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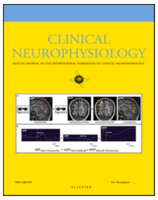

The relationship between early life EEG and brain MRI in preterm infants: A systematic review

Roos F. Meijer [1], Xiaowan Wang [1], Inge M. van Ooijen, Bauke van der Velde, Jeroen Dudink, Manon J.N.L. Benders, Maria Luisa Tataranno *

Department of Neonatology, Wilhelmina Children's Hospital, University Medical Centre Utrecht, Utrecht, the Netherlands

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ABSTRACT

Objective: To systematically review the literature on the associations between electroencephalogram (EEG) and brain magnetic resonance imaging (MRI) measures in preterm infants (gestational age $<$ 37 weeks).

Methods: A comprehensive search was performed in PubMed and EMBASE databases up to February 12th, 2024. Non-relevant studies were eliminated following the PRISMA guidelines.

Results: Ten out of 991 identified studies were included. Brain MRI metrics used in these studies include volumes, cortical features, microstructural integrity, visual assessments, and cerebral linear measurements. EEG parameters were classified as qualitative (Burdjalov maturity score, seizure burden, and background activity) or quantitative (discontinuity, spectral content, amplitude, and connectivity). Among them, discontinuity and the Burdjalov score were most frequently examined. Higher discontinuity was associated with reduced brain volume, cortical surface, microstructural integrity, and linear measurements. The Burdjalov score related to brain maturation qualitatively assessed on MRI. No other consistent correlations could be established due to the variability across studies.

Conclusions: The reviewed studies utilized a variety of EEG and MRI measurements, while discontinuity and the Burdjalov score stood out as significant indicators of structural brain development.

Significance: This review, for the first time, provides an extensive overview of EEG-MRI associations in preterm infants, potentially facilitating their clinical application.

1. Introduction

Recent advancements in neonatal care have significantly improved the survival rates of preterm infants (Patel, 2016). However, these infants often show brain developmental delay when compared to their gestational age (GA)-matched peers (Wu et al, 2020). Brain developmental delay is not merely a transient concern restricted to the neonatal period, but closely associated with long-term neurodevelopmental impairments, such as cognitive deficits at school age (Johnson & Marlow, 2017; Keunen et al., 2016; Pascoe et al., 2021). Consequently, the focus in clinical practice has shifted from ensuring survival to actively protecting the vulnerable brain of preterm infants.

Magnetic resonance imaging (MRI) is an essential tool for assessing brain development in preterm infants admitted to neonatal intensive care unit (NICU) settings (Inder et al., 2021). Techniques like structural MRI, diffusion-weighted MRI and diffusion-tensor imaging allow for in-depth in-vivo analysis of the maturation of brain tissues, such as volumes, cortical features, microstructures, visual assessments and linear measurements. However, MRI is typically performed at a later stage during the infant's NICU hospitalization (e.g. term equivalent age), which impedes early identification and timely intervention to improve their future (neuro)development.

Electroencephalogram (EEG), especially amplitude-integrated EEG (aEEG), has gained widespread popularity as a brain function monitoring tool for preterm neonates in recent years (El-Dib et al., 2023; Tao & Mathur, 2010; Toet & Lemmers, 2009). The non-invasive nature and

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Abbreviations: aEEG, Amplitude-integrated electroencephalogram; EEG, Electroencephalogram; DTI, Diffusion tensor imaging; FA, Fractional anisotropy; GA, Gestational age; IBI, Inter-burst interval; MRI, Magnetic resonance imaging; NICU, Neonatal intensive care unit; PMA, Postmenstrual age; PNA, Postnatal age; SAT, Spontaneous activity transient; TEA, Term-equivalent age.

* Corresponding author.

E-mail address: M.L.Tataranno-2@umcutrecht.nl (M.L. Tataranno).

[1] **These authors contributed equally and are shared first authors.**

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bedside applicability of EEG makes it a practical choice for continuous, real-time brain activity monitoring in the NICU. The flexibility of EEG enables its application throughout the critical neonatal period, providing complementary information to brain MRI information.

In the NICU, visual aEEG/EEG assessment is typically conducted to detect brain dysfunctions such as seizures (Rakshasbhuvankar et al., 2020; Variane et al., 2017). To provide a more objective assessment, there is a growing interest in computer-analyzed quantitative EEG measures, such as discontinuity, spectral content, and connectivity (O'Toole and Boylan, 2019). Both qualitative and quantitative EEG parameters have been found to reflect the maturational brain changes in preterm infants (Koolen et al., 2014; Niemarkt et al., 2011; Pavlidis et al., 2017) and have shown predictive value for future outcome (Fogtmann et al., 2017; van 't Westende et al., 2022; Wang et al., 2023), highlighting the clinical relevance of EEG monitoring.

