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Combining MRI and Spectral EEG for Assessment of Neurocognitive Outcomes in Preterm Infants

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Keywords
Magnetic resonance imaging · Electroencephalography · Premature · Neurocognitive outcomes · Childhood

Abstract
Introduction: Predicting impairment in preterm children is challenging. Our aim is to explore the association between MRI at term-equivalent age (TEA) and neurocognitive outcomes in late childhood and to assess whether the addition of EEG improves prognostication. ***Methods:*** This prospective observational study included forty infants with gestational age 24 + 0–30 + 6. Children were monitored with multichannel EEG for 72 h after birth. Total absolute band power for the delta band on day 2 was calculated. Brain MRI was performed at TEA and scored according to the Kidokoro scoring system. At 10–12 years of age, we evaluated neurocognitive outcomes with Wechsler Intelligence Scale for Children 4th edition, Vineland adaptive behavior scales 2nd edition and Behavior Rating Inventory of Executive Function. We performed linear regression analysis to examine the association between outcomes and MRI and EEG, respectively, and multiple regression analysis to explore the combination of MRI and EEG. ***Results:*** Forty infants were included. There was a significant association between global brain abnormality score and composite outcomes of WISC and Vineland test, but not the BRIEF test. The adjusted R^2 was 0.16 and 0.08, respectively. For EEG, adjusted R^2 was 0.34 and 0.15, respectively. When combining MRI and EEG data, adjusted R^2 changed to 0.36 for WISC and 0.16 for the Vineland test. ***Conclusion:*** There was a small association between TEA MRI and neurocognitive outcomes in late childhood. Adding EEG to the model improved the explained variance. Combining EEG and MRI data did not have any additional benefit over EEG alone.

Introduction

Preterm infants are at high risk for later neurodevelopmental impairments, in particular neurocognitive problems [1, 2]. Optimizing brain protection and predicting and preventing long-term disabilities are

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imperative [3]. However, predicting behavioral and cognitive impairment is particularly challenging, and there is a paucity of suitable biomarkers.

Electroencephalography (EEG) and magnetic resonance imaging (MRI) are complementary tools that can aid in outcome prediction [4–7]. MRI allows for more enhanced lesions characteristics than cerebral ultrasound and can help identify impairments in brain growth and maturation [5]. The MRI scoring system developed by Kidokoro et al. [8] provides a comprehensive evaluation of brain structure using conventional MRI at term-equivalent age (TEA). Multiple studies have assessed the role of the Kidokoro score in predicting both motor and neurocognitive outcomes, but the results are inconsistent, and few studies assess long-term neurocognitive outcomes [6, 7, 9].

EEG is an easy method of monitoring brain activity at the bedside during the vulnerable period after birth. There are considerable changes in the brain activity during the first 3 days after birth [10, 11]. Early brain activity affects brain growth and structural maturation at TEA [12, 13] and neurodevelopmental outcomes in early childhood [4, 14]. The spectral power of EEG is a commonly used quantitative EEG feature. Several studies show association between spectral EEG and outcomes in early childhood [10, 15]. We have recently published data that demonstrate that spectral analysis from early postnatal EEG is associated with neurocognitive outcomes also in late childhood in extremely preterm children [16].

In this study, we want to evaluate the use of MRI and EEG as biomarkers for long-term neurocognitive outcomes. The aims of this study are to evaluate the relationship between Kidokoro scores and neurocognitive outcomes in late childhood and to examine whether the combination of early postnatal EEG and TEA MRI will improve prognostication. We hypothesize that the Kidokoro score is associated with neurocognitive outcomes and that combining EEG and MRI data will improve prognostication.

Materials and Methods

Study Design and Participants

Forty-eight infants born at Oslo University Hospital, Ullevaal, Norway over a 21-month period from 2004 to 2006 were included in this prospective observational study assessing the use of early postnatal EEG and TEA MRI in preterm infants. Inclusion criteria were gestational age (GA) 24^{+0}–30^{+6}, absence of congenital abnormalities, and written parental consent. For this study, infants with early postnatal EEG, MRI at TEA, and follow-up at 10–12 years of age were eligible. The infants were divided into two groups based on GA: group 1 from GA 24^{+0} to 27^{+6} and group 2 from GA 28^{+0} to 30^{+6}. For more details on the cohort, we refer to previous studies [10, 17]. The Regional Committee Medical Ethics (REK 2011/1214) and the Norwegian Data Protection Supervisor approved the study.

