

14 730 milliseconds; echo time: 160 milliseconds; flip angle: 90°; field of view: 220 mm; and matrix: 256 × 256 (voxel size, 0.86 × 0.86 × 2 mm) with 1-mm overlap. T1-weighted MRI and single-shot echo-planar diffusion weighted images also were acquired (see **Appendix**).

Perinatal Clinical and Sociodemographic Data

Perinatal clinical and sociodemographic data were collected with permission from the Standardized Electronic Neonatal Database. They included gestational age at birth, sex, neonatal clinical variables, mother's age, and Index of Multiple Deprivation (IMD; https://tools.npeu.ox.ac.uk/imd/), which provides a composite measure of social risk in England, calculated from the mother's home address at the time of infant's birth. IMD encompasses data on income, employment, education, living environment, health, and crime.

Toddlerhood Outcomes

At 22 months of age (median = 22.16, IQR = 0.98) participants completed the Bayley Scales of Infant and Toddler Development, 3rd Edition,[21] to evaluate cognitive, language, and motor development (mean = 100; SD = 15). Each child was assessed individually by a qualified assessor. Autistic traits were assessed with the Modified-Checklist for Autism in Toddlers (M-CHAT),[22] which consists of 23 "yes/no" parent-rated questions about children's behavior. A positive screening is given when 2 of 6 critical items (namely, items: 2, 7, 9, 13-15) or 3 of any 23 items are rated as positive ("yes").

Statistical Analyses

MRI data were analyzed using a gestation-appropriate atlas, created by combining cortical gray matter parcellations from the University of North Carolina infant brain atlas[23] (82 cortical areas) and subcortical gray matter parcellations from the Gousias–Makropulos atlas (10 subcortical areas).[24,25] The final atlas consisted of 92 regions. For each study participant, the mean Jacobian determinant value for each cortical and subcortical gray matter parcellation was calculated, which characterizes the relative volume change between each image and the template and was used to represent relative gray matter volume. Larger Jacobian values refer to a relative larger regional expansion to fit the template space, hence smaller relative gray matter volume; smaller Jacobian values refer to a relative larger regional contraction to fit the template space, hence larger relative gray matter volume (see the **Appendix** for further details).

Principal component analysis (PCA) was performed for dimensionality reduction on the 92 mean Jacobian values expressing regional brain volumes.[26] Data rotation was performed using the Varimax method. Visual inspection of the scree plot was used to determine the number of factors to retain and an absolute loading factor >0.40 was chosen to group specific brain regions into a "volumetric component."

To compare brain "volumetric components" between IUGR and AGA newborns of very preterm birth, multivariate analysis of variance (MANOVA) was performed on estimated factors scores from PCA. Multivariable linear and logistic regressions were performed to investigate differences between IUGR and AGA infants born very preterm in cognitive, motor, and language outcomes and M-CHAT positive screening. In a secondary whole-sample analysis, brain "volumetric components" scores extracted from PCA were used in linear and logistic regression to explore their association with cognitive, motor outcomes, and autistic traits. Covariates in all analyses were sex, gestational age at delivery (weeks), IMD score, and total intracranial volume. Perinatal clinical variables were not included in analysis due to collinearity with gestational age at delivery: days ventilated ($r = -0.53$, $P < .001$); days on parenteral nutrition ($r = -0.58$, $P < .001$); and days on continuous positive airway pressure ($r = -0.77$, $P < .001$).

Additional sensitivity analyses on PCA "volumetric component" scores and cognitive, motor, language, and autistic traits at 22 months are presented in the **Appendix**, to ensure robustness of sampling selection. As participants with CP who were AGA were excluded from the main study, **Tables I** and **II** (both available at www.jpeds.com) report results of comparison between toddlers who were AGA born very preterm with and without CP. Second, given the retrospective design of the study, **Tables III** and **IV** (both available at www.jpeds.com) present group comparisons between IUGR and AGA infants of very preterm birth, after excluding a small subgroup of participants with IUGR born very preterm who reported antenatal signs of growth restriction on discharge records but were delivered with a BW > 10th percentile for gestational age (n = 10, mean BW percentile = 17.99, SD = 4.89). Third, **Table V**, and **Table VI** (both available at www.jpeds.com) present group comparisons between IUGR very preterm and a small group of small for gestational age (SGA) participants born very preterm (n = 32) who were excluded from main analysis as they present BW < 10th percentile in the absence of any aforementioned reported evidence of antenatal, and therefore were not classifiable as either IUGR nor as AGA.

All analyses were performed using R.[27] *P* values were corrected for multiple comparisons using a false discovery rate method[28] controlling alpha error to 5%.

Results

The current study sample comprised 314 participants born very preterm: 49 IUGR very preterm and 265 AGA very preterm. **Figure 1** (available at www.jpeds.com) shows participants' inclusion flow diagram. There was no difference between excluded and included participants in terms of IUGR: $\chi^2 = 0.0109$, $P = .917$. Baseline characteristics of the study groups are reported in **Table VII**.

Brain Development at Term

PCA on the 92 Jacobian determinants yielded a 7-factors solution, accounting for 54.3% of cumulative variance. Each component was determined by a set of regions and was

Table VII. Baseline characteristics of the study groups

Characteristics	IUGR very preterm (n = 49)	AGA very preterm (n = 265)	*P* values
Antenatal characteristics			
Maternal age, y	31.13 (6.11)	32.64 (5.77)	.12
Maternal hypertension	4 (8%)	15 (6.5%)	.73
IMD by quintiles			.90
1 (least deprived)	8 (16%)	53 (20%)	
2	6 (12%)	43 (16%)	
3	14 (29%)	70 (26%)	
4	13 (27%)	69 (26%)	
5 (most deprived)	7 (14%)	30 (11%)	
Perinatal outcomes			
Multiple pregnancy	10 (21%)	88 (35%)	.10
BW	1025 [325]	1380 [610]	<.001
BW percentile	2.77 [8.57]	46.69 [35.63]	<.001
Head circumference, cm	28.19 (3.00)	29.29 (3.06)	.027
Age at delivery, wk	30 [3]	30 [3]	.18
Sex (male)	27 (56%)	133 (50%)	.54
Ventilation, d	0 [2]	0 [2]	.86
Parenteral nutrition, d	7 [11]	5 [10]	.033
CPAP, d	5 [21]	6 [29]	.41
Surfactant (yes)	24 (49%)	130 (49%)	.91
Surgery for necrotizing enterocolitis (yes)	0 (0%)	4 (1.5%)	.87
Chorioamnionitis (yes)	0 (0%)	7 (3%)	.53
Age at MRI scan, wk	42.78 [1.79]	42.4 [1.8]	.23
Total intracranial volume, mm^3	446 959.0 (51 015.74)	475 416.4 (52 177.88)	<.001

CPAP, continuous positive airway pressure.
Data are given as No. (%), median [IQR], or mean (SD).

labeled according to the spatial characteristics of its strongest loadings: "thalamocortical," "limbic," "frontoinsular," "temporal-parietal," "frontal," "occipital," and "parietal" component. The 7 PCA volumetric components are graphically presented in **Figure 2**. Eigenvalues and standardized factor loadings of the 7-factors solution are reported in **Table VIII** (available at www.jpeds.com).