While many studies have explored the associations between EEG measures and brain maturation on MRI, there is a lack of clarity regarding which EEG parameters are the most indicative of MRI structural development. This systematic review, therefore, seeks to examine the currently available literature investigating EEG-MRI associations. In doing so, we aim to identify EEG parameters with the most significant clinical relevance, potentially guiding future interventions and neuromonitoring strategies in the NICU setting.

2. Methods

The reporting of this literature review follows the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines (Page et al., 2021). The review protocol was prospectively registered in PROSPERO (CRD42023462587).

2.1. Search method

A systematic search was performed in PubMed and Embase up to February 12th, 2024. We included research articles where the relationship between any qualitative or quantitative EEG parameters and brain MRI measurements was assessed in preterm infants, with EEG and MRI acquired up until term-equivalent age. The search strategy was initially created by one of the reviewers (RFM) and was subsequently inspected by a medical librarian from Utrecht University. Main keywords used for the search were "preterm infants", "MRI", "neuroimaging", and "EEG". The full search strategy is shown in Supplementary material.

2.2. Inclusion criteria and selection process

We selected all types of full-text original research articles written in English and peer-reviewed, with the exceptions of reviews, conference papers, study protocols, and case reports. Studies that involved infants with congenital malformations, genetic disorders, or metabolic disorders were excluded. Furthermore, studies that only focused on infants with severe brain injuries were also excluded.

All duplicates were reviewed and removed using the software Endnote (Version X9.3.3; Clarivate Analytics, PA, USA). The references and citation list of relevant studies were manually screened to determine whether any adjustments to the search strategy were required, and none were found necessary. Subsequently, two reviewers (RFM and XW) independently assessed the papers based on their titles and abstracts using the software Rayyan (Rayyan Systems Inc.), which was followed by a full-text screening. At each stage, any disagreements were resolved through discussion between the two reviewers. When needed, a third reviewer (MLT) was consulted for the final decision.

2.3. Quality assessment

The quality of the included studies was independently assessed by two reviewers (RFM and XW) using the JBI critical appraisal checklist for case series (Moola et al., 2020), which consists of 10 items for assessing risk of bias. Studies with fewer than four items receiving a double positive assessment from the reviewers were considered to have a high risk of bias and were therefore excluded from further review. In cases where the two reviewers could not reach a consensus, a third reviewer (MLT) was consulted to make the final decision.

3. Results

The flowchart of the review procedure, based on the PRISMA guidelines (Page et al., 2021), is illustrated in Fig. 1. A total of 991 studies were initially identified, and 728 studies remained after removal of duplicates. During the title and abstract screening, 717 studies were excluded according to the inclusion criteria. None of the remaining 11 studies were excluded after the full-text assessment. Subsequently, two independent reviewers (RFM and XW) assessed the quality of these studies using the JBI critical appraisal checklist, with their responses detailed in Supplementary Table S1. Out of the 11 studies, one (Biagioni et al., 2007) was excluded from further review due to high risk of bias, ultimately resulting in 10 studies being included in this review.

3.1. Study characteristics

The study and patient characteristics are shown in Table 1. Sample sizes of included studies ranged between 21 and 446, with the proportion of females ranging from 32 to 64%. The mean GA of participants ranged between 25.5 and 29.5 weeks.

Nine of the ten included studies (90%) only used aEEG. Of them, five performed aEEG monitoring within the first 72 postnatal hours, three both within the first 72 postnatal hours and then on a weekly basis, and one within the first four postnatal days. The remaining study utilized both aEEG and conventional EEG (cEEG) at 32 weeks of PMA and a follow-up cEEG at term-equivalent age. All studies had an MRI scan at term-equivalent age (around 40 weeks of PMA). Furthermore, three studies also had an MRI scan at 30 weeks of PMA and one study had an MRI scan shortly after birth. An overview of EEG and MRI measuring time points is shown in Fig. 2. In the following sections, details on the timing of MRI will only be provided if the scans are not conducted at term-equivalent age, and details on EEG timing will be mentioned only if the recordings are not made within the first 72 h after birth.

In terms of EEG analysis, we identified three different qualitative indices: seizure burden, Burdjalov maturity score, and background activity, and four different types of quantitative parameters: discontinuity, spectral content, amplitude, and connectivity (Table 2). The most frequently used parameter was EEG discontinuity, with inter-burst intervals (IBIs) and/or spontaneous activity transients (SATs) being used in four studies. The definitions of these EEG parameters are detailed in InformationBox 1.

