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Brain Development and Maternal Behavior in Relation to Cognitive and Language Outcomes in Preterm-Born Children

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ABSTRACT

BACKGROUND: Children born very preterm (≤32 weeks gestational age) show poorer cognitive and language development compared with their term-born peers. The importance of supportive maternal responses to the child's cues for promoting neurodevelopment is well established. However, little is known about whether supportive maternal behavior can buffer the association of early brain dysmaturation with cognitive and language performance.

METHODS: Infants born very preterm (N = 226) were recruited from the neonatal intensive care unit for a prospective, observational cohort study. Chart review (e.g., size at birth, postnatal infection) was conducted from birth to discharge. Magnetic resonance imaging, including diffusion tensor imaging, was acquired at approximately 32 weeks postmenstrual age and again at term-equivalent age. Fractional anisotropy, a quantitative measure of brain maturation, was obtained from 11 bilateral regions of interest in the cortical gray matter. At 3 years (n = 187), neurodevelopmental testing (Bayley Scales of Infant and Toddler Development-III) was administered, and parent-child interaction was filmed. Maternal behavior was scored using the Emotional Availability Scale-IV. A total of 146 infants with neonatal brain imaging and follow-up data were included for analysis. Generalized estimating equations were used to examine whether maternal support interacted with mean fractional anisotropy values to predict Cognitive and Language scores at 3 years, accounting for confounding neonatal and maternal factors.

RESULTS: Higher maternal support significantly moderated cortical fractional anisotropy values at term-equivalent age to predict higher Cognitive (interaction term β = 2.01, p = .05) and Language (interaction term β = 1.85, p = .04) scores.

CONCLUSIONS: Findings suggest that supportive maternal behavior following early brain dysmaturation may provide an opportunity to promote optimal neurodevelopment in children born very preterm.

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Advances in neonatal care have greatly improved the survival of infants born ≤32 weeks gestational age (GA); however, neurodevelopmental problems including cognitive and language abilities and academic difficulties in children born very preterm remain a significant challenge (1–5). While many clinical factors in the neonatal intensive care unit (NICU) have been shown to be associated with long-term brain development in children born preterm (6–10), there is wide variation in neurodevelopmental outcomes. Positive maternal interaction has been associated with neurodevelopmental outcomes of children born very preterm (11–17) and may even mitigate the adverse consequence of early-life brain injury (18,19).

Greater brain maturation early in life has been associated with better neurodevelopmental outcomes in children born very preterm (20–26). Previous research has suggested that supportive and responsive maternal behavior is associated with improved white matter maturation and better cognitive outcomes at school age in children born very preterm (12,19). Furthermore, a cognitively stimulating home environment has been associated with better child executive function (27). However, the relationships between neonatal cortical gray matter maturation, maternal-child interaction, and neurodevelopmental outcomes in children born very preterm remain unknown.

Diffusion tensor imaging (DTI) is a magnetic resonance imaging (MRI) method used to characterize the spatial distribution of water diffusion within each voxel of the brain image from which regional microstructural development can be inferred (28). Fractional anisotropy (FA), a measure of the directionality of water diffusion, has primarily been used to assess white matter maturation and early events of myelination (29,30). In contrast, cortical FA in the preterm brain demonstrates a biphasic pattern with maturation. Prior to 38 weeks postmenstrual age (PMA), FA decreases in the cortical gray matter with the disappearance of the radial glia, cell proliferation, and synapse formation (31–34). However, following 38 weeks PMA, FA increases in the cortical gray matter with increasing cellular and organelle density (35,36). Early-life cortical gray matter maturation has been associated with later cognitive and language outcomes (23,37–41). Supportive maternal behavior may also attenuate the relationship between lower cortical gray matter maturation early in life and poorer outcomes in children born very preterm.

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A meta-analysis of 34 studies conducted between 1980 and 2014 reported that mothers of children born preterm were equally as supportive and responsive toward their children as mothers of children born full term (42). Previously, it has been demonstrated that more supportive maternal behavior during early childhood is associated with better cognitive and language outcomes for children born preterm (17,43,44). Efforts to promote supportive and responsive interactions in the NICU appear to modify cortical activity and improve white matter maturation (i.e., greater FA) in infants born preterm (19,45). However, the extent that positive maternal-child interaction in early childhood is able to moderate FA within the cortical gray matter to improve neurodevelopmental outcomes in children born very preterm has not been examined. Therefore, we examined whether greater maternal supportive behavior at 3 years buffered the relationship between cortical gray matter in the neonatal period and cognitive and language outcomes in children born very preterm. We hypothesized that supportive and responsive maternal behavior would attenuate the association of early brain dysmaturation with poorer neurodevelopmental outcomes in children born very preterm, over and above neonatal illness (i.e., small for gestational age [SGA], postnatal infection), brain injury (i.e., white matter injury volume), and lower maternal education.

METHODS AND MATERIALS

This study was approved by the University of British Columbia and Children's and Women's Hospital Clinical Research Ethics Board. Parent written informed consent was obtained.

Participants

Infants born very preterm [24–32 weeks GA (46)] admitted to a tertiary-level NICU were recruited to this prospective longitudinal cohort study between April 2006 and April 2013. GA was based on the last menstrual period or early ultrasound (<24 weeks); if the difference between the two methods was >7 days, the ultrasound date was used. Multiple births were included. Exclusions were congenital malformation or syndrome, antenatal TORCH (toxoplasma, other viral, rubella, congenital cytomegalovirus, herpes) infection, or ultrasound evidence of a parenchymal hemorrhagic infarction >2 cm, because the latter was strongly predictive of early mortality, and these babies were often too unstable for early-life MRI.

Medical Chart Review

A neonatal research nurse performed day-by-day medical and nursing chart review from birth to NICU discharge or term-equivalent age (TEA), whichever came first; we were not able to account for clinical events occurring after TEA. Data included GA, sex, SGA, retinopathy of prematurity, days of mechanical ventilation, presence of chronic lung disease, number of invasive procedures, morphine exposure, necrotizing enterocolitis, and infection. Infection was defined as either clinical sepsis or confirmed infections.

Magnetic Resonance Imaging

Infants were scanned without pharmacological sedation at median 32 weeks and again at median 40 weeks PMA in an MRI-compatible isolette (Lammers Medical Technology) with a specialized neonatal head coil (Advanced Imaging Research). A Siemens 1.5-T Avanto magnet and Vb 13A software were used to obtain the following sequences: three-dimensional coronal volumetric T1-weighted images, axial fast spin echo T2-weighted images, and diffusion tensor images (see Supplemental Methods). Total white matter injury volumes were manually segmented on the T1-weighted images using the three-dimensional Visualization Display software (http://bic.mni.mcgill.ca/ServicesSoftwareVisualization) as described previously (47).

Diffusion Tensor Imaging

DTI is an MRI technique that enables the measurement of the diffusion of water in tissue. FA indicates the orientation of diffusion and provides the relative difference between the largest eigenvalue (λ_1) reflective of the primary (axial) diffusion axis as compared with other directions (λ_2 and λ_3). Using Siemens DTI and DTI Evaluation modules (Vb 13A), the DTI scans were processed and DTI parameters were collected bilaterally in 11 manually placed cortical regions of interest on both scans (precentral gyrus, postcentral gyrus, secondary somatosensory cortex, superior frontal gyrus, dorsolateral prefrontal cortex, ventrolateral prefrontal cortex, anterior and posterior insula, anterior and posterior cingulate gyrus, and occipital gray matter), given their distinct maturational trajectories and functions and ability to be assessed with high reliability by an experienced neuroscientist (JVM) [a subset of these data was published in a paper examining the impact of neonatal factors on early brain development (48)]. Previous studies have demonstrated these regions' associations with cognitive and language outcomes in children born preterm (37,40). To avoid multiple comparisons relative to our sample size, mean bilateral FA values from the 11 cortical regions of interest were averaged for analysis. Our main hypothesis related to overall cortical maturation, and given that regional cortical FA differences decrease with increasing PMA (see Supplemental Methods), the 11 cortical regions were also averaged at each time point to examine mean cortical FA early in life (median 32 weeks PMA) and at TEA.

