Neurodevelopmental Correlates of Brain Magnetic Resonance Imaging Abnormalities in Extremely Low-birth-weight Infants

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Objective To evaluate the relationship between impaired brain growth and structural brain abnormalities at term-equivalent age (TEA) and neurodevelopment in extremely low-birth-weight (ELBW) infants over the first 2 years.

Methods ELBW infants born from 2009 through 2018 and undergoing brain magnetic resonance imaging (MRI) at TEA were enrolled in this retrospective cohort study. MRI scans were reviewed using a validated quali-quantitative score, including several white and gray matter items. Neurodevelopment was assessed at 6, 12, 18, and 24 months using the Griffiths scales. The independent associations between MRI subscores and the trajectories of general and specific neurodevelopmental functions were analyzed by generalized estimating equations.

Results One hundred-nine ELBW infants were included. White matter volume reduction and delayed myelination were associated with worse general development ($b = -2.33$, $P = .040$; $b = -6.88$, $P = .049$ respectively), social skills ($b = -3.13$, $P = .019$; $b = -4.79$, $P = .049$), and eye-hand coordination ($b = -3.48$, $P = .009$; $b = -7.21$, $P = .045$). Cystic white matter lesions were associated with poorer motor outcomes ($b = -4.99$, $P = .027$), while white matter signal abnormalities and corpus callosum thinning were associated with worse nonverbal cognitive performances ($b = -6.42$, $P = .010$; $b = -6.72$, $P = .021$, respectively). Deep gray matter volume reduction correlated with worse developmental trajectories.

Conclusions Distinctive MRI abnormalities correlate with specific later developmental skills. This finding may suggest that TEA brain MRI may assist with neurodevelopmental prediction, counseling of families, and development of targeted supportive interventions to improve neurodevelopment in ELBW neonates. *(J Pediatr 2023;262:113646)*.

Despite recent improvements occurred in neonatal care, extremely low-birth-weight (ELBW) infants are at the highest risk of adverse neurodevelopment.[1] Brain magnetic resonance imaging (MRI) at term-equivalent age (TEA-MRI) allows identification of typical prematurity-related abnormalities, such as reduced brain volumes, altered white matter (WM) microstructure, and abnormal connectivity.[2,3] Following the increasing use of brain TEA-MRI in ELBW preterm neonates, several scoring systems have been proposed to assess brain metrics and the extent of gray matter and WM abnormalities.[4-7]

Brain development is characterized by an intrinsic neuroplasticity, so that timely establishment of supportive interventions can improve neurocognitive outcomes by counteracting the anatomical and functional impairments associated with prematurity. Knowledge of neurodevelopmental correlates for brain TEA-MRI abnormalities may aid prediction of which functional areas could be particularly affected to help optimize targeted habilitative approaches for at-risk preterm infants.[8] However, current evidence on the structure-function relationship between TEA-MRI findings and neurodevelopment over the first years after birth has yielded controversial results. In particular, while some authors observed significant associations between specific

BPD	Bronchopulmonary dysplasia	IUGR	Intrauterine growth restriction
CGM	Cortical gray matter	LOC	Locomotor
CP	Cerebral palsy	MRI	Magnetic resonance imaging
DGM	Deep gray matter	PCA	Postconceptional age
EC	Eye-hand coordination	PER	Nonverbal cognitive performance
ELBW	Extremely low-birth-weight		
GA	Gestational age	PS	Personal-social skill
GBAS	Global brain abnormality score	thk	Sslice thickness
GEE	Generalized estimating equation	TE	Echo time
GMDS-R	Griffiths Mental Development Scales 0–2 years	TEA-MRI	Magnetic resonance imaging at term-equivalent age
GQ	General developmental quotient	TR	Repetition time
HS	Hearing-speech	WM	White matter

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https://doi.org/10.1016/j.jpeds.2023.113646

neuroradiological abnormalities and neurodevelopmental outcomes, others failed to confirm similar associations on multivariable assessments,[9,10] and conflicting data have also been reported on the negative predictive value of TEA-MRI for early neurodevelopment.[11,12] In addition, studies investigating the relationship between TEA-MRI findings and neurodevelopment over the first years have mainly focused on specific time points.[9-12] However, as argued by a recent study,[13] investigating associations between TEA-MRI and neurodevelopmental trajectories instead of specific time points allows for understanding stability across development, guiding outcome prediction and family counseling, and facilitating early individualized interventions.