For MRI analysis, five different categories were recognized: brain volumes (including volumetric growth), cortical measurements, microstructure measurements, linear measurements, and qualitative MRI assessments (Table 2). Among these, brain volume measurements were the most commonly analyzed category, and were used in six studies.

The specific significant relationships between EEG parameters and MRI measurements, as well as the directions of these relationships, are detailed in Supplementary Table S2.

Box 1

Primary EEG parameter definitions

Qualitative EEG parameters

Among the qualitative indices, the Burdjalov maturity score and background activity visually evaluate EEG characteristics known to change with maturation. The Burdjalov score assesses the continuity, cycling, bandwidth, and amplitude of the lower border on EEG (Burdjalov et al., 2003). Higher Burdjalov (sub)scores indicate more mature brain activity and are associated with better outcome indices (Ralser et al., 2017). In contrast, the qualitative index seizure is a distinct parameter that is directly related to (brain) pathology. Seizures occurring during the neonatal period have been correlated with adverse outcomes in preterm infants (Pisani et al., 2016).

Quantitative EEG parameters

In this systematic review, four quantitative EEG parameters were identified in the included studies: Discontinuity, spectral content, amplitude and connectivity.Discontinuity is an essential measure of neonatal EEG. The premature neonatal EEG is characterized by intermittent periods of inactivity, i.e. IBIs,
(with an amplitude < 5 μV, of at least 3 s), and burst-like activity, i.e. SATs (Vecchierini et al., 2007). During maturation, the IBIs are expected to shorten and become less frequent, while SATs should lengthen in duration (Vecchierini et al., 2007). At term-equivalent age (TEA) the EEG should be almost fully continuous (Pavlidis et al., 2017). Delays in this maturation process are correlated with poor outcome (Wikström et al., 2012).The spectral content and amplitude are fundamental measure of the EEG signal. The spectral content refers to the frequency distribution within the EEG, which can be separated in the four power bands: delta
(1.0 – 4.0 Hz), theta (4.0 – 8.0 Hz), alpha (8.0 – 13.0 Hz) and beta (13.0 – 30.0 Hz). A wide range of parameters can be calculated with the spectral content, e.g., the absolute and relative spectral power of each power band. Generally, the EEG matures form a low-frequency to high-frequency signal (Niemarkt et al., 2011).The amplitude measures the strength of the EEG signal in microvolts. Due to the variations in EEG monitors and preprocessing steps, it is difficult to compare absolute amplitude measures across studies. The EEG maturation processes from a high-amplitude to low-amplitude signal in the neonatal period
(Niemarkt et al., 2011).

Connectivity is a measure of synchronous neural activity within and between the hemispheres. Evidence of connectivity between hemispheres is already observed as early as 23 weeks GA, through synchronous SATs/IBIs on multi-channel EEG (Pavlidis et al., 2017). Interhemispheric connectivity develops as the infant matures, and by TEA, asynchrony should no longer be present (Pavlidis et al., 2017).

3.2. EEG parameters and brain volumes

3.2.1. Total brain volume and intracranial volume

Four studies have linked early postnatal EEG parameters to total brain or intracranial volumes (Benders et al., 2015; De Wel et al., 2021; Vesoulis et al., 2022; Wikström et al., 2017). Wikström et al. (2017) showed that a higher degree of EEG discontinuity, indicated by longer IBIs, had significantly negative correlations with total brain volume when not adjusting for confounders, and with the ratio of total brain volume to intracranial volume after accounting for confounders. Benders et al. (2015) identified a significant relationship between IBIs and a smaller total brain volume shortly after birth.

Furthermore, Benders et al. (2015) found that longer IBIs were associated with reduced growth of total brain volume from birth to term-equivalent age. They also reported correlations between several amplitude-based EEG continuity categories and total brain volume both after birth and at term-equivalent age. However, these relationships varied in direction and significance.

Additionally, De Wel et al. (2021) reported a significantly negative association between the relative power in the beta band and total brain volume. Vesoulis et al. (2022) observed that the cumulative seizure burden was significantly negatively associated with total brain volume when not adjusting for confounders.

3.2.2. Cerebellar volume

Four studies have related early postnatal EEG parameters to cerebellar volume (De Wel et al., 2021; Tataranno et al., 2018; Vesoulis et al., 2022; Wikström et al., 2017). De Wel et al. (2021) revealed a significant association between a larger amount of EEG discontinuity, as indicated by longer IBIs or lower SAT percentage, and reduced cerebellar volume. Wikström et al. (2017) also observed a negative relationship between IBIs and cerebellar volume, which was only significant in univariate analysis and was not maintained after adjusting for confounders. Furthermore, Tataranno et al. (2018) found that IBIs and SAT rate were significantly related to the growth of cerebellar volume from 30 to 40 weeks PMA, negatively and positively, respectively.