Demographics

Parent information was obtained by questionnaire. We used mothers' level of education as an index of socioeconomic status (SES) for statistical analysis (18), categorized as primary or secondary school, undergraduate degree, or postgraduate degree. Mother's level of education is the most important SES indicator in relation to child development (49,50).

Maternal Behavior

Mothers participated in a 5-minute semistructured teaching session with their child at 18 months and 3 years, which were filmed and stored on DVDs. Three blinded coders (one primary, two reliability) trained by the developer of the Emotional Availability Scale-IV systematically rated maternal behavior using the Emotional Availability Scale-IV (see Supplemental Methods) (51,52). This scale captures four dimensions of maternal behavior: sensitivity (appropriate responses/authenticity of affect), structuring (provision of guidance), nonintrusiveness (no overstimulation/overprotection), and

nonhostility (nonthreatening/nonfrightening). Scores range from 7 to 29, with higher scores denoting more positive emotional availability. Given the importance of maternal sensitivity for neurodevelopment (11,15,44,53) and high correlations with the other three dimensions (see Supplemental Methods), only maternal sensitivity was used for analysis. Given that maternal sensitivity did not differ between 18 months (mean = 20.01, SD = 4.11) and 3 years (mean = 21.01, SD = 3.91) ($F_{1,141} = 3.75$, $p = .06$), only maternal sensitivity at 3 years was used.

Neurodevelopmental Assessment

At 3 years, neurodevelopment was assessed by experienced physiotherapy or psychology staff using the Bayley Scales of Infant and Toddler Development-III (Bayley-III) (54). Cognitive and Language composite scores were obtained (mean = 100, SD = 15). Higher composite scores indicate better neurodevelopmental functioning.

Analyses

Statistical analyses were performed using IBM SPSS Statistics version 25. Normality plots were examined for all variables considered, and no violations were detected. For descriptive purposes, a median split of maternal sensitivity was performed (lower sensitivity = total scores 10–20.5; higher sensitivity = total scores 21–29), and two-tailed *t* tests and χ^2 tests were conducted to test the differences between children and their mothers with higher and lower maternal sensitivity. Two-tailed *t* tests and χ^2 tests were also conducted to compare the data between those included and excluded for analysis. Maternal sensitivity was treated as a continuous variable for the linear models. Generalized estimating equations were used to account for twin pairings and examine whether the interactions between maternal sensitivity at 3 years and mean FA values both early in life and at TEA were associated with Bayley-III Cognitive and Language outcomes at 3 years in children born very preterm. SGA, postnatal infection, and white matter injury volumes were included as markers of neonatal illness and brain injury given their robust associations with neurodevelopmental outcomes (47,55,56). PMA at scan was included to account for normative brain maturation. Further, we included mothers' marital status and level of education as SES indicators. Models with significant interactions were repeated to account for additional neonatal confounding and maternal factors: 1) number of invasive procedures, days of mechanical ventilation, and morphine exposure and 2) necrotizing enterocolitis, retinopathy of prematurity, and maternal ethnicity.

RESULTS

Cohort Characteristics

Of the 226 survivors, 83% (187 children; 90 [48.1%] female) returned for follow-up at 3 years (Figure 1). Of those that returned (cohort characteristics in Table S1), 146 had complete data pertaining to this study (i.e., limited number that had both quality neonatal imaging data and parent-child interaction follow-up data at 3 years). There were no significant differences in GA ($t_{232} = 1.26$, $p = .21$), sex ($\chi^2_{1,193} = 0.98$, $p = .32$), size at birth ($\chi^2_{1,232} = 1.65$, $p = .20$), rates of postnatal infection ($\chi^2_{1,192} = 3.46$, $p = .06$), or white matter injury volumes ($t_{181} =$ 0.22, $p = .41$) between those with complete versus incomplete data. Further, the 146 children included in this study did not significantly differ in Cognitive ($t_{163} = -1.29$, $p = .20$) or Language ($t_{144} = -1.44$, $p = .15$) scores compared with children who returned for follow-up but with incomplete data. The 146 children included in this study were born at a median of 27.7 weeks (interquartile range: 26.0–30.0) gestation. They were scanned initially at median 32.2 (interquartile range: 30.6–33.7) weeks PMA and, when possible, again at TEA (median 40.1 [interquartile range: 38.6–42.3]). At 3 years, Cognitive and Language scores were significantly higher in children of mothers with greater sensitivity as compared with children of mothers with lower sensitivity at 3 years (Table 1).

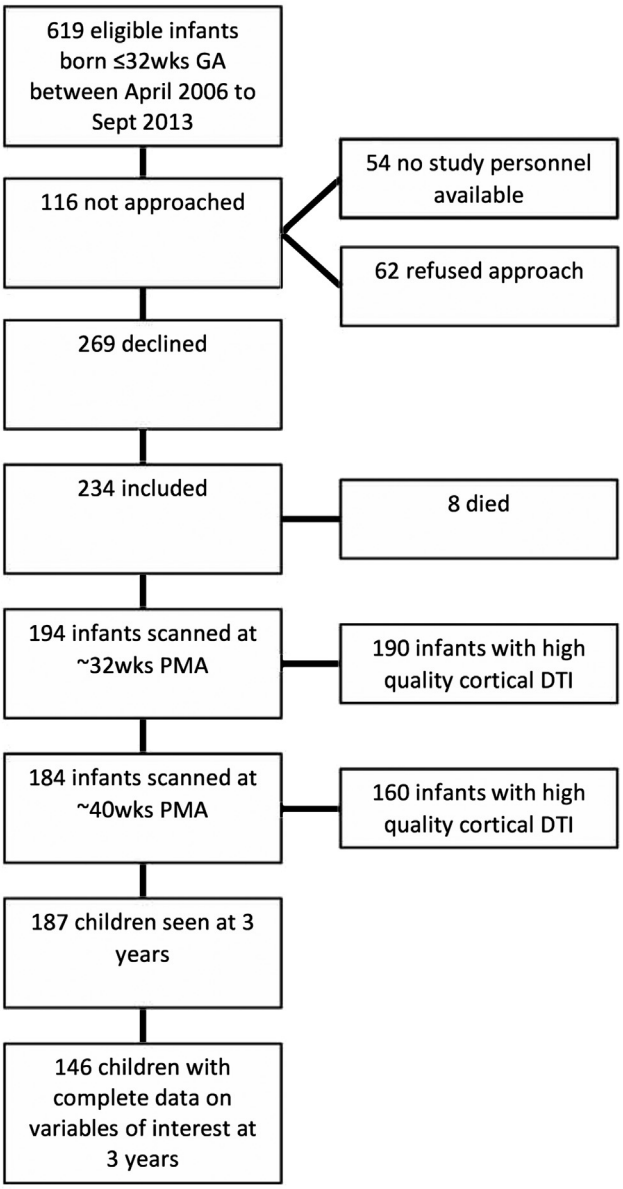

Figure 1. Participant flowchart. DTI, diffusion tensor imaging; GA, gestational age; PMA, postmenstrual age.