This study thus aimed to evaluate the relationship between impaired brain growth and structural abnormalities at TEA-MRI and the trajectories of general and specific neurodevelopmental functions in ELBW infants over the first 2 years.

Methods

Study Sample

Preterm infants with a birth weight <1000g admitted to the Neonatal Intensive Care Unit of IRCCS AOU Bologna (Italy) between January 1, 2009, and December 31, 2018, were assessed for eligibility. Congenital malformations, genetic syndromes, inherited metabolic diseases, and unavailability of brain TEA-MRI scans were exclusion criteria. This study was conducted in accordance with principles and standards of the Helsinki Declaration. Informed consent to participate was obtained from the infants' parents. The local independent ethics committee (Comitato Etico Area Vasta Emilia Centro) approved the study protocol (EM1055-2020_230/2019/Oss/AOUBo).

Maternal and neonatal charts were reviewed for the following data: maternal education (primary/lower secondary school, upper secondary school, university/master's degree), gestational age (GA), birth weight, sex, intrauterine growth restriction (IUGR) resulting in a birth weight <10th percentile for GA, culture-proven sepsis, necrotizing enterocolitis ≥ Bell stage II, bronchopulmonary dysplasia (BPD, positive airway pressure and/or supplemental oxygen at 36 weeks' postconceptional age [PCA]), retinopathy of prematurity, and postnatal steroid administration.

Brain MRI at TEA

TEA-MRI scans were performed on a 1.5 T system (Ingenia, Philips Healthcare) between 37 and 43 weeks' PCA. The scanning protocol included sagittal 3-dimensional T1-weighted (repetition time [TR] = 21 ms, echo time [TE] = 4.79 ms, voxel:1x1x1mm), axial and coronal T2-weighted (TR = 8000 ms, TE = 200 ms, slice thickness [thk] = 3 mm), axial inversion recovery T1-weighted (TR = 3420 ms, TE = 17 ms, slice thk = 3 mm), and axial 3-dimensional susceptibility-weighted imaging sequences (TR = 58 ms, TE = 52 ms, slice thk = 2 mm). Brain metrics were obtained using a Carestream PACS workstation.

All the scans were retrospectively reviewed by 2 masked pediatric neuroradiologists using the Kidokoro scoring system.[6] WM, cortical gray matter (CGM), deep gray matter (DGM), and the cerebellum were evaluated for signal abnormalities and/or abnormal metrics. In order to address potential growth effects, biparietal width, DGM areas, and transcerebellar diameters were corrected for PCA.[6] For each scan, specific WM, CGM, DGM, and cerebellum subscores were obtained. The global brain abnormality score (GBAS), calculated as the sum of the subscores, was classified as normal (0-3) or mildly (4-7), moderately (8-11), or severely abnormal (≥12).[6]

The intraclass correlation coefficients between the 2 neuroradiologists, calculated on all scans, were 0.937 (95% CI = 0.905-0.958) for WM items, 0.866 (95% CI = 0.808-0.907) for CGM items, 0.840 (95% CI = 0.771-0.889) for DGM items, 0.936 (95% CI = 0.907-0.955) for cerebellum items, and 0.955 (95% CI = 0.934-0.969) for GBAS. Discrepancies were resolved by consensus reading.

Neurodevelopment Assessment

After discharge, infants' development was evaluated at 6, 12, 18, and 24 months corrected age using the Griffiths Mental Development Scales 0–2 years (GMDS-R).[14] These scales investigate 5 developmental domains (locomotor [LOC], personal-social skills [PS], hearing-speech [HS], eye-hand coordination [EC], and nonverbal cognitive performance [PER]), providing a general developmental quotient (GQ) and 5 subscale quotients. The subscale quotients and the resulting GQ were calculated using GA-adjusted standardized quotients for the English population,[14] since an Italian standardization for the GMDS-R is currently unavailable. According to the SD of GQ (mean = 100.5 [SD, 11.8]), psychomotor impairment was classified as moderate (GQ between −2 and −3; SD, 76.8–65.1) or severe (GQ ≤ −3; SD, ≤65). The assessments were performed individually by the same clinical developmental neuropsychologist, blind to MRI scores. Cerebral palsy (CP) was diagnosed by pediatric neurologists at 24 months corrected age.

Statistical Analysis

Numerical variables were summarized as mean ± SD or median (IQR) as appropriate; categorical variables were summarized as frequencies and percentages.

GQ and subscale quotients at 6, 12, 18, and 24 months were analyzed with generalized estimating equations (GEEs). This approach take all available data into account in an unbalanced design, leading to more efficient parameter estimates.