Additionally, the weekly change in the relative power in the delta band was significantly negatively associated with cerebellar volume, as shown in De Wel et al. (2021). The cumulative seizure burden was found to have a significantly negative relationship with absolute cerebellar volume, either with or without adjusting for confounders (Vesoulis et al., 2022). However, this significance disappeared when the cerebellar volume was corrected for total intracranial volume.

3.2.3. Gray matter volume

Six studies have examined the relationship between early EEG parameters with total, cortical, or deep gray matter volumes (Benders et al., 2015; De Wel et al., 2021; Hüning et al., 2018; Tataranno et al., 2018; Vesoulis et al., 2022; Wikström et al., 2017).

Wikström et al. (2017) reported a negative correlation between the percentage of IBIs and total gray matter volume, which was significant only in univariate analysis but not after adjusting for confounders. De Wel et al., (2021) identified a negative association between the relative power in the beta band and cortical gray matter volume. Tataranno et al. (2018) found a significantly positive association of SAT rate with the growth of cortical gray matter from 30 to 40 weeks PMA, but not with IBIs.

Benders et al. (2015) observed positive associations between SAT number or percentage and both deep gray matter volume and the growth of deep gray matter volume from birth to term-equivalent age. They also showed that EEG (dis)continuity in the highest amplitude band was significantly associated to the growth of deep gray matter volume from birth to term-equivalent age. Specifically, IBIs showed a negative association, while SAT-related parameters were positively associated.

Vesoulis et al. (2022) observed that the cumulative seizure burden was significantly negatively correlated with both cortical and deep gray matter volumes, either with or without adjusting for confounders, while the significance disappeared when corrected for total intracranial volume. Hüning et al. (2018) revealed that higher Burdjalov scores, averaged over the first three days after birth and specifically on day 3, were significantly correlated with a larger deep gray matter volume in univariate analysis.

3.2.4. *White matter volume*

Two studies have explored the associations between early EEG parameters and white matter volume (Vesoulis et al., 2022; Wikström et al., 2017). As reported by Wikström et al. (2017), IBI percentage negatively correlated with unmyelinated white matter volume, which was significant in univariate analysis but not after controlling for confounders. Vesoulis et al. (2022) showed that the cumulative seizure burden was significantly negatively correlated with white matter volume, either with or without adjusting for confounders, and the significance was maintained when corrected for intracranial volume.

3.2.5. *Cerebrospinal fluid volume*

Wikström et al. (2017) and Vesoulis et al. (2022) also examined cerebrospinal fluid volume. Both the percentage of IBIs and the cumulative seizure burden were significantly negatively associated with cerebrospinal fluid volume, either with or without adjusting for confounders, and the significance remained when corrected for intracranial volume.

3.3. *EEG parameters and cortical measurements*

Three studies have evaluated the associations between early EEG parameters and cortical measurements, including cortical surface area, cortical sulcation, and gyrification index (a measure for cortical folding) (Benders et al., 2015; Tataranno et al., 2018; Vesoulis et al., 2022). Benders et al. (2015) found that the maximum IBI on the first postnatal day was significantly negatively associated with total closed cortical surface shortly after birth. They also observed significantly positive associations between EEG continuity at the middle amplitude band and both cortical sulcation and total closed cortical surface shortly after birth. Vesoulis et al. (2022) identified significant negative associations between the cumulative seizure burden and left, right, and average cortical surface area, either with or without adjusting for confounders, while no significant associations were found for the gyrification index. Tataranno et al. (2018) found a significantly positive association between early SAT rate and the increase in gyrification index from 30 to 40 weeks PMA.

3.4. *EEG parameters and white matter microstructural integrity*

Three studies have focused on microstructure measurements derived from diffusion tensor imaging (DTI) (Failla et al., 2022; Tataranno et al., 2018; Winkler et al., 2023). SAT rate was found to be positively correlated with the increase of fractional anisotropy (FA) of the corpus callosum from 30 to 40 weeks PMA (Tataranno et al., 2018). However, neither IBI (Tataranno et al., 2018) nor the activation synchrony index, a measure of synchrony of brain activity (Failla et al., 2022), showed