Table 1. Characteristics of the Cohort

Characteristics	*n*	Lower Maternal Sensitivity (Total Score 10–20.5), *n* = 69	Higher Maternal Sensitivity (Total Score 21–29), *n* = 77	*p* Value
Neonatal Characteristics				
Gestational age at birth, weeks	146	28.0 (26.4–29.7)	27.7 (25.6–30.2)	.91
Sex, male, *n* (%)	146	37 (53.6%)	40 (51.9%)	.78
Twin births, *n* (%)	146	5 (7.2%)	22 (28.6%)	<.001
Small for gestational age, *n* (%)	146	11 (15.9%)	12 (15.6%)	.98
Infection, *n* (%)	146	38 (55.1%)	36 (46.8%)	.26
Necrotizing enterocolitis, *n* (%)	146	16 (23.2%)	14 (18.2%)	.38
Retinopathy of prematurity, *n* (%)	122	–	–	.26
None	–	35 (59.3%)	36 (57.1%)	–
Without laser treatment	–	16 (27.1%)	22 (34.9%)	–
With laser treatment	–	8 (13.6%)	5 (7.9%)	–
Mechanical ventilation, days	145	5.0 (2.0–21.5)	5.5 (2.0–36.5)	.65
Chronic lung disease, *n* (%)	145	17 (24.6%)	22 (28.6%)	.55
Invasive procedures	145	95.0 (58.5–141.5)	96.0 (59.8–181.3)	.65
Morphine, mg/kg	145	0.1 (0.0–2.2)	0.1 (0.0–3.9)	.25
Postmenstrual age at scan 1, weeks	146	31.9 (30.3–33.4)	32.3 (30.9–33.9)	.09
Postmenstrual age at scan 2, weeks[a]	143	40.1 (38.0–41.8)	40.1 (38.7–42.6)	.56
White matter injury at scan 1, volume	146	0.0 (0.0–28.8)	0.0 (0.0–11.2)	.56
White matter injury at scan 2, volume[a]	142	0.0 (0.0–39.3)	0.0 (0.0–0.0)	.36
Child Characteristics at 3 Years				
Bayley-III Cognitive composite	146	100.0 (90.0–105.0)	105.0 (100.0–115.0)	.001
Bayley-III Language composite	128	106.0 (94.8–112.0)	112.0 (103.0–120.3)	.01
Maternal Characteristics at 3 Years				
Age, years	145	37.0 (32.0–41.4)	34.7 (31.9–38.9)	.26
Marital status, *n* (%)	145	–	–	.49
Single	–	5 (7.2%)	1 (1.3%)	–
Married	–	52 (75.4%)	64 (84.2%)	–
Common Law	–	9 (13.0%)	10 (13.2%)	–
Separated	–	3 (4.3%)	0 (0.0%)	–
Divorced	–	0 (0.0%)	1 (1.3%)	–
Ethnicity, *n* (%)	145			<.001
East Asian	–	19 (28.0%)	9 (11.7%)	–
First Nations	–	4 (5.9%)	1 (1.3%)	–
Hispanic	–	1 (1.5%)	4 (5.2%)	–
Mixed	–	2 (2.9%)	7 (9.0%)	–
South Asian	–	9 (13.0%)	1 (1.3%)	–
White	–	33 (48.5%)	54 (70.1%)	–
Occupation, *n* (%)[b]	146	–	–	.40
Unemployed/student	–	2 (2.9%)	1 (1.2%)	–
Stay-at-home mother	–	11 (15.9%)	11 (14.2%)	–
Maternity leave	–	1 (1.4%)	3 (3.9%)	–
Employment	–	55 (79.7%)	63 (81.8%)	–
Education, *n* (%)	146	–	–	.03
Primary or secondary school	–	10 (14.5%)	10 (13.0%)	–
Undergraduate degree	–	54 (78.3%)	47 (61.0%)	–
Postgraduate degree	–	5 (7.2%)	20 (26.0%)	–
Number of children in the home	144	2 (1.0–2.0)	2 (1.0–2.8)	.07

Values are reported as *n* (%) or median (interquartile range).

[a]Three of the 146 infants did not complete a second scan. Of the 143 with two scans, one was of poor quality and white matter injury volume could not be calculated.

[b]Two mothers with lower maternal sensitivity and 4 mothers with higher maternal sensitivity indicated that they were receiving social assistance.

Cortical FA Early in Life, Maternal Sensitivity, and Bayley-III Cognitive and Language Scores

The interaction between mean cortical FA values at approximately 32 weeks PMA and maternal sensitivity was not associated with Bayley-III Cognitive ($\beta = -1.09$, $p = .23$) or Language ($\beta = -0.68$, $p = .50$) scores at 3 years after accounting for SGA ($p < .05$), postnatal infection ($p < .05$), age at scan ($p > .05$), white matter injury volumes ($p < .01$), and mother's marital status ($p > .05$) and education ($p < .05$). See Tables 2 and 3 for full results.

Cortical FA at Term, Maternal Sensitivity, and Bayley-III Cognitive Scores

Infants were between 33.4 and 48.1 weeks PMA at their second scan (27 [18.9%] <38 weeks and 115 [80.4%] >38 weeks). Infants were scanned prior to TEA if they were discharged early or were scanned after 42 weeks PMA if they were unable to return for a TEA scan. Despite variability in PMA, there is less variability in FA on the TEA scan (see Supplemental Methods). The interaction between mean cortical FA values at TEA and maternal sensitivity was associated with Bayley-III Cognitive scores at 3 years ($\beta = 2.01$, $p = .05$) after accounting for size at birth ($\beta = 0.24$, $p = .003$), postnatal infection ($\beta = -0.19$, $p = .01$), age at scan ($\beta = 0.19$, $p = .04$), white matter injury volumes ($\beta = -0.13$, $p = .11$), and mother's marital status ($\beta = 0.12$, $p = .15$) and education ($\beta = 0.11$, $p = .15$) (Table 4). To assist with the interpretation of this interaction, post hoc analyses were conducted (Figure 2). The lowest Cognitive scores were among children with higher FA at TEA and lower maternal sensitivity at 3 years (i.e., mean Bayley-III Cognitive score = 103). The highest Cognitive scores were among children that had higher FA at TEA and mothers with greater sensitivity at 3 years (i.e., mean Bayley-III Cognitive score = 109).

Cortical FA at Term, Maternal Sensitivity, and Bayley-III Language Scores

The interaction between mean cortical FA values at TEA and maternal sensitivity ($\beta = 1.85$, $p = .04$) was associated with Bayley-III Language scores at 3 years after accounting for size at birth ($\beta = 0.16$, $p = .09$), postnatal infection ($\beta = -0.29$, $p < .001$), age at scan ($\beta = -0.04$, $p = .66$), white matter injury volumes ($\beta = -0.08$, $p = .62$), and mother's marital status ($\beta = 0.04$, $p = .64$) and education ($\beta = 0.23$, $p = .004$) (Table 5). Again, the lowest Language scores were among children with higher FA at TEA and lower maternal sensitivity at 3 years (i.e., mean Bayley-III Language score = 110) (Figure 3). The highest Language scores were among children with higher FA at TEA and mothers with greater sensitivity at 3 years (i.e., mean Bayley-III Language score = 116).

Table 2. Relationship Between Mean Cortical FA Early in Life, Maternal Sensitivity, and Cognition

	Bayley-III Cognitive Composite Scores at 3 Years, $n = 146$ (27 Twins Included)		
Predictors	β	95% CI	*p*
Small for Gestational Age	0.22	0.06 to 0.39	.008
Postnatal Infection	−0.15	−0.30 to −0.004	.04
Postmenstrual Age at Scan	0.07	−0.13 to 0.28	.48
White Matter Injury Volume	−0.33	−0.44 to −0.21	<.001
Early-Life Cortical FA	0.65	−0.35 to 1.64	.20
Marital Status	0.003	−0.15 to 0.15	.97
Mother's Level of Education	0.03	−0.10 to 0.16	.66
Maternal Sensitivity	1.15	−0.22 to 2.52	.10
Maternal Sensitivity × FA	−1.09	−2.88 to 0.70	.23

FA, fractional anisotropy.