To select the TEA-MRI subscores that predicted psychomotor outcomes, the GEE models were built using the multivariable fractional polynomial approach, which constructs a transformation for each numerical covariate and terminates when no more significant covariates are excluded.[15] Factors influencing preterm infants' neurodevelopment (ie, maternal education, GA, gender, IUGR, sepsis, necrotizing enterocolitis, BPD, retinopathy of prematurity, postnatal steroids)

or psychomotor performances (ie, CP) were forced into the models. An interaction with time was included to test whether the patterns of outcome trajectories depended on the severity of TEA-MRI abnormalities. The standard errors of the regression coefficients were estimated with the heteroscedasticity-consistent method.[16] The stability of the models was confirmed after creating 200 multivariable fractional polynomial bootstrap replications and looking at the resulting inclusion fractions.[17] Multicollinearity issues were excluded by the variance inflation factor of each regression model (GQ: 1.89; LOC: 1.98; PS: 1.94; HS: 1.83; EC: 1.88; PER: 1.82). After excluding one infant at random from each multiple birth, results remained unchanged. A multilevel mixed-effects logistic regression analysis was also performed to assess the risk of missing follow-up visits according to relevant baseline characteristics.

Data were analyzed using Stata software v.17 (StataCorp. 2017. *Stata Statistical Software:Release 15*: StataCorp LP). Significance level was 0.05.

Results

A total of 109 preterm infants were included (**Figure 1** and **Table I**). The mean age at TEA-MRI was 41 ± 1.7 (range: 37-43) weeks' PCA. The median GBAS was 3 (IQR: 2-5); according to the GBAS, TEA-MRI was normal in 55 (50.5%) infants, mildly abnormal in 38 (34.9%), moderately abnormal in 8 (7.3%), and severely abnormal in 8 (7.3%) (**Table II**).

Neurodevelopmental follow-up data at 6, 12, 18, and 24 months were available for 101 (92.7%), 100 (91.8%), 92 (84.4%), and 79 (72.5%) infants, respectively (**Table III**). A multilevel mixed-effects logistic regression analysis was performed to assess the risk of missing a follow-up visit according to relevant clinical characteristics, none of which results were associated with higher drop-out odds

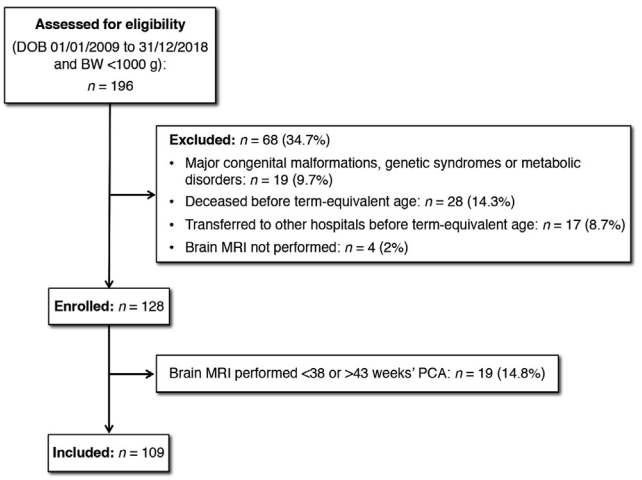

Figure 1. Flowchart of the study enrollment.

Table I. Demographic and antenatal, perinatal, and postnatal clinical characteristics of the study population

Characteristics	n = 109
Gestational age (weeks), mean ± SD	26.6 ± 2.0
Birth weight (g), mean ± SD	763 ± 141
Intrauterine growth restriction, n (%)	22 (20.2)
Antenatal steroids (complete course), n (%)	76 (69.7)
Caesarean section, n (%)	86 (78.9)
Apgar score at 5 min, median (IQR)	8 (7–9)
Male sex, n (%)	50 (45.9)
Multiple birth, n (%)	25 (22.9)
Intraventricular hemorrhage, n (%)	
Low grade (grade I-II)	22 (20.2)
High grade (grade III-IV)	13 (12.8)
Posthemorrhagic ventricular dilation requiring CSF drainage, n (%)	5 (4.6)
Sepsis, n (%)	26 (23.9)
Necrotizing enterocolitis (Bell stage ≥2), n (%)	17 (15.6)
Bronchopulmonary dysplasia at 36 weeks, n (%)	30 (27.5)
Postnatal steroids, n (%)	33 (30.3)
Retinopathy of prematurity, n (%)	
Mild (stage 1-2)	24 (22.0)
Moderate to severe (stage ≥3 or higher)	10 (9.2)
Maternal education, n (%)	
Primary or lower secondary	27 (24.8)
Upper secondary	53 (48.6)
University	29 (26.6)

CSF, cerebrospinal fluid.