Clinical Characteristics

All relevant clinical characteristics and use of sedatives were prospectively documented, including GA, birth weight, small for gestational age, multiple births, mode of delivery, sex, Apgar scores, and complications of prematurity. Complications recorded include early- and late-onset sepsis, patent ductus arteriosus, bronchopulmonary dysplasia, retinopathy of prematurity, necrotizing enterocolitis, intraventricular hemorrhage, and periventricular leukomalacia. Socioeconomic status (SES) was assessed using the Hollingshead four-factor scale at 10–12 years of age [18].

EEG Monitoring and Assessment

A multichannel EEG (NicoletOne™ version 5.2 EEG system, Natus, CA, USA) was recorded for the first 3 days of life using the following eight channels: Fp1, Fp2, P3, P4, T3, T4, O1, and O2. Total absolute band powers were calculated for the four frequency bands delta, theta, alpha, and beta (δ, 1.0–4.0; θ, 4.0–8.0; α, 8.0–13.0; β, 13.0–30.0 Hz). Automated trimming with removal of 5% of the highest tABP values was performed to remove artifacts, and the data were logarithmically transformed due to a skewed distribution. The delta band is the predominant wave in preterm infants, and a previous study has described the highest correlation between the delta band on day 2 of life and outcomes [16]. The tABP of the delta band from day 2 of life was used in the analysis. For more details on EEG monitoring, we refer to previous articles [10, 17].

Acquisition of Magnetic Resonance Imaging

Brain MRI was performed around TEA on a 1.5 Tesla MRI imaging unit (Gyroscan Philips Medical Systems, Best, The Netherlands). The scans were performed, while the infants were sleeping, without the use of sedative or sucrose. All MRI examinations included axial T1-weighted inversion-recovery (TR 3518 ms; TE 14 ms; TI 400 ms), axial T1-weighted spin-echo (TR 475 ms; TE 15 ms), axial T2-weighted spin-echo (TR 3105 ms; TE 150 ms), sagittal T1-weighted spin-echo (TR 582 ms; TE 15 ms), and diffusion-weighted imaging single-shot echo-planar imaging (TR 4040 ms; TE 93 ms, b-values zero, and 1,000 s/mm^2).

A standardized scoring system, developed by Kidokoro et al. [8], was used to assess the MRIs for abnormalities. A senior neuroradiologist (AS), board-certified in pediatric neuroradiology, and blinded to EEG data and clinical results, performed the scoring. Corrections for GA at MRI examinations were done as recommended [6].

Neurodevelopmental Assessment

At 10–12 years of age, the children were evaluated using three developmental tests focusing on the neurocognitive outcomes: the Wechsler Intelligence Scale for Children 4th edition (WISC-IV), the Vineland Adaptive Behavior Scales 2nd edition, and the Behavioral Rating Inventory of Executive Function (BRIEF). An experienced pediatric neuropsychologist with no knowledge of the child's EEG and MRI results performed the WISC test. For the Vineland and BRIEF tests, parent questionnaires were used. For the WISC and Vineland test scores 1SD below the mean (mean:

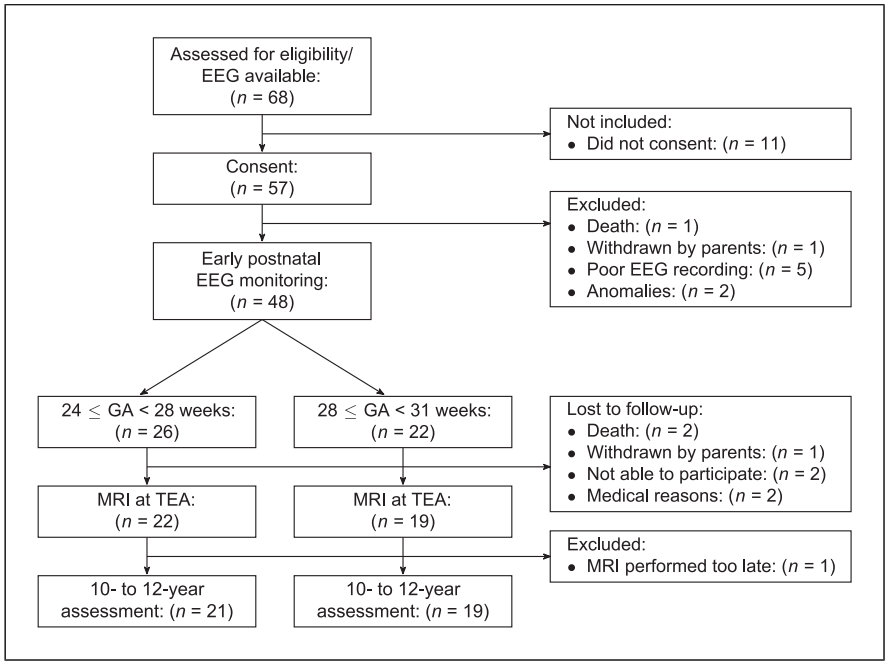

Fig. 1. Flow diagram of included children.

100; SD: 15) were considered unfavorable, while for the BRIEF test scores ≥65 were considered unfavorable. The continuous values of the tests were used in the analysis.

Statistical Analysis

Data were analyzed with Stata/SE 15.0 (StataCorp LLC, College Station, TX). Continuous data approximately normally distributed were assessed with the *t* test and presented as mean ± standard deviations (SD). Categorical variables were evaluated using χ^2 or Fisher's exact tests and presented as proportions (percentages), while ordinal data were evaluated using the Mann-Whitney U test and presented as median with quartiles or number with percentages.

We performed linear regression analysis to examine the association between outcomes and MRI and EEG, respectively. Furthermore, we performed multiple regression analysis to explore the combination of MRI and EEG. In the subsequent analysis, we controlled for SES and GA. Separate analyses were performed for group 1 and group 2.

Results

Fifty-seven infants were initially included in the cohort study, of which we have adequate EEG recording of forty-eight infants. MRI was performed too late in one infant, and seven infants were excluded, resulting in a final study cohort of forty infants. Twenty-one infants were in group 1 and nineteen infants in group 2. All forty children were evaluated at 10–12 years of age (Fig. 1).

The clinical characteristics and the neurocognitive outcomes are presented in Tables 1 and 2, respectively. Although there is a trend toward worse outcomes in group 1, the differences are not statistically significant.

MRI Analysis

The mean GA on MRI examination was 41.3 (1.1) weeks. Most of the infants had no or only mild abnormalities on TEA MRI; only 4/40 (10%) demonstrated moderate/severe abnormalities on the global brain abnormality score (GBAS) (Fig. 2).

Relationship between MRI and Neurodevelopmental Outcomes

GBAS

The results are shown in Table 3a. For the GBAS, there was an inverse association with the full-scale intelligence quotient (FSIQ) and the Vineland adaptive behavior composite (ABC). There were also significant associations with some of the subscores of the WISC and Vineland tests with an explained variance of 9.5–24% (online suppl. Table. 1; for all online suppl. material, see https://doi.org/10.1159/000530648). There was no significant association between GBAS and the BRIEF test.

Subscores

The FSIQ was related to the white matter score, the deep gray matter score, and the cerebellum score. The Vineland ABC and BRIEF global executive composite were only associated with the deep gray matter score.

Table 1. Clinical characteristics of infants with MRI performed at TEA

Characteristics	Total (*n* = 40)	Group 1 (*n* = 21)	Group 2 (*n* = 19)
GA, weeks, mean±SD	27.8±1.8	26.4±1.0	29.4±1.0
Birth weight, g, mean±SD	1044±294	865±191	1241±262
Male sex, *n* (%)	22 (55)	13 (61.9)	9 (47.4)
Small for gestational age, *n* (%)	11 (27.5)	6 (28.6)	5 (26.3)
SES, *n* %			
1	3 (7.5)	2 (9.5)	1 (5.3)
2	2 (5)	0 (0)	2 (10.5)
3	5 (12.5)	3 (14.3)	2 (10.5)
4	16 (40)	9 (42.9)	7 (36.8)
5	14 (35)	7 (33.3)	7 (36.8)
Apgar 5 min, median (IQR)	7 (6, 9)	7 (6, 8)	8 (7, 9)
Surfactant, *n* (%)	25 (62.5)	18 (85.7)	7 (36.8)
Sedation, *n* (%)	13 (32.5)	6 (28.6)	7 (36.8)
Early sepsis, *n* (%)	6 (15)	3 (14.3)	3 (15.8)
Late sepsis, *n* (%)	7 (17.5)	6 (28.6)	1 (5.3)
NEC, *n* (%)	3 (7.5)	2 (9.5)	1 (5.3)
PDA, *n* (%)	8 (20)	5 (23.8)	3 (15.8)
BPD, *n* (%)	7 (17.5)	5 (23.8)	2 (10.5)
ROP ≥3, *n* (%)	2 (5)	2 (9.5)	0 (0)
IVH, *n* (%)			
III	0 (0)	0 (0)	0 (0)
IV	1 (2.5)	1 (4.8)	0 (0)
cPVL, *n* (%)	2 (5)	1 (4.8)	1 (5.3)