Table 3. Relationship Between Mean Cortical FA Early in Life, Maternal Sensitivity, and Language

	Bayley-III Language Composite Scores at 3 Years, $n = 128$ (25 Twins Included)		
Predictors	β	95% CI	*p*
Small for Gestational Age	0.18	−0.01 to 0.38	.07
Postnatal Infection	−0.23	−0.38 to −0.08	.003
Postmenstrual Age at Scan	0.12	−0.10 to 0.33	.29
White Matter Injury Volume	−0.22	−0.37 to −0.07	.004
Early-Life Cortical FA	0.50	−0.64 to 1.63	.39
Marital Status	−0.01	−0.17 to 0.15	.94
Mother's Level of Education	0.16	0.04 to 0.29	.01
Maternal Sensitivity	0.77	−0.75 to 2.29	.32
Maternal Sensitivity × FA	−0.68	−2.65 to 1.29	.50

FA, fractional anisotropy.

Additional Neonatal and Maternal Confounding Factors

The interactions between maternal sensitivity, mean cortical FA at TEA, and Bayley-III Cognitive and Language scores remained at $p \leq .05$ after adjustment for additional neonatal and maternal factors, even when these factors were not themselves significant predictors (Tables 6–9).

DISCUSSION

In a prospective longitudinal cohort study of very preterm–born children, we examined whether maternal sensitivity at 3 years buffers the relationship between cortical gray matter

Table 4. Relationship Between Mean Cortical FA at TEA, Maternal Sensitivity, and Cognition

	Bayley-III Cognitive Composite Scores at 3 Years, $n = 127$ (22 Twins Included)		
Predictors	β	95% CI	*p*
Small for Gestational Age	0.24	0.08 to 0.40	.003
Postnatal Infection	−0.19	−0.34 to −0.05	.01
Postmenstrual Age at Scan	0.19	0.01 to 0.37	.04
White Matter Injury Volume	−0.13	−0.30 to 0.03	.11
TEA Cortical FA	−1.08	−2.27 to 0.11	.07
Marital Status	0.12	−0.04 to 0.28	.15
Mother's Level of Education	0.11	−0.04 to 0.27	.15
Maternal Sensitivity	−1.33	−2.97 to 0.31	.11
Maternal Sensitivity × FA	2.01	0.002 to 4.02	.05

FA, fractional anisotropy; TEA, term-equivalent age.

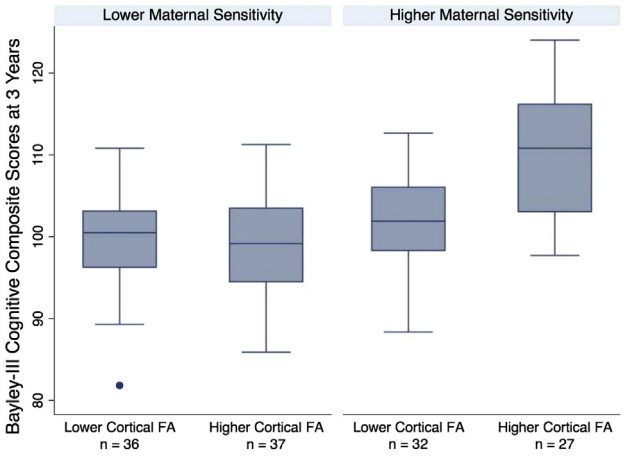

Figure 2. Maternal sensitivity, cortical brain development, and Bayley-III cognitive outcomes. Lower (25th percentile = 0.15) or higher (75th percentile = 0.18) fractional anisotropy (FA) values at term-equivalent age and lower (25th percentile = 18) or higher (75th percentile = 23.5) concurrent maternal sensitivity compared with Bayley-III Cognitive composite scores at 3 years.

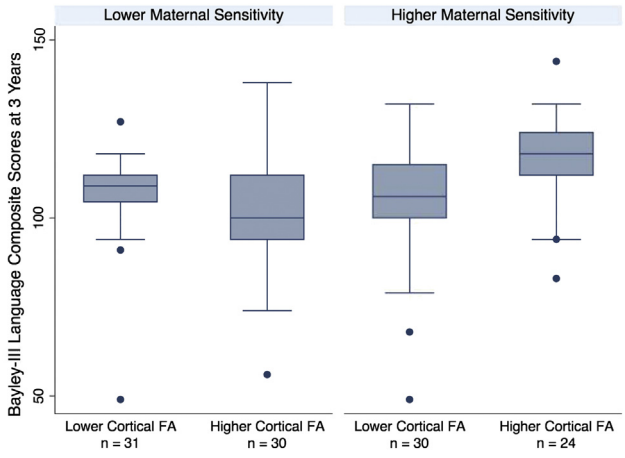

Figure 3. Maternal sensitivity, cortical brain development, and Bayley-III Language outcomes. Lower (25th percentile = 0.15) or higher (75th percentile = 0.18) fractional anisotropy (FA) values at term-equivalent age and lower (25th percentile = 18) or higher (75th percentile = 23.5) concurrent maternal sensitivity compared with Bayley-III Language composite scores at 3 years.

dysmaturation early in life and at TEA and cognitive and language abilities at 3 years after accounting for neonatal illness, brain injury, and maternal education. Consistent with previous reports, being born SGA and the presence of postnatal infections and/or brain injuries were associated with lower neurodevelopmental outcome scores (47,55,57–60). In addition, we confirmed the well-established findings that children of mothers with a lower level of education showed, on average, lower language scores (61). Greater maternal sensitivity was associated with better cognitive and language outcomes in children with less mature cortical gray matter at TEA. This builds on the recent observations of Vanes *et al.* (27) by obtaining objective measures of maternal sensitivity to provide new evidence for additional mitigatory effects of maternal behavior. Together, this work provides support for postdischarge interventions targeting maternal sensitivity, which may lead to improved neurodevelopment for children born very preterm.

In this study, maternal sensitivity buffered DTI measures of cortical dysmaturation at TEA but not early in life. Previously, using an animal model of prematurity, it was found that disruptions to MRI-defined cortical microstructure occur by disturbing neuronal arborization (62). Prior to 36 weeks PMA, the linearity of water movement can still be readily measured within the cerebral cortex owing to the presence of radial glial cells and the relative immaturity of neurons and synapses (31,63,64). The immaturity of the cerebral cortex at 32 weeks PMA, which is the approximate age of our first scan in infants, may explain why we were not able to fully capture the disruption to the dendritic arborization associated with cognitive and language outcomes at 3 years to show maternal

Table 5. Relationship Between Mean Cortical FA at TEA, Maternal Sensitivity, and Language

	Bayley-III Language Composite Scores at 3 Years, *n* = 111 (20 Twins Included)		
Predictors	β	95% CI	*p*
Small for Gestational Age	0.16	−0.03 to 0.35	.09
Postnatal Infection	−0.29	−0.45 to −0.13	<.001
Postmenstrual Age at Scan	−0.04	−0.23 to 0.15	.66
White Matter Injury Volume	−0.08	−0.42 to 0.25	.62
TEA Cortical FA	−0.89	−1.95 to 0.16	.10
Marital Status	0.04	−0.13 to 0.21	.64
Mother's Level of Education	0.23	0.08 to 0.39	.004
Maternal Sensitivity	−1.28	−2.70 to 0.15	.08
Maternal Sensitivity × FA	1.85	0.09 to 3.61	.04

FA, fractional anisotropy; TEA, term-equivalent age.