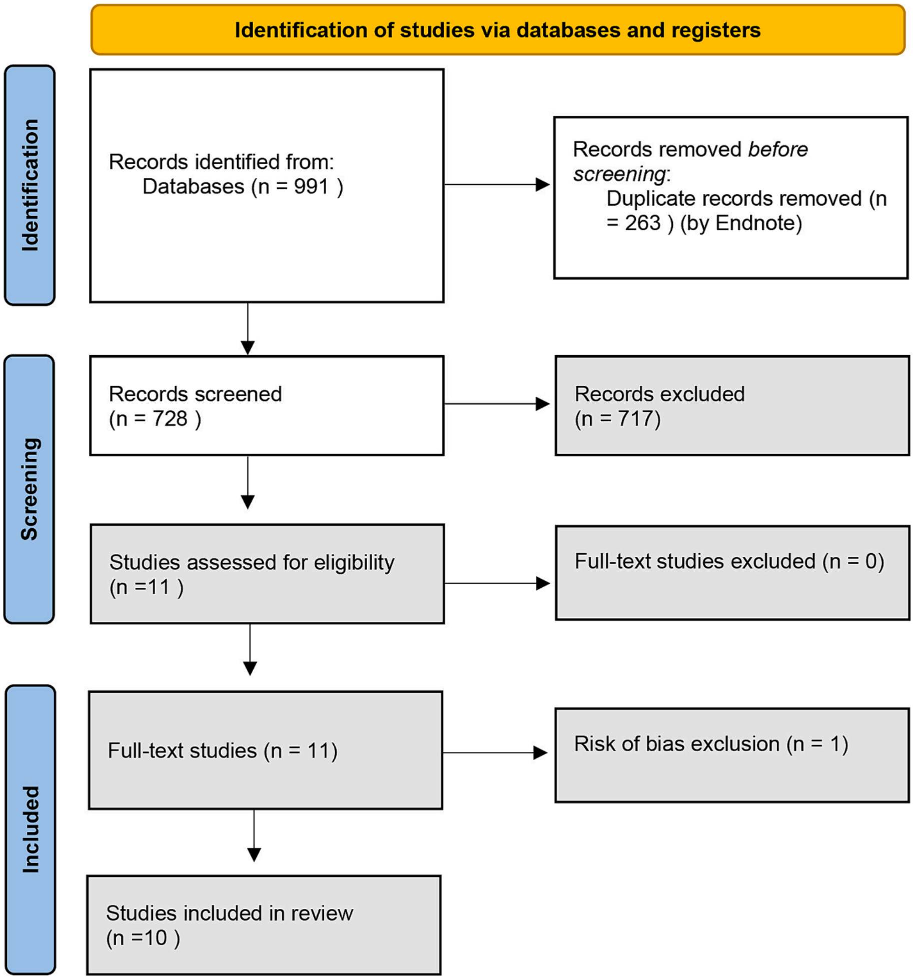

Fig. 1. Prisma Flow Diagram.

Table 1
Study and patient characteristics.

Study	Sample size	GA at birth, weeks	Female, n (%)	Infants with severe brain injury, n (%) [a]	Birth weight, grams	EEG type and channels analyzed	EEG monitoring time	EEG length analyzed	MRI scanning time	PMA at the time of MRI scanning, weeks	Confounders adjusted in statistical analysis	Administration of medications affecting brain activity [b]
Natalucci et al. (2013)	39	29.5 (1.4; 27.0 –31.9)	20 (51%)	At least 1 (3%)	1230 (330; 680–2020)	aEEG from single cross-cerebral channel: P3-P4	Within the first 4 postnatal days	The entire recording period	Term-equivalent age	41.2 (37.1–44.1)	GA at birth, PMA at MRI scanning, morphine administration	Seven patients received morphine sedation (maximum 12 μg/kg/h)) during aEEG; no infants received other sedatives during aEEG; no information on other medications affecting brain activity
Benders et al. (2015)	21	29.3 (2.5; 25.6–35.6)	10 (48%)	0 (0%)	1242 (469; 770–2730)	aEEG from single cross-cerebral channel: P3-P4	First 72 postnatal hours	One hour of good-quality data during 20–24 postnatal hours for amplitude analysis; 2.5 h of good-quality data for discontinuity analysis	Two MRI scans: MRI1: as soon as possible after birth MRI2: term-equivalent age	MRI1: 30.5 (2.4; 26.7–35.7); MRI2: 40.5 (0.8; 39.0–42.9)	GA at birth, morphine administration, minor punctate MRI lesions	Four infants with morphine or midazolam on mechanical ventilation; no information on other medications affecting brain activity
Wikström et al. (2017)	38	25.5 (23.0–30.0)	Not stated	At least 3 (8%)	843 (460–1716)	aEEG from single cross-cerebral channel: P3-P4	First 72 postnatal hours	As long as possible between 24 and 72 postnatal hours without artifacts or seizures	Term-equivalent age	40.1 (0.6)	GA at birth, the number of postnatal morbidities, the number of morphine doses in the first three days, postnatal head circumference growth	Eighteen patients received 1–5 bolus doses of morphine (0.1–0.3 mg/kg) during the study period; no continuous sedative infusions were used; no information on other medications affecting brain activity
Tataranno et al. (2018)	33	26.0 (1.0)	21 (64%)	0 (0%)	916 (157)	aEEG from single cross-cerebral channel: P3-P4	First 72 postnatal hours	One hour of good-quality data during the last 4 h each day	Two MRI scans: MRI1: 30 weeks PMA MRI2: term-equivalent age	MRI1: 30.5 (29.3–32.0); MRI2: 41.1 (40.0–41.8)	GA at birth, birth weight z-score, white matter injury score; PMA at MRI scanning [c]	One patient received 10 mg/kg of phenobarbital on day 2; no infants received any other medication influencing brain activity during aEEG monitoring
Hüning et al. (2018)	38	28.2 (2.3; 23.9–31.6)	18 (47%)	At least 4 (11%)	1039 (404; 450–2085)	aEEG from single channel using two of four electrodes C3, P3, C4, and P4 (the channel name is not specified)	First 72 postnatal hours	The first 4 h within each day showing good quality	Term-equivalent age	40.0 (0.5; 38.9–41.4)	Not used	No sedation/analgesic for patients without intubation within 12 h before EEG recording; no information on other medications affecting brain activity
De Wel et al. (2021)	49	26.4 (1.0)	16 (33%)	At least 1 (2%)	901 (172)	aEEG from two channels: F3-P3, F4-P4	First 72 postnatal hours, and weekly within the first 4–5	One hour of good-quality data each day	Two MRI scans: MRI1:30 weeks PMA MRI2: term-	Not stated	GA at birth and morphine administration; PMA at MRI scanning [c]	Thirty-four infants received morphine during their NICU stay; no information on other medications affecting brain activity