NEC, necrotizing enterocolitis; PDA, patent ductus arteriosus; BPD, bronchopulmonary dysplasia; ROP, retinopathy of prematurity; IVH, intraventricular hemorrhage; cPVL, cystic periventricular leukomalacia.

Subgroups

For extremely preterm infants (group 1), MRI scores explained more of the variance than in the total group, and there were also significant inverse associations between all subscores of the Kidokoro score and WISC FSIQ and Vineland ABC (online suppl. Table 2a). In group 2, there was little association between MRI scores and outcomes (online suppl. Table 2b).

Relationship between MRI, EEG, and Neurodevelopmental Outcomes

Spectral analysis of EEG, using the logarithmic delta from day 2 of life, showed an association with FSIQ and Vineland ABC (Table 3a). There were also significant associations between early EEG and all subtests of the WISC and the Vineland tests as shown in online supplementary Table 1. There was no association with the BRIEF test. Combining EEG and MRI data improved the explained variance compared to MRI alone, but for most scores, there was no benefit compared to EEG alone (Table 3b; online suppl. Tables 3a, b).

Table 4 shows the results from the multiple regression analysis for MRI scores and EEG, respectively, after adjusting for GA and SES. The addition of MRI or EEG increased R^2 compared to GA and SES alone.

Discussion

In this study, we found an association between TEA MRI and neurocognitive outcomes in late childhood, but the explained variance was low. Adding EEG to the model improved the explained variance for most outcomes, but combining EEG and MRI data did not increase the explained variance much compared to EEG alone.

In the original Kidokoro data, 35% of the cohort had moderate to severe abnormalities on TEA MRI [8]. Our cohort demonstrated relatively low brain injury scores with only 10% having moderate to severe abnormalities on GBAS. However, the brain scores in our data are comparable to data published by Brouwer et al. [6] and Mayock et al. [19]. We also found significant associations between brain scores and WISC and Vineland tests with explained variances similar to findings reported by Brouwer et al. [6] ($R^2 \leq 0.219$). When dividing the cohort

Table 2. Neurocognitive outcomes at 10–12 years of age of children with MRI performed at TEA

	Total (n = 40)	Group 1 (n = 21)	Group 2 (n = 19)
WISC FSIQ, mean±SD	92.8±16.6	89.0±20.6	96.9±9.3
Vineland ABC, mean±SD	91.5±22.4	90.0±26.7	93.1±17.0
BRIEF GEC, mean±SD	49.7±10.6	50.6±11.9	48.7±9.2
WISC FSIQ ≤85, n (%)	5 (12.5)	4 (19.0)	1 (5.3)
Vineland ABC ≤85, n (%)	13 (32.5)	6 (28.6)	7 (36.8)
BRIEF GEC ≥65, n (%)	5 (12.5)	4 (19.1)	1 (5.3)

WISC FSIQ, WISC Full Scale Intelligence Quotient; Vineland ABC, Vineland adaptive behavior composite; BRIEF GEC, BRIEF global executive composite.