Table 6. Relationship Between Mean Cortical FA at TEA, Maternal Sensitivity, and Cognition, Accounting for Invasive Procedures

	Bayley-III Cognitive Composite Scores at 3 Years, *n* = 113 (20 Twins Included)		
Predictors	β	95% CI	*p*
Small for Gestational Age	0.28	0.12 to 0.44	<.001
Postnatal Infection	−0.04	−0.25 to 0.17	.71
Number of Invasive Procedures	0.001	−0.27 to 0.27	.99
Days of Mechanical Ventilation	−0.16	−0.42 to 0.10	.23
Morphine Exposure	−0.04	−0.14 to 0.07	.49
Postmenstrual Age at Scan	0.16	−0.01 to 0.32	.06
White Matter Injury Volume	−0.06	−0.18 to 0.06	.32
TEA Cortical FA	−1.05	−2.20 to 0.11	.08
Marital Status	0.01	−0.12 to 0.15	.83
Mother's Level of Education	0.07	−0.08 to 0.21	.34
Maternal Sensitivity	−1.24	−2.79 to 0.31	.12
Maternal Sensitivity × FA	1.90	−0.001 to 3.82	.05

FA, fractional anisotropy; TEA, term-equivalent age.

Table 7. Relationship Between Mean Cortical FA at TEA, Maternal Sensitivity, and Language, Accounting for Invasive Procedures

	Bayley-III Language Composite Scores at 3 Years, n = 98 (18 Twins Included)		
Predictors	β	95% CI	p
Small for Gestational Age	0.20	0.01 to 0.39	.04
Postnatal Infection	−0.05	−0.22 to 0.13	.61
Number of Invasive Procedures	−0.18	−0.47 to 0.11	.22
Days of Mechanical Ventilation	−0.19	−0.48 to 0.11	.22
Morphine Exposure	0.03	−0.08 to 0.15	.54
Postmenstrual Age at Scan	−0.12	−0.26 to 0.03	.11
White Matter Injury Volume	0.13	−0.12 to 0.37	.32
TEA Cortical FA	−0.81	−1.81 to 0.20	.12
Marital Status	−0.03	−0.16 to 0.10	.64
Mother's Level of Education	0.13	−0.01 to 0.27	.07
Maternal Sensitivity	−1.11	−2.42 to 0.20	.10
Maternal Sensitivity × FA	1.64	0.03 to 3.25	.05

FA, fractional anisotropy; TEA, term-equivalent age.

Table 9. Relationship Between Mean Cortical FA at TEA, Maternal Sensitivity, and Language, Accounting for Additional Neonatal Factors and Ethnicity

	Bayley-III Language Composite Scores at 3 Years, n = 91 (13 Twins Included)		
Predictors	β	95% CI	p
Small for Gestational Age	0.17	−0.03 to 0.37	.09
Postnatal Infection	−0.28	−0.50 to −0.06	.01
Necrotizing Enterocolitis	−0.04	−0.24 to 0.16	.70
Retinopathy of Prematurity	−0.14	−0.38 to 0.10	.25
Postmenstrual Age at Scan	−0.05	−0.27 to 0.17	.67
White Matter Injury Volume	−0.09	−0.42 to 0.23	.57
TEA Cortical FA	−1.08	−2.19 to 0.03	.06
Marital Status	0.001	−0.18 to 0.18	.99
Mother's Level of Education	0.23	0.06 to 0.40	.01
Maternal Ethnicity	0.21	−0.06 to 0.47	.13
Maternal Sensitivity	−1.60	−3.13 to −0.07	.04
Maternal Sensitivity × FA	2.21	0.34 to 4.08	.02

FA, fractional anisotropy; TEA, term-equivalent age.

moderation of outcomes. Indeed, using the fetal ovine cortex, Dean *et al.* (62) demonstrated progressive developmental decrease in cortical FA, which became disrupted 4 weeks after preterm ischemia during the late gestational period as a direct result of the reduced elaboration of basal dendritic arbors of pyramidal neurons.

As hypothesized, we found that children with the lowest cognitive and language outcomes had greater cortical dysmaturation (higher FA values on the term MRI scan) and lower maternal sensitivity at 3 years. Children with the highest cognitive and language outcomes also had higher FA values at term and greater maternal sensitivity at 3 years. Cortical FA in the preterm brain demonstrates a biphasic pattern with cortical maturation. Prior to 38 weeks PMA, FA typically demonstrates a steep decrease, consistent with the disappearance of radial glial fibers and neuronal/glial proliferation, dendritic arborization, and synapse formation (31–34). However, following 38 weeks PMA, FA increases in cortical gray matter with increasing cellular and organelle density (35,36). Therefore, dependent on their PMA, relatively higher values of FA at their term scan could demonstrate cortical dysmaturation or greater cortical maturation. Maternal sensitivity may moderate cortical dysmaturation, given that higher cognitive and language outcome scores were observed among the children whose mothers demonstrated greater maternal sensitivity at 3 years.

Table 8. Relationship Between Mean Cortical FA at TEA, Maternal Sensitivity, and Cognition, Accounting for Additional Neonatal Factors and Ethnicity

	Bayley-III Cognitive Composite Scores at 3 Years, n = 106 (15 Twins Included)		
Predictors	β	95% CI	p
Small for Gestational Age	0.24	0.06 to 0.41	.01
Postnatal Infection	−0.21	−0.46 to 0.03	.09
Necrotizing Enterocolitis	−0.12	−0.32 to 0.08	.25
Retinopathy of Prematurity	0.02	−0.23 to 0.27	.88
Postmenstrual Age at Scan	0.20	−0.02 to 0.41	.07
White Matter Injury Volume	−0.13	−0.31 to 0.05	.16
TEA Cortical FA	−1.27	−2.63 to 0.09	.07
Marital Status	0.12	−0.05 to 0.28	.17
Mother's Level of Education	0.12	−0.06 to 0.32	.19
Maternal Ethnicity	−0.01	−0.23 to 0.20	.90
Maternal Sensitivity	−1.55	−3.43 to 0.34	.11
Maternal Sensitivity × FA	2.31	−0.02 to 4.64	.05

FA, fractional anisotropy; TEA, term-equivalent age.

Other studies have also reported a positive association between sensitive maternal interactions and improved cognitive outcomes. Previously, it was reported that mothers' interactions with a combined group of preterm and full-term children predicted 17% of the variance in child cognitive scores and 22% of the variance in receptive communication skills at 18 months after accounting for prematurity, sex, child behavior, paternal behavior, and family SES (44). Moreover, positive mother-infant relationships predicted approximately a 5-point increase in IQ in adults born very preterm after accounting for confounding factors such as SES (65). However, interacting with infants born very preterm poses different challenges for mothers compared with full-term mother-infant dyads. Infants born preterm are less responsive, vocalize less, and avert their gaze more, and generally the interaction is less positive (14,66–70). Even 3 years after their birth, mothers rated their preterm-born child as being less confident, relaxed, quiet, calm, generous, and satisfied than their term-born siblings (71). Furthermore, children with poorer cognitive or language function may present more of a challenge for maternal engagement. Despite these differences in child behavior, mothers of children born preterm have been found to be equally as sensitive and responsive toward their children as mothers of children born full term (42). However, children born very preterm are more sensitive to environmental context, including their interactions with their parents, than their term-born peers (15,53,72,73).

In this study, mothers in the higher sensitivity group had more education. Recently, we showed that the association of brain injury with poorer cognition was attenuated in children born to mothers with higher education (18). Mothers with greater social advantage may themselves have more social support, thereby providing more opportunities for sensitive interactions with their children (74). Moreover, mothers of children with greater brain maturation and cognitive and language outcomes may be less stressed and thus better able to engage and sensitively interact with their children. Although we did not find differences in maternal sensitivity between 18 months and 3 years, future research would benefit from assessing maternal sensitivity at multiple time points from birth to further examine critical windows when sensitive maternal interaction can best moderate brain and neurodevelopmental trajectories. In support of this study, parenting behaviors assessed in the NICU have been related to later parenting interaction quality (75). This suggests that maternal sensitivity may modulate long-term outcomes in infants born very preterm. These data also highlight the importance of assessing maternal involvement both in the NICU and on follow-up and providing intervention for mothers showing difficulties.