Table IX shows PCA "volumetric component" scores of newborns of very preterm birth with IUGR compared with peers who were AGA born very preterm; a graphical representation is provided in **Figure 3** (available at www.jpeds.com). MANOVA results showed a significant main effect of group (IUGR very preterm vs AGA very preterm) on PCA-derived brain "volumetric component" scores after

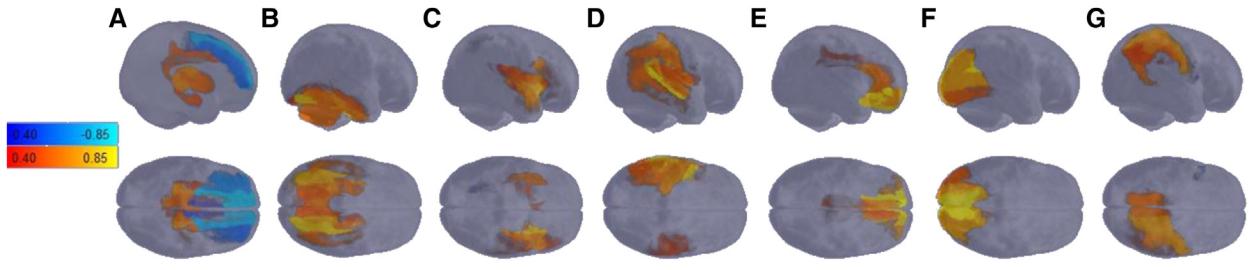

Figure 2. Three-dimensional display of "volumetric components" identified by PCA. The following components are shown (*left to right*): **A,** Thalamocortical: superior and middle frontal gyrus, supplementary motor area, median and posterior cingulate, Heschl gyrus, thalamus, and pallidum. **B,** Limbic: hippocampus and parahippocampal gyrus, amygdala, fusiform gyrus, inferior temporal gyrus, and cerebellum. **C,** Frontoinsular: pars opercularis, pars triangularis, inferior orbitofrontal gyrus, Rolandic operculum, insula, superior parietal gyrus, caudate nucleus, putamen and superior temporal pole, and olfactory cortex. **D,** Temporal-parietal: inferior orbitofrontal gyrus, Rolandic operculum, postcentral gyrus, inferior parietal gyrus, supramarginal gyrus, angular gyrus, and superior and middle temporal gyrus. **E,** Frontal: superior and middle orbitofrontal gyrus, superior frontal gyrus, gyrus rectus, and anterior cingulate. **F,** Occipital: lingual gyrus, calcarine fissure, cuneus, superior and medial and inferior occipital gyrus. **G,** Parietal: pars triangularis, postcentral gyrus, superior parietal gyrus, angular gyrus, precuneus, and paracentral lobule. The *top row* shows right sagittal plane; the *bottom row* is the axial plane. *Colored regions* represent Jacobian determinants with absolute standardized factor loadings >0.40. *Cold colors* reflect a negative relation of the regional Jacobian determinant to the "volumetric component"; *warm colors* reflect positive relation of the regional Jacobian determinant to the "volumetric component."

Table IX. PCA-derived "volumetric component" scores in infants with IUGR or who were AGA born very preterm

PCA-derived "volumetric components"	IUGR very preterm (n = 49)	AGA very preterm (n = 265)	Effect size [95% CI]	Unadjusted *P*	Adjusted* *P*
Thalamocortical	0.037 (0.927)	−0.007 (1.014)	*d* = −0.05 [−0.35 to 0.26]	.77	.30
Limbic	0.593 (1.092)	−0.109 (0.944)	*d* = −0.73 [−1.04 to −0.42]	<.001	<.001
Frontoinsular	−0.236 (0.923)	0.043 (1.009)	*d* = 0.28 [−0.03 to −0.059]	.13	.045
Temporal-parietal	−0.343 (1.191)	0.063 (0.949)	*d* = 0.41 [0.10-0.72]	.030	.011
Frontal	−0.299 (0.926)	0.055 (1.004)	*d* = 0.36 [0.05-0.66]	.052	.045
Occipital	−0.106 (1.027)	0.019 (0.996)	*d* = 0.13 [−0.18 to 0.43]	.59	.85
Parietal	0.064 (0.965)	−0.012 (1.007)	*d* = −0.08 [−0.38 to 0.23]	.73	.36

Data are given as mean (SD). All *P* values are corrected for FDR.[28]
*Adjusted for sex, gestational age at delivery, IMD score, and total intracranial volume.

controlling for sex, gestational age at delivery, IMD score, and total intracranial volume (F [7, 301] = 6.64, $P < .001$). IUGR infants of very preterm birth compared with infants who were AGA born very preterm had smaller relative gray matter volume in a limbic component ($b = 0.69$, SE = 0.15, t [307] = 4.64, $P < .001$), and larger relative gray matter volume in frontoinsular ($b = -0.34$, SE = 0.15, t [307] = −2.24, $P = .045$), temporal-parietal ($b = -0.46$, SE = 0.15, t [307] = −2.99, $P = .011$) and frontal components ($b = -0.36$, SE = 0.16, t [308] = −2.28, $P = .045$). **Table X** (available at www.jpeds.com) shows MANOVA results comparing all the 92 regional brain volumes used to perform PCA between infants with IUGR born very preterm and infants who were AGA born very preterm (F [92, 217] = 2.08, $P < .001$).

Developmental Outcomes at 22 Months

In total, 284 (90%) children born very preterm completed the follow-up assessment. There were no differences between participating and nonparticipating children in rates of IUGR ($\chi^2 = 0.009$, $P = .923$) and demographic characteristics (**Table XI**; available at www.jpeds.com). Toddlers with IUGR born very preterm compared with toddlers who were AGA born very preterm had lower Bayley Scales of Infant and Toddler Development, 3rd Edition (composite cognitive, motor, and language) (**Figure 4**; available at www.jpeds.com). They were also more likely to score positively on the M-CHAT (**Table XII**). After we adjusted for sex, gestational age at birth, IMD score, and total intracranial volume, results remained significant for cognition and motor outcomes and M-CHAT positive screening (**Table XII**).