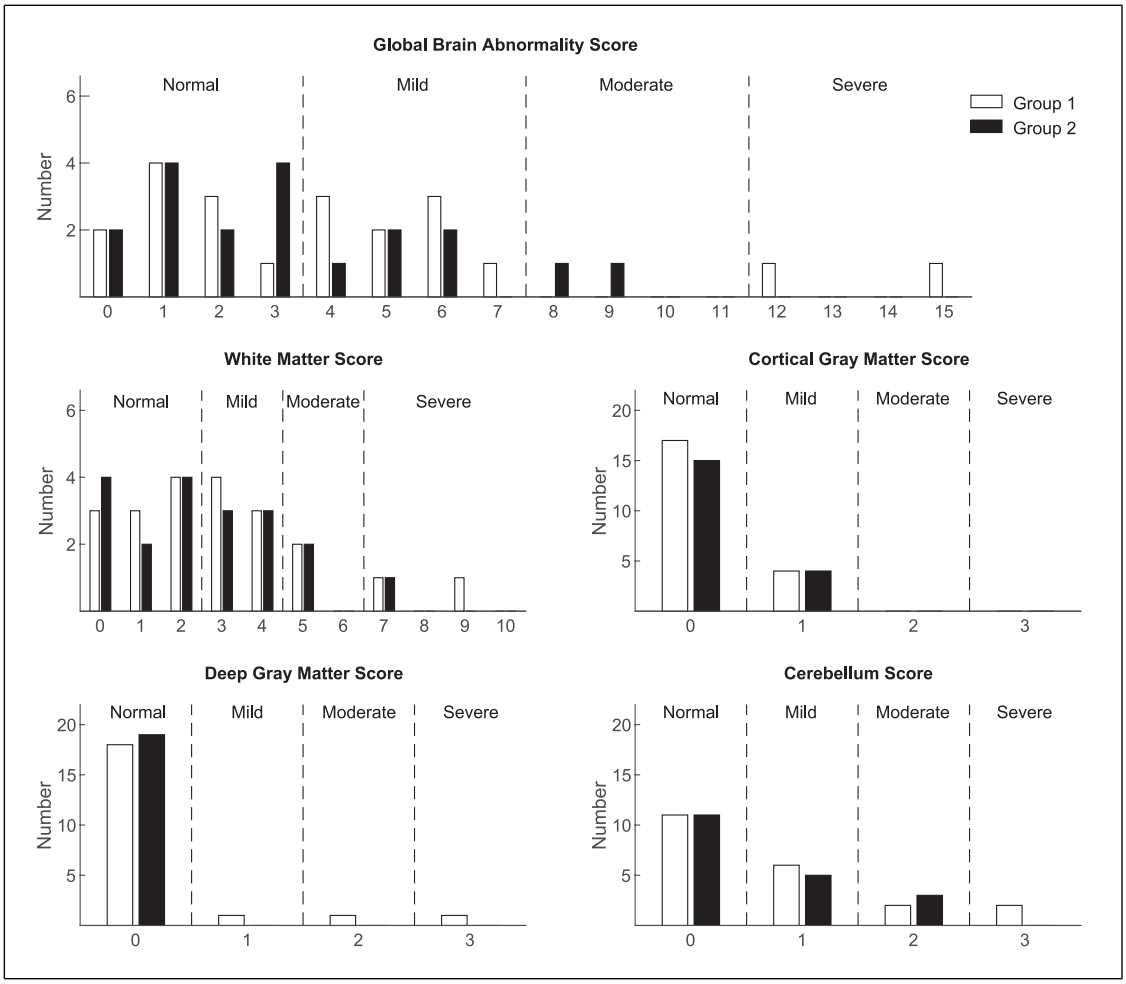

Fig. 2. Distribution of the global brain abnormality score and the subscores for group 1 and group 2.

into two groups based on GA, we found an association between brain scores and outcomes mainly in group 1. The lack of association between brain scores and outcomes in group 2 may be due to insufficient sample size combined with few children with unfavorable outcomes. Another hypothesis is that the more mature brains are less susceptible to injuries caused by prematurity as functional brain networks are already established [20].