(*continued on next page*)

Table 1 (*continued*)

Study	Sample size	GA at birth, weeks	Female, n (%)	Infants with severe brain injury, n (%) [a]	Birth weight, grams	EEG type and channels analyzed	EEG monitoring time	EEG length analyzed	MRI scanning time	PMA at the time of MRI scanning, weeks	Confounders adjusted in statistical analysis	Administration of medications affecting brain activity [b]
							weeks after birth		equivalent age			
Failla et al. (2022)	25	26.2 (0.9)	8 (32%)	At least 3 (12%)	962 (153)	aEEG from two channels: F3-P3, F4-P4	First 72 postnatal hours and one week after birth	3–5 epochs of 5 min during active sleep each day	Two MRI scans: MRI1: 30 weeks PMA MRI2: term-equivalent age	MRI1: 30.6 (0.9; 28.7–32) MRI2: 41.3 (0.6; 40.0 – 42.7)	Birth weight z-score, white matter injury score, morphine administration; PMA at MRI scanning [c]	Twelve patients received morphine within the first week after birth; no information on other medications affecting brain activity
Tarocco et al. (2022)	91	27.9 (2.0)	Not stated	38 (42%)	1035 (330)	aEEG from two channels: C3-P3, C4-P4; cEEG from eight electrodes: F3, F4, C3, C4, O1, O2, T3, T4 (channel number and names are not specified)	aEEG: 32 weeks PMA; cEEG: both 32 weeks and term-equivalent age	The entire recording: for aEEG, at least four hours; for cEEG, at least 30 min	Term-equivalent age	Not stated	Not used	No information on medications affecting brain activity
Vesoulis et al. (2022)	99	26.3 (1.8)	53 (54%)	At least 9 (9%)	899 (234)	aEEG from two channels: C3-P3, C4-P4	First 72 postnatal hours	The entire recording periods: as long as possible during the first 72 postnatal hours	Term-equivalent age	38 (35–42)	GA at birth, antenatal steroids, grade of intraventricular hemorrhage, grade of white matter injury, culture positive sepsis, necrotizing enterocolitis, bronchopulmonary dysplasia, and postnatal steroids	No patients received anti-epileptic medications as they were not identified clinically as having seizures; no information on other medications affecting brain activity
Winkler et al. (2023)	446 (MRI: 446; EEG: 222–383)	29.4 (2.0; 23.7 – 31.9)	209 (46%)	At least 11 (3%)	1274 (375; 400– 2180)	aEEG from two channels: C3-P3, C4-P4	First 72 postnatal hours, and weekly within the first 4 weeks after birth	Six hours of good-quality data each day during the first 72 h. 3–6 h of good-quality data each week	Term-equivalent age	40.6 (40.1 – 40.9)	GA at birth, 5-min Apgar score, sedation at birth and during the neonatal period, cerebral injury, days on mechanical ventilation, sepsis, treated patent ductus arteriosus, PMA at MRI scanning	In 245 cases, sedation was given in the delivery room (benzodiazepines, opioid derivatives, ketamine, and opioid antagonists); 109 patients received sedation during the neonatal period, type of sedation not specified; no information on other medications affecting brain activity

Data are shown in n (%), mean (SD; range), mean (SD). EEG = electroencephalogram, MRI = magnetic resonance imaging, PMA = postmenstrual age, GA = gestational age, NICU = Neonatal intensive care unit.