Brain Development at Term and Developmental Outcomes at 22 Months

The results of linear and logistic regressions to assess, in the whole sample, the association between gray matter "volumetric components" scores and cognitive, motor, and M-CHAT positive screening, accounting for sex, IMD score, gestational age at delivery, and total intracranial volume revealed lower cognitive scores were associated with larger volumes of the frontal ($b = 1.54$, SE = 0.72, t [278] = 2.14, $P = .033$) and occipital components ($b = 1.50$, SE = 0.73, t [278] = 2.06, $P = .041$); lower motor scores were associated with larger volumes of the parietal component ($b = 1.47$, SE = 0.69, t [278] = 2.11, $P = .036$); and no significant difference in size of "volumetric components" was found between children with a positive and those with a negative M-CHAT screening.

Discussion

This longitudinal study, in a large sample of participants born very preterm, showed that IUGR (compared with AGA) was associated with extensive relative volumetric brain differences at term-equivalent age and with poorer cognitive and motor outcomes and a greater positive autism screening risk at 22 months. The absence of severe focal brain lesions and of significant differences in postnatal courses (ie, days of ventilation and parenteral nutrition, days of continuous

Table XII. Cognitive, motor, language, and behavioral scores for toddlers with IUGR vs toddlers who were AGA at 22 months

Developmental outcomes	IUGR very preterm (n = 45)	AGA very preterm (n = 239)	Effect size [95% CI]	Unadjusted *P*	Adjusted* *P*
Bayley-III Cognitive scale	88.78 (10.88)	94.25 (13.31)	*d* = 0.42 [0.10-0.74]	.019	.018
Bayley-III Motor scale	91.71 (11.69)	96.46 (11.62)	*d* = 0.41 [0.09-0.73]	.019	.018
Bayley-III Language scale	87.00 (15.90)	92.62 (17.10)	*d* = 0.33 [0.01-0.65]	.042	.093
Positive M-CHAT	20 (44%)	64 (27%)	OR = 2.12 [1.11-4.05]	.024	.018

Data are given as No. (%) or mean (SD). All *P* values are corrected for FDR.[28]
*Adjusted for sex, gestational age at delivery, IMD score, and total intracranial volume.

positive airway pressure) between newborns with IUGR born very preterm and newborns who were AGA born very preterm suggests that the observed developmental alterations may be triggered by prenatal events.[29] However, as MRI was performed at term-equivalent age, we cannot empirically exclude the possibility that other (unmeasured) events occurring between birth and time of assessment also contributed to establishing the observed brain differences. These findings add to the growing body of research that highlights the links between antenatal events and child neurodevelopment, suggesting biological stress, such as IUGR, has a long-lasting mark on cognitive, and motor growth and early autistic traits, beyond the well-known effect of prematurity.[30]

At term-equivalent age, differences in the relative volume of gray matter were observed between infants with IUGR born very preterm and infants who were AGA born very preterm in 4 of 7 "volumetric components." "Relative" refers to smaller total intracranial volume in the IUGR very preterm compared with the AGA very preterm group and the fact that imaging analyses accounted for individual variation in head size. Infants of very preterm birth with IUGR had greater Jacobian PCA-derived limbic component values in comparison with infants of very preterm birth who were AGA, which reflect smaller relative gray matter volume compared with the template. Group difference had large effect size. Furthermore, infants of very preterm birth with IUGR had lower Jacobian PCA-derived scores in comparison with infants of very preterm birth who were AGA, which reflect larger relative gray matter volume compared with the template, in frontoinsular, temporal-parietal, and frontal components, which included subcortical regions such as the caudate nucleus and the putamen (ie, part of the basal ganglia). Group differences had small-to-medium effect sizes. These results could be interpreted in the context of the brain's hierarchical maturational patterns, which follows a primary-to-higher order sequence[31] and are controlled by genetic mechanisms.[32] Higher-order processing areas, such as the frontal and temporal cortices, exhibit increased maturational priority over the sensory–motor regions and become key areas for the regulation of neural activity and neurocognitive development.[33] Specific attention could be directed at the brain's developmental trajectories in typically developing babies at the time our study participants received MRI, at around term-equivalent age. We recently showed that between 37 and 44 weeks of postmenstrual age, sensory and limbic areas and posterior parietal regions display more pronounced maturational changes compared with areas related to higher order functions (eg, prefrontal cortex).[34] Widespread differential brain maturational patterns have been documented in neonates born preterm,[35-39] as well as in babies exposed to adverse intrauterine environments.[40] Our results suggest that an adverse intrauterine environment may lead to developmental changes that exceed those typically seen in children born very preterm. Previous studies also have reported altered cortical development (ie, increased cortical sulcation in proportion to surface) and reduced cortical thickness[14] and reduced cortical[12] and hippocampal volume[41] in neonates born very preterm with IUGR compared with those without IUGR. Potential causal pathways leading to IUGR-related brain alterations include hypoglycemia, neuroinflammation (ie, microglia activation), and maternal nutrient restriction.[42,43] Animal models have helped to elucidate the microstructural, functional, and biochemical mechanisms that may contribute to such brain alterations, and include but are not limited to, neuronal cell loss, altered developmental progression of oligodendrocytes and myelination, decreased dendritic outgrowth, reduced cellular connectivity, and reduced structural integrity of the neurovascular unit.[43]

The most pronounced relative volumetric differences between infants of very preterm birth with IUGR and infants who were AGA born very preterm birth observed here indicate that the early maturing limbic areas may be particularly vulnerable to poor intrauterine growth, as previously observed in terms of both volumetric reductions[41] and altered regional brain network topology.[44] This could be due to the susceptibility of the limbic system, and especially amygdala and hippocampus, to hypoxic–ischemic injury and maternal preconception health,[45] as well as fetal exposure to glucocorticoid levels that are heightened under conditions of maternal stress and/or placental dysfunction.[42,46] However, the more modest differences observed between infants born very preterm with IUGR and infants who are AGA born very preterm birth in frontal, frontoinsular, and temporal-parietal components, indicating relative larger gray matter volume in the IUGR very preterm compared the AGA very preterm group, suggest that the spectrum of brain alterations associated with IUGR is heterogenous, possibly reflecting both antenatal in utero compromise due to placental dysfunction and other complications associated with very preterm birth. We tentatively interpret the relative larger gray matter volumes in the IUGR very preterm group in the context of adaptive brain-sparing processes, which refer to the growth restricted fetus' cardiac output redistribution to favor vital organs,[47,48] to support development of critical brain regions.[49] Fetal brain sparing includes a hierarchical prioritization of oxygen supply to the frontal lobes, as a response to chronic hypoxia/placental insufficiency, followed by a decrease in supply if the fetal condition worsens to favor (in order to protect) the basal ganglia.[50] Hence, the vulnerability or preservation of selective brain areas depends on the stage of fetal hemodynamic compromise.[51] Furthermore, research has shown that a compromised fetal development might increase developing infants' sensitivity to postnatal environmental influences.[52] We speculate that increases in volume of temporal-parietal cortices could reflect the effects of ex utero experience that may be enhanced in IUGR compared with infants who are AGA born very preterm, as these areas are involved in hearing (Heschl gyrus or primary auditory cortex) and sensory processing (primary and secondary somatosensory cortex). Previous research has shown larger white matter volume in the occipital cortex[15] and increased functional connectivity in the visual network[51] in 12-month-old infants with