Impairments in executive function are of particular concern in preterm children [21]. Several studies have reported a significant association between changes in white matter, deep gray matter, and cerebellum and

Table 3. Scores from the Kidokoro scoring system and EEG in relation to neurodevelopmental outcomes according to linear regression analysis (a) and multiple regression analysis when combining MRI scores and EEG (b)

	WISC FSIQ			Vineland ABC			BRIEF GEC		
	β (95% CI)	*p* value	adj R^2	β (95% CI)	*p* value	adj R^2	β (95% CI)	*p* value	adj R^2
a									
GBAS	−2.2 (−3.7; −0.7)	0.006	0.161*	−2.2 (−4.3;−0.1)	0.045	0.078*	0.6 (−0.4; 1.7)	0.225	0.013
Cerebral white matter	−2.9 (−5.2; −0.5)	0.019	0.114*	−3.0 (−6.3; 0.3)	0.077	0.056	1.0 (−0.6; 2.6)	0.214	0.015
Cortical gray matter	3.7 (−9.7; 17.1)	0.580	≤0.0	2.1 (−16.1; 20.2)	0.819	≤0.0	−7.1 (−15.4; 1.2)	0.090	0.050
Deep gray matter	−16.9 (−24.4; −9.3)	<0.005	0.331*	−17.0 (−28.4; −5.6)	0.005	0.173*	6.1 (0.4; 11.8)	0.036	0.087*
Cerebellum	−6.3 (−12.1; −0.6)	0.032	0.092*	−5.7 (−13.8; 2.3)	0.160	0.026	1.8 (−2.1; 5.6)	0.365	≤0.0
EEG	13.9 (7.7; 20.1)	<0.005	0.335*	13.1 (3.6; 22.6)	0.008	0.149*	−3.3 (−8.1; 1.5)	0.171	0.024*
	FSIQ			Vineland ABC			BRIEF GEC		
	β (95% CI)	*p* value	adj R^2	β (95% CI)	*p* value	adj R^2	β (95% CI)	*p* value	adj R^2
b									
GBAS + EEG									
GBAS	−1.1 (−2.6; 0.3)	0.126	0.359*	−1.2 (−3.5; 1.0)	0.273	0.155*	0.4 (−0.7; 1.6)	0.472	0.012
EEG	11.8 (5.1; 18.5)	0.001		10.8 (0.4; 21.1)	0.042		−2.5 (−7.8; 2.8)	0.341	
Cerebral white matter + EEG									
Cerebral white matter	−1.6 (−3.7; 0.5)	0.128	0.359*	−1.8 (−5.1; 1.5)	0.269	0.155*	0.7 (−0.9; 2.4)	0.381	0.018
EEG	12.4 (6.0; 18.8)	<0.005		11.4 (1.5; 21.4)	0.025		−2.6 (−7.7; 2.4)	0.297	
Cortical gray matter + EEG									
Cortical gray matter	0.4 (−10.7; 11.4)	0.945	0.317*	−1.1 (−18.0; 15.8)	0.897	0.127*	−6.5 (−14.8; 1.9)	0.125	0.060
EEG	13.9 (7.5; 20.2)	<0.005		13.2 (3.5; 22.9)	0.009		−2.8 (−7.6; 2.0)	0.240	
Deep gray matter + EEG									
Deep gray matter	−10.1 (−19.6; −0.7)	0.036	0.394*	−11.5 (−26.3; 3.4)	0.125	0.181*	6.0 (−1.6; 13.5)	0.117	0.063
EEG	8.5 (0.8; 16.3)	0.031		7.0 (−5.1; 19.2)	0.249		−0.2 (−6.3; 6.0)	0.957	
Cerebellum + EEG									
Cerebellum	−1.9 (−7.4; 3.6)	0.482	0.326*	−1.5 (−10.0; 6.9)	0.719	0.129*	0.8 (−3.5; 5.1)	0.720	0.001
EEG	12.9 (5.9; 19.8)	0.001		12.3 (1.7; 22.9)	0.025		−2.9 (−8.3; 2.5)	0.283	

β, beta coefficient; CI, confidence interval; adj R^2, adjusted R^2; GBAS, global brain abnormality score; WISC FSIQ, WISC full-scale intelligence quotient; Vineland ABC, Vineland adaptive behavior composite; BRIEF GEC, BRIEF global executive composite. *p value <0.05.

executive function [7, 22, 23]. In contrast to Haebich et al. [7], we were not able to find any significant association between GBAS and the BRIEF test. There was a small, though significant, association between the deep gray matter score and the behavioral regulation index and the composite score of the BRIEF test. In our cohort, there were few children with unfavorable outcomes on the BRIEF test (5/40), and those who had an unfavorable score were all between 65 and 70. There were also few children with abnormalities in the deep gray matter. The small sample size and relatively healthy preterm population may mask a possible association between global brain score and executive function, and further studies with larger sample sizes are needed to clarify this.