Given the important role of parent-child interaction for promoting positive outcomes (14), many parent-based interventions have been developed with the goals of improving parent-infant attachment, reducing parent stress, and improving parent efficacy in supporting their infant in the NICU and after discharge. Two randomized controlled trials of parent-based interventions have demonstrated increased brain maturation in infants belonging to the intervention group relative to standard care. Infants of mothers in a combined NICU and home-based intervention (Mother-Infant Transaction Program) had greater white matter maturation at term and better communicative and symbolic behavior at 6 months than infants of mothers randomized to standard care (16,19). Similarly, infants of mothers enrolled in a NICU-based intervention (Family Nurture Intervention) that promotes emotional connection had increased regional independence of frontopolar electrocortical activity at TEA and higher Bayley-III Cognitive and Language scores at 18 months relative to children whose mothers were randomized to standard care (76,77). Therefore, parent-based early interventions in the NICU resulted in improved cortical maturation and cognitive and language outcomes for children born very preterm. However, a recent meta-analysis of early developmental interventions for preterm infants revealed that once these children reached school age, a substantial benefit was no longer evident (78). There is increasing evidence that the needs of the individual family need to be assessed and addressed. Stage-specific, individualized, and targeted approaches may be more beneficial to child outcomes (79).

Our cognitive and language outcomes were quite high, likely because the Bayley-III yields higher scores than previous versions of this scale (80–82). It is also important to note that the majority of mothers in this sample were university educated. Therefore, our results likely underestimate the role of mother involvement for very preterm children with more social disadvantage.

There were several limitations to our study. Medical and nursing chart review was conducted from birth to NICU discharge or TEA, whichever came first; therefore, clinical events past term age were not considered. We were also unable to compare our findings with a full-term control group with birth MRI and follow-up data. Further, by averaging FA values from bilateral regions of interest to avoid multiple comparisons, we were not able to detect possibly important lateralized or regional interactions between FA, maternal sensitivity, and outcomes. Results by Vanes *et al.* (27) were also not lateralized.

Future research should include whole-brain assessments of cortical microstructural development with more sophisticated diffusion models not available at the time this cohort was studied (36,83). Advances in MRI acquisition and analysis that allow for automatic segmentation and quantification of cortical FA in early life may refine our ability to detect relationships between FA, maternal sensitivity, and neurodevelopmental outcomes.

Conclusions

Maternal sensitivity is an important determinant of cognitive and language development in children born very preterm at 3 years of age. Promoting greater maternal sensitivity may offer an opportunity to optimize neurodevelopmental outcomes in these children, particularly among mothers with less education. Infants who are born SGA or have postnatal infections or brain injuries may benefit from early and targeted interventions. The results from this study support continued development and facilitation of parent-directed interventions to improve parent sensitivity to help children born very preterm reach their full potential.

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All authors had full access to the full data in the study and accept responsibility to submit for publication. JVM conducted the formal analysis, assisted with the investigation and visualization, wrote the original draft, and contributed to writing, reviewing, and editing. VC assisted with data curation, investigation, writing, reviewing, and editing. AS assisted with the investigation, resources, writing, reviewing, and editing. SPM and REG contributed to conceptualization, funding acquisition, methodology, supervision, writing, reviewing, and editing. All authors had access to and verified the underlying data. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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REFERENCES