IUGR, as well as accelerated neurophysiologic maturation (ie, shorter visual evoked potential latencies in 6-month-old infants with IUGR).[53]

Toddlers born very preterm with IUGR at 22 months had significantly poorer cognitive, language, and motor outcomes compared with their peers who were AGA born very preterm. When taking possible confounders into account, language scores were not significantly lower in the IUGR very preterm group, possibly highlighting the importance of postnatal environmental factors (ie, socioeconomic status) for linguistic functions.[54] The effect of IUGR on neurodevelopment has been documented across the gestational age spectrum and at different stages of development,[55] and studies demonstrated that several functions, including adjustment to school, language, and memory, continue to be compromised in IUGR samples later in development.[56,57]

We found that toddlers with IUGR born very preterm were more likely to score positively on an autism-screening questionnaire (ie, M-CHAT) compared with peers who were AGA born very preterm (43% vs 27%). Rates of positive M-CHAT screening have ranged between 21% and 41% in children born preterm, with greater prevalence in those with a younger gestational age.[58,59] Positive M-CHAT screening also has been reported in 25% of children of very low BW (<1500 g) aged 2 years[60] and in 31% of 12-month-old toddlers with IUGR born very preterm (<34 weeks of gestational age).[51] Mechanisms potentially explaining the association between IUGR and autism outcomes might involve shared genes that predispose to IUGR and autism risk.[61] IUGR may further represent a marker of prenatal factors that may be associated with autism risk such as metabolic alterations, ie, reduced insulin-like growth factor,[62] fetal hypoxia,[63] and perinatal inflammation.[64]

When exploring the association between relative brain volumes at term-equivalent age and cognitive, motor outcomes, and autistic traits at 22 months in the whole sample, we found that relative larger frontal (ie, later maturing) and occipital (ie, showing pronounced maturational changes around term in typically developing infants[34]) component volumes were associated with poorer cognitive outcomes. We also found that a relative larger parietal component volume was associated with worse motor function at 22 months. These results suggest that the brain alterations we interpreted as possibly reflecting brain-sparing processes could also highlight fetal compromise. Fetal cerebral hemodynamic redistribution, indexed by vasodilatation of the middle cerebral artery, has in fact been associated with increased risk of neonatal acidosis, indicative of fetal distress and diminished fetal reserve.[65] In previous work, infants with evidence of brain sparing had worse neurologic outcomes at age 2 years and lower IQ at age 5 years.[66,67] With regards to the observed association between increased relative gray matter volume in occipital and parietal cortices and poorer motor and cognitive outcomes, a tentative explanation could involve asynchronicity in complementary maturational patterns in gray and white matter[68] and previous research showing that relative gray matter expansion in very preterm samples is often accompanied by reduction in neighboring white matter.[69]

Our results failed to observe an association between relative brain volumetric alterations in limbic component at term (where between-group differences were most pronounced) and childhood outcomes. We interpret this finding in the context of age-dependent relationships between brain and cognitive maturation[70] and speculate that limbic alterations might affect the development of IUGR infants' emotional skills that will emerge only later in childhood. Studies in individuals with IUGR have highlighted reduced social awareness and social cognition,[71] poor social interactions,[12,72] and adaptive behaviors[15,73] and greater levels of negative affectivity and temperament difficulties.[74] As the limbic circuitry has been implicated in such functions,[75-77] the observed limbic volumetric changes observed in infants with IUGR of very preterm birth may increase their vulnerability to develop emotion and behavior regulation problems later in life.[78]

A major strength of our analysis is the use of gestation appropriate atlases to achieve accurate anatomical intensity-based segmentations of brain MRI,[25] together with a whole-brain approach to localize IUGR-AGA group differences at an early stage of postnatal growth within a large sample of very preterm individuals. Moreover, participants' high retention rate at follow-up assessment enabled the investigation of brain–function associations. This study also has limitations. First, the relatively small sample size of our IUGR group might have limited the statistical power to detect associations between neonatal volumetric alterations and childhood outcome and increased the risk of obtaining less reliable estimates of group differences.[79] Second, scarcity of antenatal information did not allow us to determine how long infants with IUGR of very preterm birth were exposed to a suboptimal intrauterine environment and therefore the severity of IUGR that might have influenced, in various degrees, the different outcomes. In addition, the lack of differences in brain growth and toddler's outcome found between the IUGR very preterm and the SGA very preterm groups highlights the need for better in utero surveillance for both SGA for unclear causes and infants with IUGR. Similarly, information on postnatal growth also might have informed on the influence of growth failure or catch-up in understanding brain–outcome associations.[80,81] Third, as all infants underwent MRI at term-equivalent age, we did not account for other (unmeasured) potential factors influencing brain development that occurred after birth.

IUGR in children born very preterm might confer a neurodevelopmental risk that is greater than that posed by very preterm birth alone, where the stress of the environment experienced antenatally alters brain growth and global development early in life. These findings might help identifying time-dependent prenatal factors impacting brain development and in particular an atypical development of IUGR very preterm individuals' "emotional brain" that is associated with both cognitive and psychiatric risk. ■

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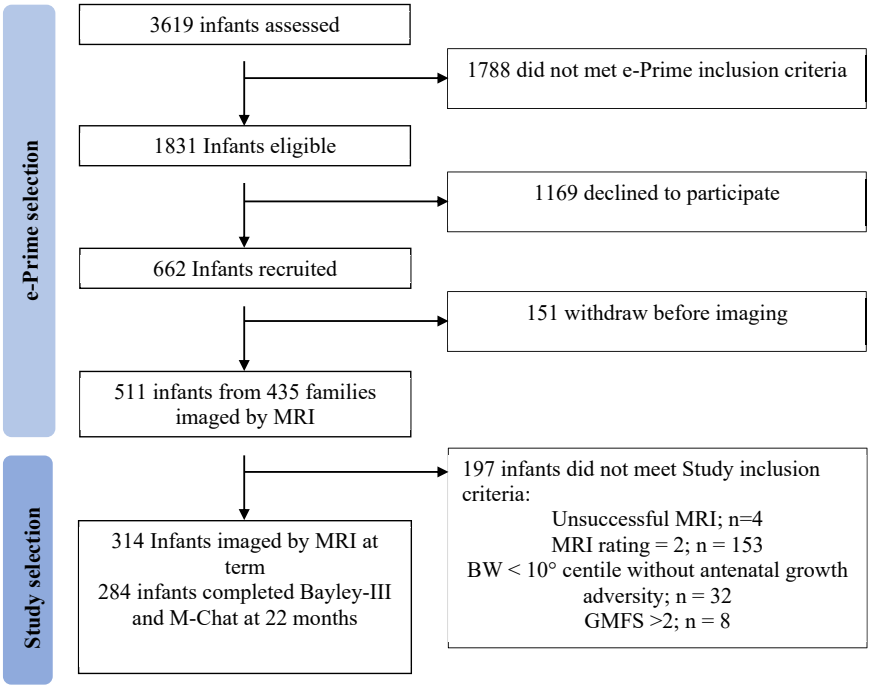

Figure 1. Study participants' selection flow diagram. *Bayley-III*, Bayley Scales of Infant and Toddler Development, 3rd Edition; *GMFS*, Gross Motor Function Classification System score.