Huning et al. [24] have previously shown that the combination of aEEG and MRI contributes to the prediction of outcomes at 2 years corrected age. Combining EEG and MRI data improved the explained variance compared to MRI alone for both the composite score and most subscores of the WISC and Vineland tests in our cohort. To our surprise, the combination of MRI and EEG gave almost the same explained variance for the outcomes as EEG alone. In our cohort, we gain very little added benefit from performing conventional MRI when we have an early postnatal EEG. MRI performed at TEA, compared to early postnatal EEG, will encompass the morbidities that occur during the neonatal intensive care course. However, structural brain abnormalities do not

Table 4. Multiple regression analysis when adjusting for GA and SES

	WISC FSIQ			Vineland ABC			BRIEF GEC		
	β (95% CI)	*p* value	adj R^2	β (95% CI)	*p* value	adj R^2	β (95% CI)	*p* value	adj R^2
GA/SES									
GA	3.1 (0.6; 5.6)	0.015	0.277*	1.9 (−1.9; 5.8)	0.325	0.049	−0.5 (−2.4; 1.4)	0.593	≤0.0
SES	6.0 (2.1; 9.9)	0.003		5.1 (−1.0; 11.1)	0.098		−1.1 (−4.1; 1.9)	0.455	
GBAS/GA/SES									
GBAS	−1.6 (−3.0; −0.2)	0.027	0.353*	−1.9 (−4.1; 0.4)	0.097	0.096	0.6 (−0.6; 1.7)	0.313	≤0.0
GA	2.4 (−0.1; 4.8)	0.058		1.0 (−2.9; 4.9)	0.609		−0.2 (−2.2; 1.8)	0.814	
SES	5.6 (1.9; 9.3)	0.004		4.6 (−1.4; 10.5)	0.127		−1.0 (−4.0; 2.0)	0.521	
Cer white matter/GA/SES									
Cerebral white matter	−2.5 (−4.6; −0.5)	0.017	0.366*	−2.9 (−6.2; 0.4)	0.088	0.100	1.0 (−0.7; 2.7)	0.242	≤0.0
GA	2.4 (0.0; 4.8)	0.049		1.1 (−2.8; 5.0)	0.572		−0.2 (−2.2; 1.7)	0.812	
SES	6.3 (2.6; 10.0)	0.001		5.4 (−0.5; 11.3)	0.073		−1.2 (−4.2; 1.8)	0.412	
Cortical gray matter/GA/SES									
Cortical gray matter	10.2 (−1.2; 21.6)	0.079	0.319*	7.2 (−11.1; 25.6)	0.429	0.040*	−8.9 (−17.5; −0.2)	0.044	0.056
GA	3.2 (0.8; 5.7)	0.010		2.0 (−1.9; 5.9)	0.311		−0.6 (−2.4; 1.2)	0.514	
SES	7.0 (3.1; 11.0)	0.001		5.8 (−0.6; 12.1)	0.073		−2.0 (−4.9; 1.0)	0.189	
Deep gray matter/GA/SES									
Deep gray matter	−12.7 (−20.3; −5.0)	0.002	0.434*	−15.0 (−27.6; −2.4)	0.021	0.159*	6.0 (−0.4; 12.4)	0.064	0.039
GA	1.8 (−0.5; 4.2)	0.124		0.3 (−3.5; 4.2)	0.856		0.1 (−1.8; 2.1)	0.906	
SES	4.6 (1.0; 8.2)	0.013		3.4 (−2.5; 9.2)	0.251		−0.4 (−3.4; 2.5)	0.770	
Cerebellum/GA/SES									
Cerebellum	−3.5 (−8.9; 1.8)	0.191	0.292*	−3.7 (−12.1; 4.7)	0.374	0.044	1.3 (−2.8; 5.5)	0.521	≤0.0
GA	2.8 (0.3; 5.3)	0.030		1.6 (−2.4; 5.5)	0.431		−0.4 (−2.3; 1.6)	0.694	
SES	5.4 (1.5; 9.4)	0.009		4.4 (−1.8; 16.7)	0.157		−0.9 (−4.0; 2.2)	0.564	
EEG/GA/SES									
EEG	10.2 (2.8; 17.7)	0.009	0.388*	12.4 (0.4; 24.4)	0.044	0.128*	−3.2 (−9.4; 3.0)	0.299	≤0.0
GA	1.1 (−1.6; 3.8)	0.418		−0.6 (−5.0; 3.9)	0.798		0.1 (−2.1; 2.4)	0.906	
SES	4.2 (0.4; 8.1)	0.030		2.9 (−3.2; 9.1)	0.344		−0.6 (−3.7; 2.6)	0.727	