1. Doyle LW, Roberts G, Anderson PJ, Victorian Infant Collaborative Study Group (2011): Changing long-term outcomes for infants 500–999 g birth weight in Victoria, 1979-2005. Arch Dis Child Fetal Neonatal Ed 96:F443–F447.
2. Johnson S, Hennessy E, Smith R, Trikic R, Wolke D, Marlow N (2009): Academic attainment and special educational needs in extremely preterm children at 11 years of age: The EPICure study. Arch Dis Child Fetal Neonatal Ed 94:F283–F289.
3. Larroque B, Delobel M, Arnaud C, Marchand L, Groupe Epipage (2008): Devenir à 5 et 8 ans des enfants grands prématurés dans l'étude Épipage: développement cognitif, troubles du comportement et scolarisation [Outcome at 5 and 8 years of children born very preterm]. Arch Pediatr 15:589–591.
4. Synnes AR, Anson S, Arkesteijn A, Butt A, Grunau RE, Rogers M, Whitfield MF (2010): School entry age outcomes for infants with birth weight ≤ 800 grams. J Pediatr 157:989–994.e1.
5. Moore T, Hennessy EM, Myles J, Johnson SJ, Draper ES, Costeloe KL, Marlow N (2012): Neurological and developmental outcome in extremely preterm children born in England in 1995 and 2006: The EPICure studies. BMJ 345:e7961.
6. Ball G, Aljabar P, Nongena P, Kennea N, Gonzalez-Cinca N, Falconer S, *et al.* (2017): Multimodal image analysis of clinical influences on preterm brain development. Ann Neurol 82:233–246.
7. Vinall J, Miller SP, Bjornson BH, Fitzpatrick KPV, Poskitt KJ, Brant R, *et al.* (2014): Invasive procedures in preterm children: Brain and cognitive development at school age. Pediatrics 133:412–421.
8. Ranger M, Zwicker JG, Chau CMY, Park MTM, Chakravarthy MM, Poskitt K, *et al.* (2015): Neonatal pain and infection relate to smaller cerebellum in very preterm children at school age. J Pediatr 167:292–298.e1.
9. Chau CMY, Ranger M, Bichin M, Park MTM, Amaral RSC, Chakravarty M, *et al.* (2019): Hippocampus, amygdala, and thalamus volumes in very preterm children at 8 years: Neonatal pain and genetic variation. Front Behav Neurosci 13:51.
10. Smith GC, Gutovich J, Smyser C, Pineda R, Newnham C, Tjoeng TH, *et al.* (2011): Neonatal intensive care unit stress is associated with brain development in preterm infants. Ann Neurol 70:541–549.
11. Grunau RE, Whitfield MF, Petrie-Thomas J, Synnes AR, Cepeda IL, Keidar A, *et al.* (2009): Neonatal pain, parenting stress and interaction, in relation to cognitive and motor development at 8 and 18 months in preterm infants. Pain 143:138–146.
12. Treyvaud K, Doyle LW, Lee KJ, Ure A, Inder TE, Hunt RW, Anderson PJ (2016): Parenting behavior at 2 years predicts school-age performance at 7 years in very preterm children. J Child Psychol Psychiatry 57:814–821.
13. Brummelte S, Grunau RE, Synnes AR, Whitfield MF, Petrie-Thomas J (2011): Declining cognitive development from 8 to 18 months in preterm children predicts persisting higher parenting stress. Early Hum Dev 87:273–280.
14. Miles MS, Holditch-Davis D (1997): Parenting the prematurely born child: Pathways of influence. Semin Perinatol 21:254–266.
15. Tu MT, Grunau RE, Petrie-Thomas J, Haley DW, Weinberg J, Whitfield MF (2007): Maternal stress and behavior modulate relationships between neonatal stress, attention, and basal cortisol at 8 months in preterm infants. Dev Psychobiol 49:150–164.
16. Milgrom J, Newnham C, Martin PR, Anderson PJ, Doyle LW, Hunt RW, *et al.* (2013): Early communication in preterm infants following intervention in the NICU. Early Hum Dev 89:755–762.
17. Rahkonen P, Heinonen K, Pesonen AK, Lano A, Autti T, Puosi R, *et al.* (2014): Mother-child interaction is associated with neurocognitive outcome in extremely low gestational age children. Scand J Psychol 55:311–318.
18. Benavente-Fernández I, Synnes A, Grunau RE, Chau V, Ramraj C, Glass T, *et al.* (2019): Association of socioeconomic status and brain injury with neurodevelopmental outcomes of very preterm children. JAMA Netw Open 2:e192914.
19. Milgrom J, Newnham C, Anderson PJ, Doyle LW, Gemmill AW, Lee K, *et al.* (2010): Early sensitivity training for parents of preterm infants: Impact on the developing brain. Pediatr Res 67:330–335.
20. Dimitrova R, Pietsch M, Christiaens D, Ciarrusta J, Wolfers T, Batalle D, *et al.* (2020): Heterogeneity in brain microstructural development following preterm birth. Cereb Cortex 30:4800–4810.
21. Anderson PJ, Treyvaud K, Neil JJ, Cheong JLY, Hunt RW, Thompson DK, *et al.* (2017): Associations of newborn brain magnetic resonance imaging with long-term neurodevelopmental impairments in very preterm children. J Pediatr 187:58–65.e1.
22. Karolis VR, Froudist-Walsh S, Brittain PJ, Kroll J, Ball G, Edwards AD, *et al.* (2016): Reinforcement of the brain's rich-club architecture following early neurodevelopmental disruption caused by very preterm birth. Cereb Cortex 26:1322–1335.
23. Keunen K, Išgum I, van Kooij BJM, Anbeek P, van Haastert IC, Koopman-Esseboom C, *et al.* (2016): Brain volumes at term-equivalent age in preterm infants: Imaging biomarkers for neurodevelopmental outcome through early school age. J Pediatr 172:88–95.
24. Girault JB, Munsell BC, Puechmaille D, Goldman BD, Prieto JC, Styner M, Gilmore JH (2019): White matter connectomes at birth accurately predict cognitive abilities at age 2. Neuroimage 192:145–155.
25. Duerden EG, Foong J, Chau V, Branson H, Poskitt KJ, Grunau RE, *et al.* (2015): Tract-based spatial statistics in preterm-born neonates predicts cognitive and motor outcomes at 18 months. AJNR Am J Neuroradiol 36:1565–1571.
26. Malavolti AM, Chau V, Brown-Lum M, Poskitt KJ, Brant R, Synnes A, *et al.* (2017): Association between corpus callosum development on magnetic resonance imaging and diffusion tensor imaging, and neurodevelopmental outcome in neonates born very preterm. Dev Med Child Neurol 59:433–440.
27. Vanes LD, Hadaya L, Kanel D, Falconer S, Ball G, Batalle D, *et al.* (2021): Associations between neonatal brain structure, the home environment, and childhood outcomes following very preterm birth. Biol Psychiatry Glob Open Sci 1:146–155.
28. Mukherjee P, Miller JH, Shimony JS, Philip JV, Nehra D, Snyder AZ, *et al.* (2002): Diffusion-tensor MR imaging of gray and white matter development during normal human brain maturation. AJNR Am J Neuroradiol 23:1445–1456.
29. Bonifacio SL, Glass HC, Chau V, Berman JI, Xu D, Brant R, *et al.* (2010): Extreme premature birth is not associated with impaired development of brain microstructure. J Pediatr 157:726–732.e1.
30. Drobyshevsky A, Song SK, Gamkrelidze G, Wyrwicz AM, Derrick M, Meng F, *et al.* (2005): Developmental changes in diffusion anisotropy coincide with immature oligodendrocyte progression and maturation of compound action potential. J Neurosci 25:5988–5997.
31. McKinstry RC, Mathur A, Miller JH, Ozcan A, Snyder AZ, Schefft GL, *et al.* (2002): Radial organization of developing preterm human cerebral cortex revealed by non-invasive water diffusion anisotropy MRI. Cereb Cortex 12:1237–1243.
32. Marín-Padilla M (1992): Ontogenesis of the pyramidal cell of the mammalian neocortex and developmental cytoarchitectonics: A unifying theory. J Comp Neurol 321:223–240.
33. Mrzljak L, Uylings HB, Kostovic I, Van Eden CG (1988): Prenatal development of neurons in the human prefrontal cortex: I. A qualitative Golgi study. J Comp Neurol 271:355–386.
34. Rakic P (2003): Developmental and evolutionary adaptations of cortical radial glia. Cereb Cortex 13:541–549.
35. Batalle D, O'Muircheartaigh J, Makropoulos A, Kelly CJ, Dimitrova R, Hughes EJ, *et al.* (2019): Different patterns of cortical maturation before and after 38 weeks gestational age demonstrated by diffusion MRI in vivo. Neuroimage 185:764–775.