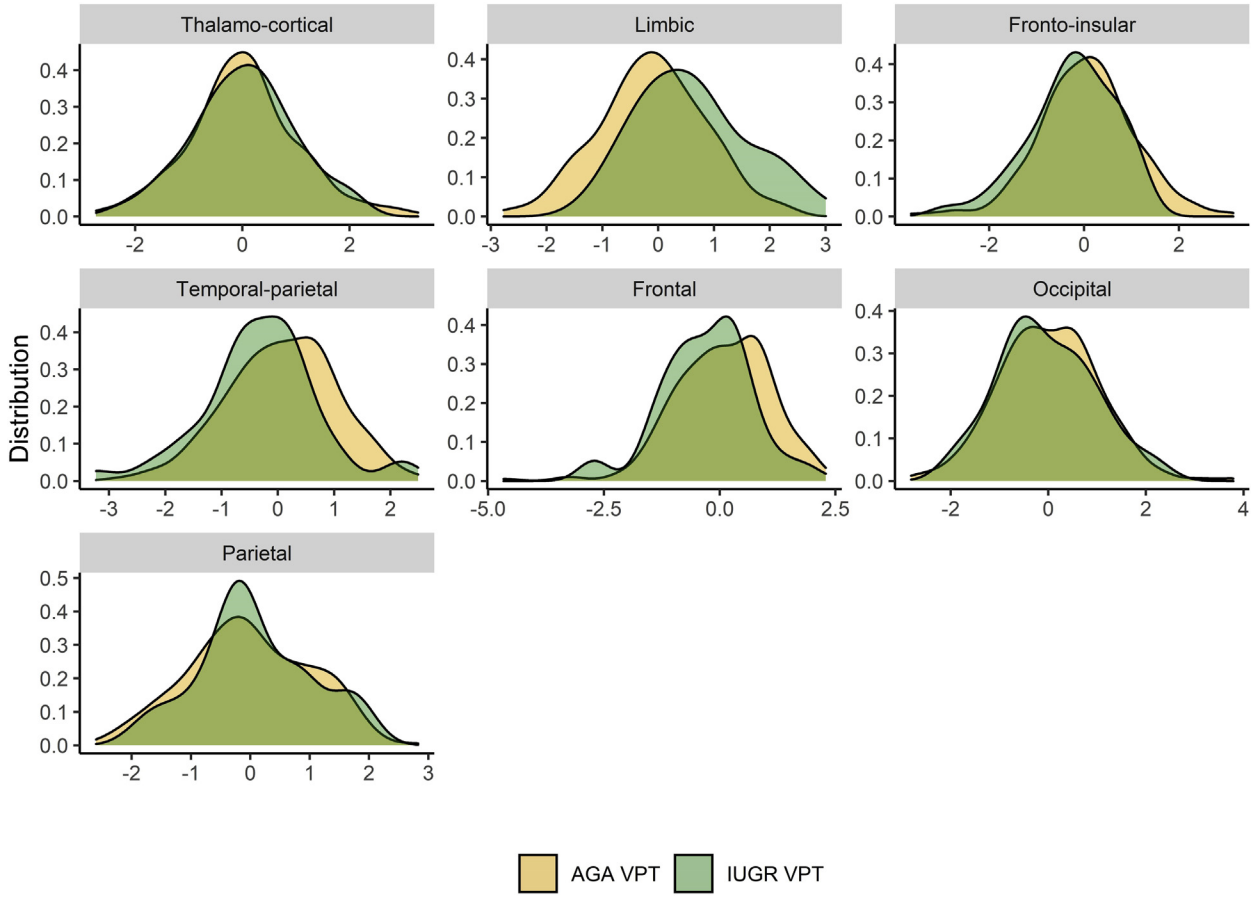

Figure 3. PCA factor score distribution in the newborns born very preterm with IUGR or who were AGA born very preterm.

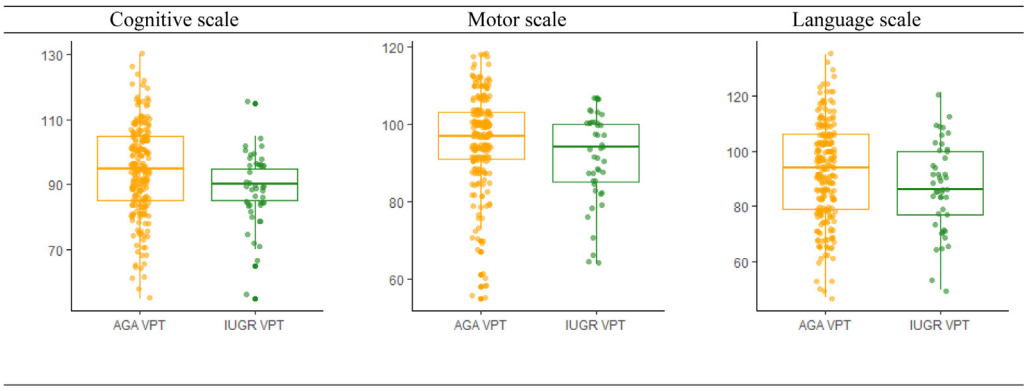

Figure 4. Bayley–III outcomes at 22 months in toddlers with IUGR or who were AGA born very preterm. Boxplots for the distribution of Bayley–III cognitive, motor, and language scores in toddlers with IUGR or who were AGA born very preterm. *Dots* represent participants, *middle line* represents group's mean, and *boxes* represent IQR.