β, beta coefficient; CI, confidence interval; adj R^2, adjusted R^2; GA, gestational age; SES, socioeconomic status; GBAS, global brain abnormality score; Cer white matter, cerebral white matter; WISC FSIQ, WISC full-scale intelligence quotient; Vineland ABC, Vineland adaptive behavior composite; BRIEF GEC, BRIEF global executive composite. *p value <0.05.

explain all long-term consequences of preterm birth, and some infants will have major neurodevelopmental adversities in spite of an uncomplicated neonatal intensive care unit course [25]. Brain activity during postnatal adaptation appears to have a significant impact on subsequent neurodevelopmental outcomes, suggesting that some adversity may already be present at or just after birth [25, 26]. EEG is an easy and cost-effective investigation that can be performed bedside, providing valuable information on the brain during the transition period. With the development and implementation of automatic EEG analysis, the analysis is also simplified [17]. On the other hand, it is possible that the Kidokoro score is not sensitive enough to detect subtle abnormalities and that more sophisticated MRI techniques that focus on microstructure and connectivity are superior in the evaluation and prognostication of preterm infants. The combination of EEG and more advanced neuroimaging should be further evaluated. Due to the small sample size in this cohort, we do not have enough data for EEG nor MRI to define cutoff values that predict poor neurocognitive impairment. An aim for future research would be developing a GA-specific percentile-spectral EEG chart that can aid in outcome prediction and selection of patients for the intensive follow-up.

SES is recognized as an important factor for brain structure and neurodevelopment in both term and preterm infants [27]. GA at birth is associated with later outcomes [28]. GA will also influence the effect of EEG as preterm EEG evolves over the neonatal period and varies considerably with GA [29]. We performed a multiple regression analysis where we included SES and GA and

then added MRI or EEG. Both MRI and EEG increased the explained variance for most tests compared to the combination of SES and GA, implying that both MRI and EEG play an additive role in our cohort.

Several limitations to the study need to be addressed. The main limitation of the study is the small sample size. In addition, we do not have clinical information on nonrecruited infants. Preferably, more advanced neuropsychological tests should have been performed, but this was unfortunately unattainable due to limited funding. SES was first measured at the 10–12 years' follow-up, as earlier assessment was not allowed by the data protection in the hospital. Due to limited sample size, adjusting for additional factors such as gender and total disease burden was not feasible. The strengths of the study include its prospective design, the long follow-up, and the minimal dropout rates. We evaluated all 40 children with adequate EEG and MRI at 10–12 years of age.

In conclusion, our data show that there is an association between TEA MRI using the Kidokoro score and neurocognitive outcomes in late childhood. The prognostic value of the Kidokoro score improves by adding EEG data, but combining EEG and MRI shows little added benefit over EEG alone. Our results indicate that EEG may be a better biomarker than standard MRIs for preterm infants. Further studies with larger sample sizes are needed to confirm the results.

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Statement of Ethics

The study was approved by The Regional Committee Medical Ethics (approval number REK 2011/1214). Written informed consent was given by the parents before inclusion in the study.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Tone Nordvik conceptualized the study, carried out the statistical analysis, interpreted the data, drafted, and finalized the manuscript. Andres Server reviewed and scored the MRIs. Cathrine N. Espeland contributed to data analysis and designed the figures. Eva M. Schumacher conceptualized and designed the study and contributed to acquisition of data. Pål G. Larsson contributed to the study design. Are H. Pripp supervised the statistical analysis. Tom Stiris conceptualized and designed the study and made important contributions to the manuscript. All authors critically reviewed the manuscript, approved the final version of the manuscript to be published, and agree to be accountable for all aspects of the work.

Data Availability Statement

All data generated or analyzed during this study are included in this article and its supplementary material files. Further inquiries can be directed to the corresponding author.

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