[a] Severe brain injury is defined by intraventricular hemorrhage grade III or IV, post-hemorrhagic ventricular dilatation requiring invasive therapy, cystic periventricular leukomalacia grade II or III, cerebellar hemorrhage with a visual score of 3 or greater, and/or total Kidokoro score severely abnormal.

[b] Medications affecting brain activity include morphine, anti-epileptic medications, or other sedatives.

[c] MRI measurements are adjusted for PMA at the time of MRI scanning.

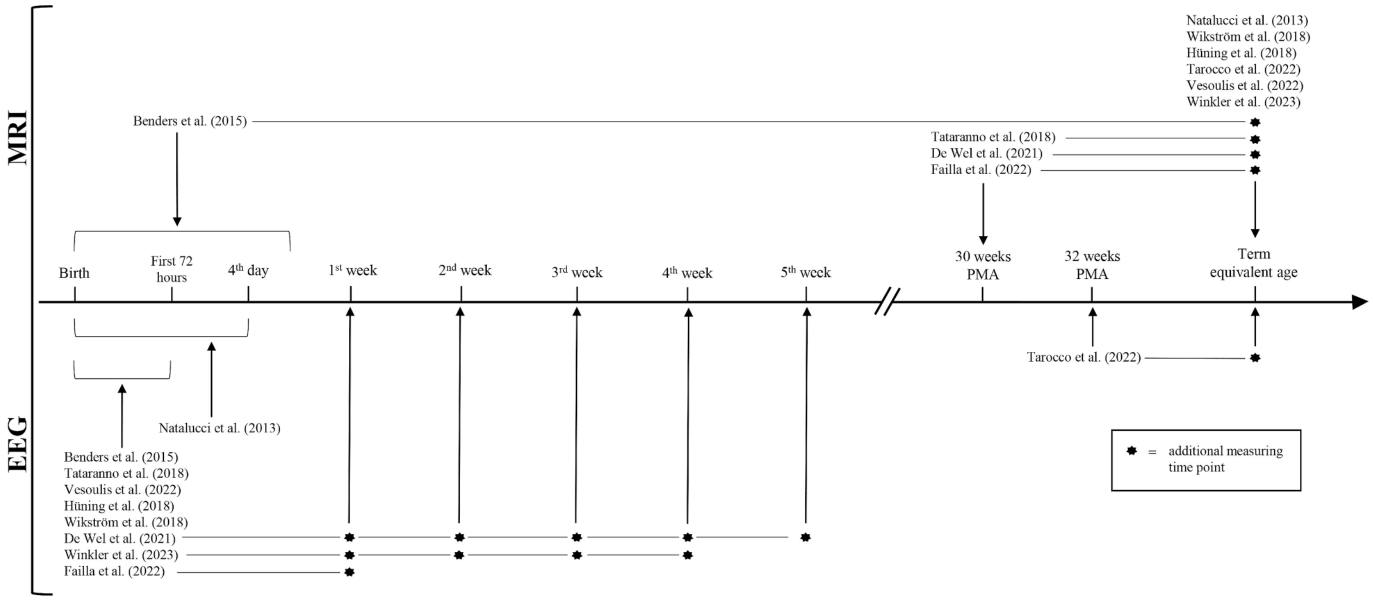

Fig. 2. Timeline of EEG and MRI measuring time points.

significant correlations with the same DTI measure. Additionally, Tataranno et al. (2018) assessed the relationship between SAT rate or IBI and the increase of FA of the posterior limb of the internal capsule; however, no significant results were found. Winkler et al (2023) collected aEEG at multiple time points (days 1–3, weeks 1–4) and performed qualitative aEEG analysis using the Burdjalov scoring system, which includes a total score and four sub-scores: continuity, cycling, bandwidth, and amplitude of the low border. Higher Burdjalov (sub) scores indicate more mature brain activity. By calculating the Spearman rank's correlation coefficients, they found that the total Burdjalov maturation score at every time point was significantly correlated with FA (positively) and apparent diffusion coefficient (a measure of the degree of diffusion; negatively) of the genu corpus callosum. After adjusting for confounders, the correlation on day 2 and day 3 remained significant, while the significance of the correlation at week 3 and week 4 was partially attenuated (on apparent diffusion coefficient). At most time points, similar association patterns were also found for the splenium corpus callosum. Additionally, the total Burdjalov maturation score on day 2 showed significant correlations with microstructural features of the posterior limb of the internal capsule (both FA and apparent diffusion coefficient) and centrum semiovale (only FA). More details can be found in Supplementary Table S2.