Table I. PCA-derived "volumetric components" scores in infants who were AGA born very preterm with and without CP

PCA-derived "volumetric components"	AGA with CP (n = 8)	AGA without CP (n = 265)	Effect size [95% CI]	Unadjusted *P*	Adjusted* *P*
Thalamocortical	0.073 (1.017)	−0.007 (1.014)	*d* = −0.079 [−0.783 to 0.626]	.83	.61
Limbic	−0.346 (1.010)	−0.109 (0.944)	*d* = 0.251 [−0.454 to 0.955]	.54	.58
Frontoinsular	−0.334 (1.309)	0.043 (1.009)	*d* = 0.370 [−0.335 to 1.075]	.50	.58
Temporal-parietal	−0.316 (1.664)	0.063 (0.949)	*d* = 0.388 [−0.317 to 1.093]	.50	.29
Frontal	−0.257 (1.741)	0.055 (1.004)	*d* = 0.302 [−0.403 to 1.007]	.54	.39
Occipital	−1.088 (0.852)	0.019 (0.996)	*d* = 1.116 [0.404-1.827]	.005	.003
Parietal	−1.751 (0.872)	−0.012 (1.007)	*d* = 1.733 [1.012-2.454]	<.001	<.001

d, Cohen *d*; *FDR*, false discovery rate.
Data are given as No. (%) and mean (SD). All *P* values are corrected for FDR.[28]
*Adjusted for sex, gestational age at delivery, IMD score, and total intracranial volumes.

Table II. Cognitive, motor, language, and behavioral scores at 22 months in toddlers who were AGA born very preterm with and without CP

Developmental outcomes	AGA with CP (n = 8)	AGA without CP (n = 239)	Effect size [95% CI]	Unadjusted *P*	Adjusted* *P*
Bayley-III Cognitive scale	69.38 (13.21)	94.25 (13.31)	*d* = 1.87 [1.15-2.59]	.00	.00
Bayley-III Motor scale	55.75 (12.08)	96.46 (11.62)	*d* = 3.50 [2.73-4.27]	.00	.00
Bayley-III Language scale	75.5 (20.26)	92.62 (17.10)	*d* = 0.99 [0.29-1.71]	.006	.037
Positive M-CHAT screening†	8 (100%)	64 (27%)	–	–	–

Bayley-III, Bayley Scales of Infant and Toddler Development, 3rd Edition.
Data are given as No. (%) and mean (SD). All *P* values are corrected for FDR.[28]
*Adjusted for: sex, gestational age at delivery, IMD score, and total intracranial volume.
†OR and statistical significance no computed for no variability in the AGA with CP group.

Table III. PCA-derived "volumetric components" scores in infants with IUGR or who were AGA of very preterm birth, excluding participants with IUGR and very preterm birth with BW > 10th centile for gestational age (n = 10)

PCA-derived "volumetric components"	IUGR very preterm (n = 39)	AGA very preterm (n = 265)	Effect size [95% CI]	Unadjusted *P*	Adjusted* *P*
Thalamocortical	0.098 (.972)	−0.007 (1.014)	*d* = −0.10 [−0.44 to 0.23]	.66	.34
Limbic	0.498 (1.076)	−0.110 (0.944)	*d* = −0.63 [−0.97 to −0.29]	.002	.003
Frontoinsular	−0.291 (0.954)	0.044 (1.010)	*d* = 0.33 [−0.00 to 0.67]	.092	.050
Temporal-parietal	−0.364 (1.211)	0.063 (0.949)	*d* = 0.43 [0.10-0.77]	.042	.018
Frontal	−0.313 (.913)	0.055 (1.000)	*d* = 0.37 [0.03-0.71]	.073	.060
Occipital	−0.045 (1.070)	0.019 (0.996)	*d* = 0.06 [−0.27 to 0.40]	.71	.76
Parietal	0.086 (.998)	−0.012 (1.008)	*d* = −0.10 [−0.43 to 0.24]	.66	.35

Data are given as mean (SD). All *P* values are corrected for FDR.[28]
*Adjusted for sex, gestational age at delivery, IMD score, and total intracranial volume.

Table IV. Cognitive, motor, language, and behavioral scores at 22 months in toddlers with IUGR or who were AGA born very preterm, excluding participants with IUGR born very preterm with BW > 10th percentile for gestational age (n = 10)

Developmental outcomes	IUGR very preterm (n = 36)	AGA very preterm (n = 239)	Effect size [95% CI]	Unadjusted *P*	Adjusted* *P*
Bayley-III Cognitive scale	88.57 (11.67)	94.25 (13.31)	*d* = 0.43 [0.08-0.79]	.018	.036
Bayley-III Motor scale	91.29 (12.19)	96.46 (11.62)	*d* = 0.44 [0.09-0.76]	.018	.035
Bayley-III Language scale	84.97 (16.46)	92.61 (17.10)	*d* = 0.49 [0.14-0.84]	.018	.036
Positive M-CHAT screening	19 (53)	64 (27)	OR = 3.04 [1.49-6.21]	.002	.001

Data are given as No. (%) and mean (SD). All *P* values are corrected for FDR.[28]
*Adjusted for: sex, gestational age at delivery, IMD score, and total intracranial volume.

Table V. PCA-derived "volumetric component" scores in infants with IUGR or who were SGA of very preterm birth

PCA-derived "volumetric components"	IUGR very preterm (n = 49)	SGA very preterm (n = 32)	Effect size [95% CI]	Unadjusted *P*	Adjusted* *P*
Thalamocortical	0.037 (0.927)	−0.129 (0.784)	*d* = −0.19 [−0.64 to 0.26]	.57	.93
Limbic	0.593 (1.092)	0.252 (1.005)	*d* = −0.32 [−0.77 to −0.13]	.40	.45
Frontoinsular	−0.236 (0.923)	0.029 (0.983)	*d* = 0.28 [−0.17 to 0.73]	.40	.82
Temporal-parietal	−0.343 (1.191)	−0.293 (0.888)	*d* = 0.05 [−0.40 to 0.49]	.84	.93
Frontal	−0.299 (0.926)	0.003 (1.093)	*d* = 0.31 [−0.14 to 0.75]	.40	.57
Occipital	−0.106 (1.027)	0.027 (0.965)	*d* = 0.13 [−0.31 to 0.58]	.66	.93
Parietal	0.064 (0.965)	−0.209 (0.872)	*d* = −0.29 [−0.74 to 0.15]	.40	.67

Data are given as mean (SD). All *P* values are corrected for FDR.[28]
*Adjusted for: sex, gestational age at delivery, IMD score, and total intracranial volume.

Table VI. Cognitive, motor, language, and behavioral scores for toddlers with IUGR vs toddlers who were SGA born very preterm at 22 months

Developmental outcomes	IUGR very preterm (n = 45)	SGA very preterm (n = 30)	Effect size [95% CI]	Unadjusted *P*	Adjusted* *P*
Bayley-III Cognitive scale	88.78 (10.88)	91.50 (14.57)	*d* = 0.22 [−0.25 to 0.68]	.54	.72
Bayley-III Motor scale	91.71 (11.69)	96.53 (9.94)	*d* = 0.44 [−0.03 to 0.90]	.20	.26
Bayley-III Language scale	87.00 (15.90)	87.47 (18.51)	*d* = 0.03 [−0.434 to 0.49]	.91	.72
Positive M-CHAT	20 (44%)	11 (37%)	OR = 1.38 [0.54-3.56]	.55	.56

Data are given as No. (%) and mean (SD). All *P* values are corrected for FDR.[28]
*Adjusted for sex, gestational age at delivery, IMD score, and total intracranial volume.