(**Table IV**). The prevalence of moderate and severe psychomotor impairment was 4.6% (n = 5) and 3.7% (n = 4) at 6 months, 5.5% (n = 6) and 6.4% (n = 7) at 12 months, 12.8% (n = 14) and 14.8% (n = 16) at 18 months, and 6.4% (n = 7) and 13.8% (n = 15) at 24 months. Five (4.6%) infants were diagnosed with CP.

General, LOC, PS, HS, and PER quotients decreased over time during the follow-up period (general: $b^{1/2} = -18.35$, $P < .001$; LOC: $b^{-2} = 14.45$, $P < .001$; PS: $b^{-1/2} = 42.58$, $P < .001$; HS: ln $(b) = -22.12$, $P < .001$; PER: $b^{2} = -0.77$, $P < .001$) (**Figure 2**). An inverse association was observed between GQ trajectories and the severity of delayed myelination ($b = -6.88$, $P = .049$), WM ($b = -2.33$, $P = .040$), and DGM volume reduction ($b^{-2} = 19.42$, $P = .001$) (**Appendix 1**, available at www.jpeds.com). Motor performances were inversely correlated with cystic WM degeneration ($b = -4.99$, $P = .027$) and reduced DGM volume ($b^{-2} = 12.99$, $P = .037$); of note, WM degeneration exhibited a significant interaction effect with time ($b = 5.06$, $P = .004$), indicating a progressive decline in motor performances among infants with higher lesion severity. PS were associated with the severity of volume reduction in the WM ($b = -3.13$, $P = .019$) and DGM ($b^{-2} = 13.68$, $P = .034$) and with delayed myelination ($b = -4.79$, $P = .049$). Volume reduction in the DGM correlated with poorer trajectories of hearing and communicative skills ($b^{-2} = 16.41$, $P = .026$). A significant association of EC with delayed WM myelination ($b = -7.21$, $P = .045$), volume reduction in the WM ($b = -3.48$, $P = .009$), and in the DGM ($b^{-2} = 17.19$, $P = .018$) was documented. PERs showed an inverse

Table II. Neuroradiological items of Kidokoro scoring system for white matter, cortical gray matter, deep gray matter, and cerebellum subscores in the study population (n = 109). The number of infants for each item is indicated in brackets

White matter score

Variable	Score 0	Score 1	Score 2	Score 3	Score 4
Cystic lesions	None (97)	Focal unilateral (1)	Focal bilateral (2)	Extensive unilateral (6)	Extensive bilateral (3)
Focal signal abnormality	None (102)	Focal punctate (4)	Extensive punctate (0)	Linear (3)	
Myelination	PLIC, corona radiata (101)	Only PLIC (5)	Minimal/no PLIC (3)		
Thinning of the corpus callosum	None (92)	Partial (genu/body <13 mm OR splenium <20 mm) (10)	Global (genu/body <13 mm AND splenium <20 mm) (7)		
Dilated lateral ventricles	Both VD < 7.5 mm (55)	One side VD 7.5-9.9 mm (23)	Both sides VD 7.5-9.9 mm or one side ≥10 mm (22)	Both sides VD ≥ 10 mm (9)	
Volume reduction	cBPW >77 mm (16)	cBPW 72-77 mm (40)	cBPW 67-71 mm (42)	cBPW<67 mm (11)	

Cortical gray matter score

Variable	Score 0	Score 1	Score 2	Score 3	Score 4
Signal abnormality	None (105)	Focal unilateral (1)	Focal bilateral (0)	Extensive unilateral (2)	Extensive bilateral (1)
Gyral maturation	Delay <2 wks (109)	Delay 2-4 wks (0)	Delay ≥4 wks (0)		
Increased extracerebral space	IHD <4 (77)	IHD 4-4.9 mm (19)	IHD 5-5.9 mm (7)	IHD ≥6 mm (6)	

Deep gray matter score

Variable	Score 0	Score 1	Score 2	Score 3	Score 4
Signal abnormality	None (106)	Focal unilateral (2)	Focal bilateral (0)	Extensive unilateral (1)	Extensive bilateral (0)
Volume reduction	cDGMA ≥9.5 (100)	cDGMA 8.5-9.4 (7)	cDGMA 7.5-8.4 (1)	cDGMA <7.5 (1)	