36. Ouyang M, Jeon T, Sotiras A, Peng Q, Mishra V, Halovanic C, *et al.* (2019): Differential cortical microstructural maturation in the preterm human brain with diffusion kurtosis and tensor imaging. Proc Natl Acad Sci U S A 116:4681–4688.
37. Ball G, Pazderova L, Chew A, Tusor N, Merchant N, Arichi T, *et al.* (2015): Thalamocortical connectivity predicts cognition in children born preterm. Cereb Cortex 25:4310–4318.
38. Ball G, Srinivasan L, Aljabar P, Counsell SJ, Durighel G, Hajnal JV, *et al.* (2013): Development of cortical microstructure in the preterm human brain. Proc Natl Acad Sci U S A 110:9541–9546.
39. Rathbone R, Counsell SJ, Kapellou O, Dyet L, Kennea N, Hajnal J, *et al.* (2011): Perinatal cortical growth and childhood neurocognitive abilities. Neurology 77:1510–1517.
40. Kersbergen KJ, Leroy F, Išgum I, Groenendaal F, de Vries LS, Claessens NHP, *et al.* (2016): Relation between clinical risk factors, early cortical changes, and neurodevelopmental outcome in preterm infants. Neuroimage 142:301–310.
41. Monson BB, Anderson PJ, Matthews LG, Neil JJ, Kapur K, Cheong JLY, *et al.* (2016): Examination of the pattern of growth of cerebral tissue volumes from hospital discharge to early childhood in very preterm infants. JAMA Pediatr 170:772–779.
42. Bilgin A, Wolke D (2015): Maternal sensitivity in parenting preterm children: A meta-analysis. Pediatrics 136:e177–e193.
43. Beckwith L, Rodning C (1996): Dyadic processes between mothers and preterm infants: Development at ages 2 to 5 years. Infant Ment Health J 17:322–333.
44. Magill-Evans J, Harrison MJ (1999): Parent-child interactions and development of toddlers born preterm. West J Nurs Res 21:292–307; discussion 308–212.
45. Myers MM, Grieve PG, Stark RI, Isler JR, Hofer MA, Yang J, *et al.* (2015): Family Nurture Intervention in preterm infants alters frontal cortical functional connectivity assessed by EEG coherence. Acta Paediatr 104:670–677.
46. World Health Organization: Preterm birth. Available at: https://www.who.int/news-room/fact-sheets/detail/preterm-birth. Accessed January 13, 2022.
47. Guo T, Duerden EG, Adams E, Chau V, Branson HM, Chakravarty MM, *et al.* (2017): Quantitative assessment of white matter injury in preterm neonates: Association with outcomes. Neurology 88:614–622.
48. Vinall J, Grunau RE, Brant R, Chau V, Poskitt KJ, Synnes AR, Miller SP (2013): Slower postnatal growth is associated with delayed cerebral cortical maturation in preterm newborns. Sci Transl Med 5:168ra8.
49. Böhm B, Katz-Salamon M, , Karolinska Institute, Smedler AC, Lagercrantz H, Forssberg H (2002): Developmental risks and protective factors for influencing cognitive outcome at 5 1/2 years of age in very-low-birthweight children. Dev Med Child Neurol 44:508–516.
50. Resnick MB, Stralka K, Carter RL, Ariet M, Bucciarelli RL, Furlough RR, *et al.* (1990): Effects of birth weight and sociodemographic variables on mental development of neonatal intensive care unit survivors. Am J Obstet Gynecol 162:374–378.
51. Saunders H, Kraus A, Barone L, Biringen Z (2015): Emotional availability: Theory, research, and intervention. Front Psychol 6:1069.
52. Biringen Z, Derscheid D, Vliegen N, Closson L, Easterbrooks MA (2014): Emotional availability (EA): Theoretical background, empirical research using the EA Scales, and clinical applications. Dev Rev 34:114–167.
53. Vinall J, Miller SP, Synnes AR, Grunau RE (2013): Parent behaviors moderate the relationship between neonatal pain and internalizing behaviors at 18 months corrected age in children born very prematurely. Pain 154:1831–1839.
54. Bayley N (2006): Bayley Scales of Infant Development, Third Edition San Antonio, TX: Harcourt.
55. Sacchi C, Marino C, Nosarti C, Vieno A, Visentin S, Simonelli A (2020): Association of intrauterine growth restriction and small for gestational age status with childhood cognitive outcomes: A systematic review and meta-analysis. JAMA Pediatr 174:772–781.
56. Stoll BJ, Hansen NI, Adams-Chapman I, Fanaroff AA, Hintz SR, Vohr B, *et al.* (2004): Neurodevelopmental and growth impairment among extremely low-birth-weight infants with neonatal infection. JAMA 292:2357–2365.
57. Padilla N, Falcón C, Sanz-Cortés M, Figueras F, Bargallo N, Crispi F, *et al.* (2011): Differential effects of intrauterine growth restriction on brain structure and development in preterm infants: A magnetic resonance imaging study. Brain Res 1382:98–108.
58. Schneider J, Miller SP (2019): Preterm brain Injury: White matter injury. Handb Clin Neurol 162:155–172.
59. Rand KM, Austin NC, Inder TE, Bora S, Woodward LJ (2016): Neonatal infection and later neurodevelopmental risk in the very preterm infant. J Pediatr 170:97–104.
60. Alshaikh B, Yusuf K, Sauve R (2013): Neurodevelopmental outcomes of very low birth weight infants with neonatal sepsis: Systematic review and meta-analysis. J Perinatol 33:558–564.
61. Hart B, Risley TR (1995): Meaningful Differences in the Everyday Experience of Young American Children. Baltimore, MD: Paul H. Brookes Publishing.
62. Dean JM, McClendon E, Hansen K, Azimi-Zonooz A, Chen K, Riddle A, *et al.* (2013): Prenatal cerebral ischemia disrupts MRI-defined cortical microstructure through disturbances in neuronal arborization. Sci Transl Med 5:168ra7.
63. Deipolyi AR, Mukherjee P, Gill K, Henry RG, Partridge SC, Veeraraghavan S, *et al.* (2005): Comparing microstructural and macrostructural development of the cerebral cortex in premature newborns: Diffusion tensor imaging versus cortical gyration. Neuroimage 27:579–586.
64. Schneider J, Kober T, Bickle Graz M, Meuli R, Hüppi PS, Hagmann P, Truttmann AC (2016): Evolution of T1 relaxation, ADC, and fractional anisotropy during early brain maturation: A serial imaging study on preterm infants. AJNR Am J Neuroradiol 37:155–162.
65. Breeman LD, Jaekel J, Baumann N, Bartmann P, Wolke D (2017): Neonatal predictors of cognitive ability in adults born very preterm: A prospective cohort study. Dev Med Child Neurol 59:477–483.
66. Field TM (1977): Effects of early separation, interactive deficits, and experimental manipulations on infant-mother face-to-face interaction. Child Dev 48:763–771.
67. Bakeman R, Brown JV (1980): Early interaction: Consequences for social and mental development at three years. Child Dev 51:437–447.
68. Crnic KA, Ragozin AS, Greenberg MT, Robinson NM, Basham RB (1983): Social interaction and developmental competence of preterm and full-term infants during the first year of life. Child Dev 54:1199–1210.
69. Alfasi G, Schwartz FA, Brake SC, Fifer WP, Fleischman AR, Hofer MA (1985): Mother-infant feeding interactions in preterm and full-term infants. Infant Behav Dev 8:167–180.
70. Segal LB, Oster H, Cohen M, Caspi B, Myers M, Brown D (1995): Smiling and fussing in seven-month-old preterm and full-term black infants in the still-face situation. Child Dev 66:1829–1843.
71. Bidder RT, Crowe EA, Gray OP (1974): Mothers' attitudes to preterm infants. Arch Dis Child 49:766–770.
72. Crnic KA, Greenberg MT (1987): Transactional relationships between perceived family style, risk status, and mother-child interactions in two-year-olds. J Pediatr Psychol 12:343–362.
73. Brummelte S, Chau CMY, Cepeda IL, Degenhardt A, Weinberg J, Synnes AR, Grunau RE (2015): Cortisol levels in former preterm children at school age are predicted by neonatal procedural pain-related stress. Psychoneuroendocrinology 51:151–163.
74. Zelkowitz P, Papageorgiou A, Bardin C, Wang T (2009): Persistent maternal anxiety affects the interaction between mothers and their very low birthweight children at 24 months [published correction appears in Early Hum Dev 2009; 85:337]. Early Hum Dev 85:51–358.
75. Gerstein ED, Poehlmann-Tynan J, Clark R (2015): Mother-child interactions in the NICU: Relevance and implications for later parenting. J Pediatr Psychol 40:33–44.
76. Welch MG, Stark RI, Grieve PG, Ludwig RJ, Isler JR, Barone JL, Myers MM (2017): Family nurture intervention in preterm infants increases early development of cortical activity and independence of regional power trajectories. Acta Paediatr 106:1952–1960.

77. Welch MG, Firestein MR, Austin J, Hane AA, Stark RI, Hofer MA, *et al.* (2015): Family Nurture Intervention in the Neonatal Intensive Care Unit improves social-relatedness, attention, and neurodevelopment of preterm infants at 18 months in a randomized controlled trial. J Child Psychol Psychiatry 56:1202–1211.
78. Spittle A, Orton J, Anderson PJ, Boyd R, Doyle LW (2015): Early developmental intervention programmes provided post hospital discharge to prevent motor and cognitive impairment in preterm infants. Cochrane Database Syst Rev 2015:CD005495.
79. The NICHD Early Child Care Research Network, editor (2005): Child Care and Child Development: Results from the NICHD Study of Early Child Care and Youth Development. New York: The Guilford Press.
80. Johnson S, Moore T, Marlow N (2014): Using the Bayley-III to assess neurodevelopmental delay: Which cut-off should be used? Pediatr Res 75:670–674.
81. Vohr BR, Stephens BE, Higgins RD, Bann CM, Hintz SR, Das A, *et al.* (2012): Are outcomes of extremely preterm infants improving? Impact of Bayley assessment on outcomes. J Pediatr 161:222–228.e3.
82. Aylward GP (2013): Continuing issues with the Bayley-III: Where to go from here. J Dev Behav Pediatr 34:697–701.
83. Eaton-Rosen Z, Melbourne A, Orasanu E, Cardoso MJ, Modat M, Bainbridge A, *et al.* (2015): Longitudinal measurement of the developing grey matter in preterm subjects using multi-modal MRI. Neuroimage 111:580–589.