Table VIII. PCA eigenvalues and standardized factors loading

	TC	Li	FI	TP	F	O	P
Eigenvalues	10.08	8.58	6.78	6.68	6.39	6.20	5.29
Explained variance, %	11	9	7	7	7	7	6
Factor loadings (>.40)							
Superior frontal gyrus							
L	−0.73						
R	−0.69						
Middle frontal gyrus							
L	−0.62						
R	−0.55						
Supplementary motor area							
L	−0.49						
R	−0.50						
Superior frontal gyrus, medial							
L	−0.72						
R	−0.7						
Median cingulate gyrus							
L	0.57						
R	0.47						
Posterior cingulate gyrus							
L	0.58			0.49			
R	0.53			0.45			
Heschl gyrus							
L	0.42			0.45			
R	0.53						
Thalamus							
R	0.63						
L	0.63						
Globus pallidus							
R	0.56						
L	0.48		0.44				
Hippocampus							
L	0.53	0.56					
R	0.52	0.53					
Amygdala							
L	0.51	0.42					
R	0.51	0.43	0.44				
Parahippocampal gyrus							
L		0.58					
R		0.52					
Fusiform gyrus							
L		0.71					
R		0.76					
Inferior temporal gyrus							
L		0.58		0.41			
R		0.56					
Cerebellum							
L		0.60					
R		0.58					
Pars opercularis							
R			0.62				
Pars triangularis							
R			0.47				
Inferior orbitofrontal gyrus							
R			0.44				
Rolandic operculum							
R			0.53	0.48			
Olfactory cortex							
L			0.56				
R			0.49				
Insula							
L			0.58				
R			0.73				
Superior parietal gyrus							
L			−0.46				0.41
Caudate nucleus							
L			0.41				
Putamen							
L			0.41				
R			0.48				

(*continued*)

Table VIII. Continued

	TC	Li	FI	TP	F	O	P
Superior temporal pole							
L			0.45				
R			0.63				
Inferior orbitofrontal gyrus							
L				0.49			−0.49
Rolandic operculum							
L				0.77			
Postcentral gyrus							
L				0.64			
Inferior parietal gyrus							
L				0.57			
Supramarginal gyrus							
L				0.71			
R				0.43			0.47
Angular gyrus							
L				0.55			
Superior temporal gyrus							
L				0.8			
R			0.46	0.52			
Middle temporal gyrus							
L				0.57			
Superior orbitofrontal gyrus							
L					0.81		
R					0.76		
Middle orbitofrontal gyrus							
L					0.63		
R					0.64		
Superior frontal gyrus, medial orbital							
L					0.82		
R					0.79		
Rectus gyrus							
L					0.73		
R					0.71		
Anterior cingulate gyrus							
L					0.66		
R					0.56		
Lingual gyrus							
L		0.48				0.51	
R		0.45				0.55	
Calcarine fissure							
L						0.71	
R						0.68	
Cuneus							
L						0.81	
R						0.8	
Superior occipital gyrus							
L						0.67	
R						0.66	
Medial occipital gyrus							
L						0.55	
R						0.68	
Inferior occipital gyrus							
L						0.46	
R						0.55	
Pars triangularis							
L							−0.41
Postcentral gyrus							
R							0.66
Superior parietal gyrus							
L							0.67
R							0.61
Angular gyrus							
R							0.47
Precuneus							
L							0.57
R							0.58
Paracentral lobule							
L							0.44
Paracentral lobule							
R							0.52

F, frontal component; *FS*, frontoinsular component; *L*, left hemisphere; *Li*, limbic component; *O*, occipital component; *P*, parietal component; R, right hemisphere; *TC*, thalamocortical component; *TP*, temporal-parietal component.

Table X. Regional Jacobian determinants for IUGR and AGA very preterm groups

Anatomical regions	IUGR very preterm (n = 49)	AGA very preterm (n = 265)	*P*
Precentral gyrus			
L	1.051 (0.115)	1.009 (0.105)	.034
R	1.046 (0.084)	1.009 (0.087)	.032
Superior frontal gyrus			
L	1.047 (0.114)	1.022 (0.112)	ns
R	1.120 (0.135)	1.069 (0.122)	ns
Superior orbitofrontal gyrus			
L	0.912 (0.083)	0.931 (0.085)	ns
R	0.910 (0.082)	0.945 (0.082)	.017
Middle frontal gyrus			
L	1.028 (0.082)	1.013 (0.102)	ns
R	1.009 (0.089)	1.001 (0.094)	ns
Middle orbitofrontal gyrus			
L	0.959 (0.100)	0.913 (0.112)	.015
R	0.944 (0.100)	0.918 (0.105)	ns
Pars opercularis			
L	1.005 (0.158)	1.044 (0.142)	ns
R	0.973 (0.082)	1.000 (0.105)	ns
Pars triangularis			
L	0.969 (0.094)	0.997 (0.115)	ns
R	0.997 (0.096)	1.005 (0.097)	ns
Inferior orbitofrontal gyrus			
L	1.032 (0.085)	1.014 (0.094)	ns
R	1.012 (0.080)	0.994 (0.086)	ns
Rolandic operculum			
L	0.897 (0.126)	0.950 (0.096)	.010
R	0.918 (0.096)	0.967 (0.093)	**.002**
Supplementary motor area			
L	1.221 (0.227)	1.176 (0.175)	ns
R	1.318 (0.283)	1.242 (0.226)	ns
Olfactory cortex			
L	0.951 (0.073)	0.982 (0.083)	ns
R	0.950 (0.077)	0.984 (0.085)	.014
Superior frontal gyrus, medial			
L	1.120 (0.190)	1.106 (0.198)	ns
R	1.182 (0.262)	1.170 (0.272)	ns
Superior frontal gyrus, medial orbital			
L	0.890 (0.100)	0.930 (0.111)	ns
R	0.879 (0.103)	0.920 (0.107)	.050
Gyrus rectus			
L	0.931 (0.094)	0.977 (0.088)	.006
R	0.912 (0.099)	0.971 (0.090)	**<.001**
Insula			
L	0.930 (0.099)	0.967 (0.085)	.051
R	0.931 (0.103)	0.954 (0.086)	ns
Anterior cingulate gyrus			
L	0.904 (0.115)	0.939 (0.124)	ns
R	0.967 (0.095)	0.979 (0.106)	ns
Median cingulate gyrus			
L	0.884 (0.105)	0.911 (0.110)	ns
R	0.933 (0.090)	0.948 (0.106)	ns
Posterior cingulate gyrus			
L	0.999 (0.155)	0.977 (0.141)	ns
R	1.002 (0.142)	0.993 (0.143)	ns
Hippocampus			
L	1.020 (0.110)	0.967 (0.096)	**.002**
R	1.020 (0.117)	0.958 (0.099)	**<.001**
Parahippocampal gyrus			
L	1.010 (0.094)	0.974 (0.104)	ns
R	1.028 (0.101)	0.991 (0.100)	ns
Amygdala			
L	1.002 (0.125)	0.971 (0.095)	ns
R	1.012 (0.119)	0.977 (0.087)	.032
Calcarine fissure			
L	0.913 (0.129)	0.930 (0.130)	ns
R	0.907 (0.145)	0.918 (0.132)	ns
Cuneus			
L	0.953 (0.161)	0.958 (0.137)	ns
R	0.957 (0.155)	0.968 (0.131)	ns