Cerebellum score

Variable	Score 0	Score 1	Score 2	Score 3	Score 4
Signal abnormality	None (102)	Focal unilateral (0)	Focal bilateral (2)	Extensive unilateral (3)	Extensive bilateral (2)
Volume reduction	cTCD ≥50 mm (82)	cTCD 47-49 mm (7)	cTCD 44-46 mm (9)	cTCD <44 mm (11)	

PLIC, posterior limb of internal capsula; *VD*, ventricular diameter; *cBPW*, corrected biparietal width; *IHD*, interhemispheric distance; *cDGMA*, corrected deep gray matter area; *cTCD*, corrected transcerebellar diameter.

correlation with the extent of corpus callosum thinning ($b = -6.72$, $P = .021$), volume reduction in the DGM ($b^{-2} = 21.29$, $P < .001$), and the presence of WM signal abnormalities ($b = -6.42$, $P = .010$).

Table III. Results of multilevel mixed-effects logistic regression analysis assessing the risk of missing follow-up visits according to relevant demographic and clinical characteristics

Variable	OR	95% CI	*P* value
Educational attainment	1.19	0.74-1.90	.470
Gestational age (weeks)	1.07	0.92-1.25	.388
Birth weight (g)	1.00	0.99-1.01	.540
Intrauterine growth restriction (ref: no)	1.25	0.59-2.68	.560
Sex (ref: male)	1.03	0.57-1.86	.931
Sepsis (ref: no)	0.79	0.39-1.59	.503
Necrotizing enterocolitis (ref: no)	0.74	0.29-1.91	.538
Bronchopulmonary dysplasia (ref: no)	1.04	0.51-2.10	.922
Retinopathy of prematurity (ref: no)	1.51	0.81-2.80	.195
Postnatal steroids (ref: no)	1.15	0.61-2.16	.669
Periventricular leukomalacia (ref: no)	1.60	0.36-6.18	.428
Intraventricular hemorrhage (ref: no)	1.09	0.55-2.18	.803
Kidokoro MRI GBAS	1.01	0.93-1.10	.752

GBAS, Global Brain Abnormality Score; *MRI*, magnetic resonance imaging; *ref*, reference category.

The multivariable models also documented significant associations between neurodevelopment and specific clinical and demographic covariates (**Appendix 1**, available at www.jpeds.com). Compared with primary or lower secondary school, higher maternal education degrees were associated with higher GQ (upper secondary school: $b = 6.96$, $P = .013$; university: $b = 6.95$, $P = .021$) and higher subquotients for EC (upper secondary school: $b = 7.31$, $P = .029$), HS (university: $b = 6.02$, $P = .049$), and PER (upper secondary school: $b = 8.38$, $P = .001$; university: $b = 10.93$, $P = .001$). A significant correlation of GA with HS ($b = 1.74$, $P = .034$) and PER ($b = 2.23$, $P = .010$) was identified. Lower GQ ($b = -7.37$, $P = .032$) and PER subquotient ($b = -12.64$, $P < .001$) were observed in IUGR infants. BPD was associated with decreased GQ ($b = -7.71$, $P = .008$), LOC ($b = -11.52$, $P = .003$), PS ($b = -7.22$, $P = .007$), HS ($b = -5.35$, $P = .022$), and EC ($b = -7.32$, $P = .016$) subquotients. No significant independent effects were observed for the other covariates.

Discussion

This study investigated the association between specific brain abnormalities at TEA-MRI and neurodevelopmental

Table IV. General quotients and subquotients of the Griffiths Mental Development Scales at each follow-up evaluation

Variable	6 months (n = 101)	12 months (n = 100)	18 months (n = 92)	24 months (n = 79)
Corrected age (months), mean ± SD	6.2 ± 0.4	12.2 ± 0.4	18.2 ± 0.5	24.2 ± 0.4
Quotients, mean ± SD				
General	98.0 ± 14.5	93.3 ± 15.1	82.6 ± 16.0	83.5 ± 18.4
Locomotor	94.6 ± 18.0	85.6 ± 19.7	75.9 ± 20.5	85.2 ± 25.8
Personal and social skills	101.8 ± 13.8	92.3 ± 13.7	80.7 ± 18.5	84.7 ± 20.7
Hearing and language	113.5 ± 14.8	100.9 ± 16.1	89.4 ± 14.2	84.7 ± 20.8
Eye and hand coordination	89.5 ± 18.0	95.1 ± 19.3	89.9 ± 18.9	88.2 ± 17.0
Performance	89.3 ± 16.6	95.7 ± 16.6	82.4 ± 19.1	83.4 ± 21.9

trajectories during the first 24 months in a longitudinal cohort of ELBW infants, showing significant independent correlations between specific functional skills and distinctive MRI features.

With regard to WM abnormalities, the composite quotient of the infants' abilities was associated with both delayed myelination and volume reduction, consistent with previous findings in very preterm infants.[5,18-20] Cortical myelination is a primary driver for CGM development, whose order substantially reflects that of WM: first in the primary somatosensory, motor, visual, and auditory cortex, and finally in the temporal, prefrontal, and association cortices.[21] Early noxious insults or inflammation may disrupt this input, with possible neurodevelopmental sequelae.[10] Similarly, a reduction of WM volume can negatively affect neural connections.[20]

Myelination delay and reduced WM volume also showed a strong correlation with personal and social skills, which are complex functions involving extensive WM networks and the frontal, prefrontal, and temporal cortices.[22] It is therefore plausible that a reduced WM volume and, consequently, less developed neural networks may result in a greater impairment of such sophisticated skills.[23] Furthermore, in line with previous data on visuospatial coordination development in preterm infants,[24,25] delayed myelination and reduced WM volume were associated with an altered EC; while myelination of dorsal and ventral streams is important for visual development during early postnatal phases, interhemispheric and intrahemispheric connections of secondary and associative areas are necessary to develop oculomotor responses in the following months and years.[26]

We observed significant associations between the trajectories of PERs, corpus callosum thinning, and WM alterations, consistent with those reported by Thompson et al.[27,28] who assessed developmental trajectories up to age 7, and with the role of intrahemispheric and interhemispheric connections in the development of higher executive functions.

The relationship between cystic WM degeneration and motor impairment, which confirms other findings,[12,28] showed a cumulative effect of severity and time, with worsening motor performances in infants with greater cystic degeneration, supporting the evolutionary nature of these injuries.

With regard to the gray matter, a reduced DGM volume may reflect the consequences of injury at different areas,[6] with relevant functional implications. Hence, it is not surprising that a DGM volume reduction showed the greatest number of correlations with the developmental trajectories evaluated in this study, confirming previous observations on very preterm children tested at 4 years of age and supporting the value of this parameter for neurodevelopmental prediction.[29] Among the observed correlations, the one between reduced DGM volume and language dysfunction is noteworthy; in line with previous evidence on language performances of children with DGM alterations aged 3 to 7 years,[30,31] this finding supports the key role of the thalamus and basal ganglia in the development and maintenance of morphosyntactic and semantic processing.

We did not observe a significant correlation between psychomotor skills, CGM, and cerebellar scales. Given the low number of cases with isolated CGM and cerebellar abnormalities in our cohort, it is possible that the associations observed between WM and DGM abnormalities, which can exert downstream negative effects on other connected structures, may have obscured any relationships between neurodevelopment and abnormal CGM and cerebellar findings, consistent with previous evidence.[32] Moreover, cerebellar injury has been recently associated with poorer neurocognitive outcomes at school age or later[33] but not at earlier ages, such as those of the present cohort.[34]

Notably, GQ and all subquotients significantly decreased over time. This time trend has been previously described by comparing the longitudinal trajectories of extremely low-gestational-age and very-low-gestational-age infants with those of full-term infants.[35,36] This may be due to the increasing complexity of GMDS-R tasks and the gradual differentiation of developmental functions during infancy.[37] Indeed, while at 6 months, cognitive, motor, social, and language functions are not highly differentiated, during infancy they become gradually specialized; hence, increasingly complex intellectual functions can be achieved from the integration of basic sensorimotor skills. However, the abilities required for more complex tasks (eg, precision, adaptability, capacity to persist) may be acquired only partially by former ELBW children compared with age-matched full-term peers, reflecting a different timing and development of the underlying brain networks. A selection bias related to the potential dropout of healthier infants at follow-up is less likely to underlie this finding, as suggested by the lack of association