(*continued*)

Table X. Continued

Anatomical regions	IUGR very preterm (n = 49)	AGA very preterm (n = 265)	*P*
Lingual gyrus			
L	0.987 (0.116)	0.957 (0.088)	.028
R	1.013 (0.133)	0.978 (0.097)	.018
Superior occipital gyrus			
L	0.940 (0.118)	0.952 (0.118)	ns
R	0.950 (0.129)	0.975 (0.118)	ns
Middle occipital gyrus			
L	0.884 (0.104)	0.889 (0.099)	ns
R	0.892 (0.109)	0.906 (0.093)	ns
Inferior occipital gyrus			
L	0.923 (0.112)	0.909 (0.092)	ns
R	0.907 (0.131)	0.920 (0.095)	ns
Fusiform gyrus			
L	0.965 (0.097)	0.929 (0.082)	.009
R	0.980 (0.121)	0.938 (0.072)	**.001**
Postcentral gyrus			
L	0.990 (0.126)	0.994 (0.103)	ns
R	0.998 (0.095)	0.985 (0.083)	ns
Superior parietal gyrus			
L	1.020 (0.145)	1.047 (0.168)	ns
R	1.106 (0.135)	1.093 (0.161)	ns
Inferior parietal gyrus			
L	0.963 (0.157)	0.979 (0.128)	ns
R	0.950 (0.104)	0.949 (0.116)	ns
Supramarginal gyrus			
L	0.954 (0.206)	0.990 (0.192)	ns
R	0.962 (0.117)	1.014 (0.111)	.002
Angular gyrus			
L	0.953 (0.160)	0.960 (0.152)	ns
R	0.963 (0.103)	0.962 (0.097)	ns
Precuneus			
L	1.020 (0.108)	1.019 (0.107)	ns
R	1.036 (0.140)	1.033 (0.111)	ns
Paracentral lobule			
L	1.151 (0.263)	1.080 (0.195)	ns
R	1.211 (0.319)	1.130 (0.235)	ns
Caudate nucleus			
L	0.946 (0.071)	0.972 (0.088)	ns
R	0.956 (0.076)	0.967 (0.081)	ns
Putamen			
L	0.910 (0.134)	0.930 (0.115)	ns
R	0.903 (0.144)	0.912 (0.107)	ns
Heschl gyrus			
L	0.865 (0.118)	0.907 (0.104)	ns
R	0.889 (0.092)	0.917 (0.096)	ns
Superior temporal gyrus			
L	0.911 (0.146)	0.944 (0.118)	ns
R	0.942 (0.085)	0.977 (0.081)	.028
Superior temporal pole			
L	1.067 (0.145)	1.058 (0.157)	ns
R	1.111 (0.123)	1.099 (0.163)	ns
Middle temporal gyrus			
L	0.889 (0.121)	0.889 (0.108)	ns
R	0.928 (0.083)	0.93 (0.072)	ns
Middle temporal pole			
L	1.059 (0.141)	1.077 (0.189)	ns
R	1.026 (0.124)	1.049 (0.151)	ns
Inferior temporal gyrus			
L	0.949 (0.106)	0.942 (0.089)	ns
R	0.962 (0.096)	0.953 (0.073)	ns
Cerebellum			
L	1.020 (0.125)	0.980 (0.101)	.019
R	1.027 (0.133)	0.977 (0.099)	.008
Thalamus			
L	1.007 (0.074)	0.958 (0.080)	**<.001**
R	1.015 (0.078)	0.969 (0.082)	**<.001**
Globus pallidus			
L	0.882 (0.107)	0.889 (0.094)	ns
R	0.882 (0.095)	0.899 (0.093)	ns

ns, not significant.
Data are given as mean (SD). *P* values corrected for FDR[28]; bold *P* values also significant with Bonferroni correction.

Table XI. Demographic characteristics of participants with and without 22-months follow-up assessment

Characteristics	Followed-up (n = 284)	Lost to follow-up (n = 30)	*P*
Antenatal characteristics			
Maternal age, y	32.42 (5.87)	32.38 (5.56)	.98
Maternal hypertension	17 (6%)	2 (7%)	>.99
IMD, by quintiles			.03
1 (least deprived)	57 (20%)	4 (13%)	
2	39 (14%)	10 (33%)	
3	75 (26%)	9 (30%)	
4	77 (27%)	5 (17%)	
5 (most deprived)	36 (13%)	1 (3%)	
Perinatal outcomes			
IUGR	45 (16%)	4 (13%)	.92
Multiple pregnancy	86 (30%)	12 (39%)	.10
BW	1300 [646.25]	1240 [546.25]	.46
BW percentile	41.75 [41.49]	33.57 [34.61]	.18
Head circumference, cm	29.13 (3.09)	28.94 (2.99)	.76
Age at delivery, wk	30.17 [3.60]	30.7 [4.53]	.71
Sex (male)	150 (52%)	10 (32%)	.092
Ventilation, d	0 [2]	0 [2]	.92
Parenteral nutrition, d	5 [10.5]	7.5 [8.25]	.32
Continuous positive airway pressure, d	6 [28]	7 [19]	.89
Surfactant (yes)	143 (50%)	11 (37%)	.40
Surgery for necrotizing enterocolitis (yes)	4 (1.4%)	0 (0%)	>.99
Chorioamnionitis (yes)	6 (2)	1 (3)	>.99
Age at MRI scan, wk	42.4 [1.93]	41.4 [2.14]	.068

Data are given as No. (%), mean (SD), and median [IQR]. Median and range used for non-normal distributions.
P values were calculated using the Student *t* test, Pearson χ^2 test, and Mann–Whitney *U* test.