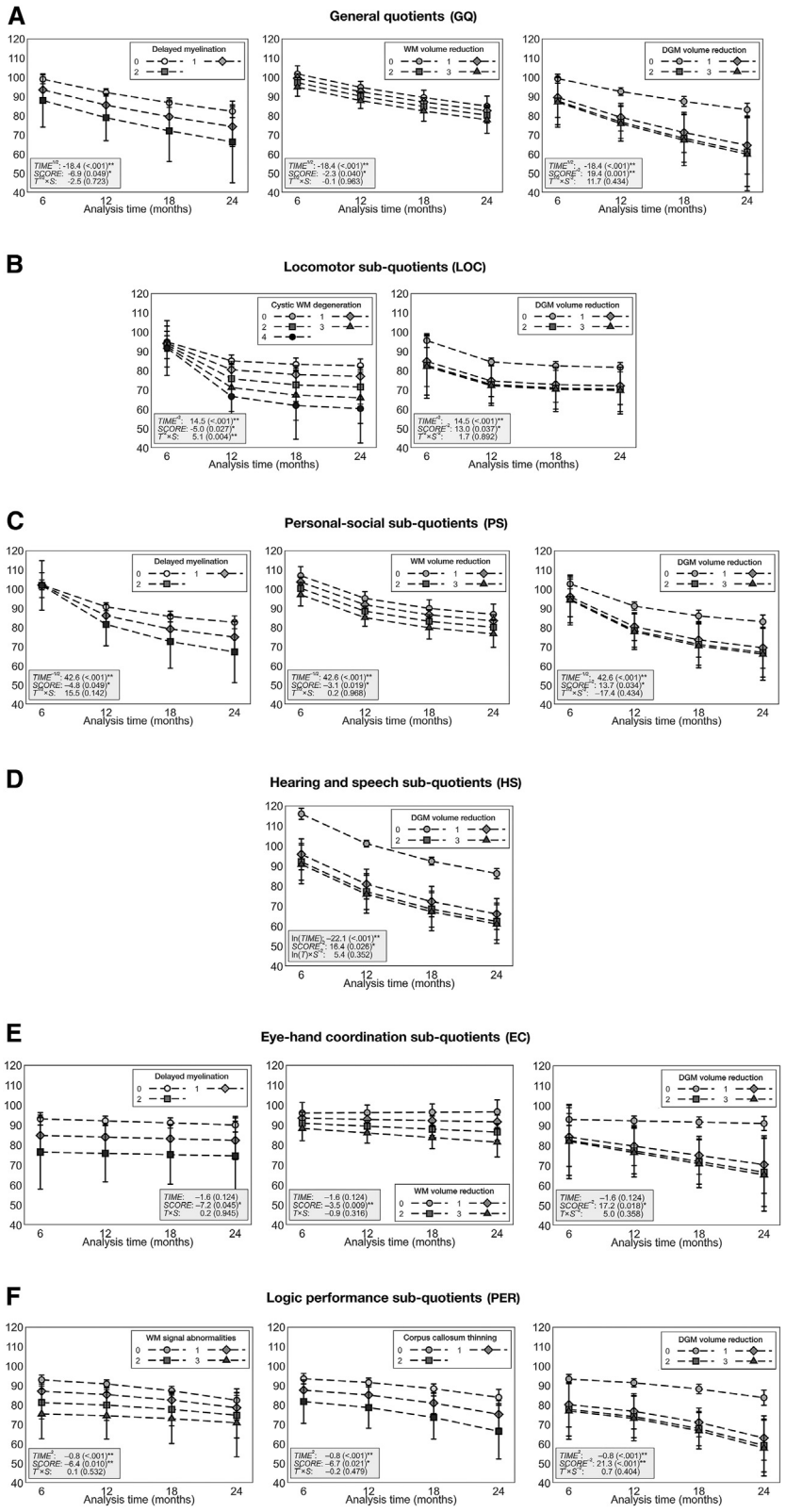

Figure 2. Predicted general quotients **A,** and locomotor **B,** personal-social **C,** hearing and speech **D,** eye-hand coordination **E,** and logic performance **F,** subquotients at 6, 12, 18, and 24 months by severity of the items of the Kidokoro scoring system significantly associated on multivariable regression analysis. The error bars represent the 95% CIs for predictions. The gray boxes include the regression coefficients (*P* values) for time, Kidokoro score, and time-score interaction; statistical significance at 5% and 1% is marked with * and **, respectively. To account for nonlinear trends in neurobehavioral development, time was log-transformed **A, B, C, F,** or power-transformed **D,** via multivariable fractional polynomials.

between relevant clinical morbidities and the odds of missing a follow-up visit.

Our results have been adjusted for several demographic and clinical characteristics showing significant independent associations with neurodevelopmental outcomes, consistent with current evidence.[38] However, our findings further add to the available literature by highlighting how these characteristics may serve as neurodevelopmental predictors toward specific functional areas, thus deserving particular attention.

Lower GA was associated with worse HS function and PERs, consistent with the brain abnormalities associated with increasingly preterm birth.[2,3,26,39] We found that infants with BPD had a significantly lower GQ and a greater motor compromise which was not mediated by postnatal steroids, often used to wean them off the respiratory support. Due to the combination of chronic hypoxia and prolonged oxygen therapy, BPD is characterized by a significant oxidative burden, which triggers a systemic inflammatory state that may affect brain maturation and especially WM development, with later psychomotor sequelae.[40-42] Compared with appropriate-for-GA peers, IUGR neonates had poorer general and PERs; this is consistent with the increased cognitive vulnerability throughout childhood observed in these infants, independent of their degree of prematurity.[43] Finally, we tested the relationship between maternal education, which is known to influence preterm infants' neurodevelopment,[44] and GQ and each subscale, finding a robust association between higher maternal educational attainment and better cognitive functions in the infant.

TEA-MRI effectively identifies brain abnormalities and maturational disturbances in the preterm population but has several limitations such as cost, limited accessibility in low-resource settings, and the need for experienced neuroradiologists for its interpretation.[45,46] Nevertheless, compared with such a low-cost and widely available technique as cranial ultrasound, TEA-MRI has proven to be more sensitive to evaluate brain maturation and detect brain injury, especially in the WM and cerebellum,[47] and it may represent a useful adjunct tool for the prediction of neurodevelopmental outcomes.[46-48] Hence, TEA-MRI could aid at identifying infants who may benefit from early rehabilitative strategies that may not be otherwise available within the first months, which are a critical window of opportunity for neurodevelopment.[45]

The strength of this study relies on the combined use of the GMDS-R, which allowed evaluation of different functional skills, and a validated tool such as the Kidokoro scoring system, which provides a quali-quantitative assessment of brain abnormalities in different areas. Compared with the MRI subscores reported by Kidokoro et al.,[6,7] our cohort showed lower scores for corpus callosum thickness, bilateral ventricular diameter, myelination status, basal ganglia volume, and cerebellar volume, whereas the distribution of the other subscores and the prevalence of intraventricular hemorrhage were similar (32% in both cohorts). A possible explanation for this finding may lie in the different time periods during which the study sample was enrolled (ie, from 2007 to 2010 for the cohort of Kidokoro et al. and from 2009 to 2018 for the present cohort). Advances in the management of extremely preterm infants during this time may partially underlie the better neuroradiological outcomes observed in our cohort.

The relatively small number of infants with moderate-to-severe MRI abnormalities, the study at a single center, and the 10-year study period are potential study limitations. To address these possible biases, the year of birth was included in the GEE models, and a sensitivity analysis was performed, confirming the study results. Moreover, since motor impairment may affect infants' performances at developmental tests that require fine and gross motor skills, GEE results for HS, PS, EC, and PER were also adjusted for CP. The flexible modeling technique we adopted aims to select important variables and determine a suitable functional form for quantitative predictors with good empirical evidence; however, due to the data-dependent nature of all automated techniques, our findings need to be validated in larger samples. The dropout at follow-up is also a limitation; however, only 9.2% of the study infants missed 2 consecutive visits, and since GEEs assume linear and constant trajectories around a missing visit, this is not expected to produce severely biased results.

The observed correlations between specific MRI abnormalities and subsequent developmental outcomes may provide valuable information on the use of TEA-MRI in counseling preterm infants' parents on future neurodevelopment and may contribute to development of targeted supportive interventions (eg, early motor rehabilitation in WM cystic degeneration, sensorimotor integration training in DGM impairments, etc.). Nevertheless, further larger studies are needed to validate these findings and to establish their possible clinical impact. Whether the observed correlations between specific MRI features and impaired neurodevelopmental skills may persist into childhood or even later also warrants investigation. ■

Declaration of Competing Interest

This study was supported by the grant PRIN 2017 (2017HRCPE4_004) "Early markers of Language-Learning Impairment," awarded to AS, as PI of the Unit of Bologna by the Italian Ministry of Education, University and Research (MIUR). The funder had no role in the design and conduct of the study. The authors declare no conflicts of interest.

The authors would like to gratefully thank Dr Silvia Savini, who performed follow-up assessments.

Submitted for publication Feb 3, 2023; last revision received Jun 19, 2023; accepted Jul 25, 2023.

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