3.5. EEG parameters and qualitative MRI assessment

Three studies have used qualitative MRI assessment to evaluate brain development in relation to EEG parameters (Hüning et al., 2018; Natalucci et al., 2013; Tarocco et al., 2022). Hüning et al. (2018) and Tarocco et al. (2022) used an MRI scoring system developed by Kidokoro et al. (2013) (hereafter referred to as "Kidokoro score"). Natalucci et al. (2013) used a system developed by Childs et al. (2001) (hereafter referred to as the "Childs maturation score"). The injury-related scores in the Kidokoro system were not parameters of interest and were, therefore, not considered in this review. Higher developmental sub-scores in the Kidokoro system indicate delayed brain development, while higher Childs maturation (sub)scores indicate higher brain maturation.

Qualitative scoring of aEEG traces in all the three studies was performed using the Burdjalov scoring system. Both Hüning et al. (2018) and Natalucci et al. (2013) performed EEG scoring within the first 72 h after birth, while Tarocco et al. (2022) conducted EEG scoring at 32 weeks PMA.

Tarocco et al. (2022) analyzed the total Burdjalov score and three Burdjalov sub-scores (continuity, cycling, and bandwidth), using an univariate analysis without adjusting for confounders. They found that each of the four Burdjalov scores was significantly negatively related to at least one of the two following Kidokoro sub-scores: gyration or myelination delay (see details in Supplementary Table S2). Hüning et al. (2018) did not find any significant associations between Burdjalov (sub) scores and Kidokoro scores.

Natalucci et al. (2013) analyzed the total Burdjalov score, one Burdjalov sub-score (cycling), and two quantitative aEEG features: maximum and minimum aEEG amplitude. They found that total Burdjalov score, cycling sub-score, and maximum aEEG amplitude were significantly positively associated with total Childs maturation score in univariate analysis, and only the former two remained significant after adjusting for confounders. They also observed that each of the four aEEG scores was significantly positively associated with at least one of the four Childs maturation sub-scores: the degree and localization of myelination and cortical folding, the presence and distribution of the germinal matrix, and the bands of migrating glial cells (see details in Supplementary Table S2).

3.6. EEG parameters and linear MRI measurements

Two studies have also investigated linear measurements on MRI, referring to direct measurement of straight-line distances within the brain, in relation to EEG features (De Wel et al., 2021; Hüning et al., 2018). De Wel et al. (2021) observed the following significant associations: positive correlation between multiscale entropy and mid-sagittal cerebellar height at 30 weeks PMA, positive correlation between SAT percentage and mid-sagittal cerebellar width at 40 weeks PMA and its growth from 30 and 40 weeks PMA, negative correlation of IBI duration and relative power in alpha band with mid-sagittal cerebellar width at 40 weeks PMA, and negative correlation between relative power in beta band and coronal cerebellar width. They also reported a significantly positive relationship between weekly changes in the relative power in the theta band and interhemispheric distance. Hüning et al. (2018) observed that total Burdjalov score had significantly positive correlations with biparietal width and coronal cerebellar width.

Table 2
Summary of used EEG and MRI parameters in included papers.

				Natalucci et al. (2013)	Benders et al. (2015)	Wikström et al. (2017)	Tataranno et al. (2018)	Hüning et al. (2018)	De Wel et al. (2021)	Failla et al. (2022)	Tarocco et al. (2022)	Vesoulis et al. (2022)	Winkler et al. (2023)
EEG parameters used in statistical analysis	Quantitative	Discontinuity	Spontaneous activity transients [a]		•		•		•				
			Inter-burst interval [b]		•	•	•		•				
		Spectral content	Relative power						•				
			Spectral edge frequency						•				
			Multiscale entropy						•				
		Amplitude	EEG continuity at amplitude bands		•								
			aEEG amplitude	•									
		Connectivity	Interhemispheric synchrony							•			
	Qualitative	Visual assessment	Cumulative seizure burden									•	
			Burdjalov maturity score (s)	• [c]				• [c]			• [c]		•
			EEG background analysis								•		
MRI measurements used in statistical analysis	Quantitative	Brain volumes [d]	Total or intracranial brain volume		•	•			•			•	
			Cerebellum			•	•		•			•	
			Total gray matter			•							
			Cortical gray matter				•		•			•	
			Deep gray matter		•			•				•	
			Total white matter									•	
			Unmyelinated white matter			•							
			Cerebrospinal fluid			•						•	
		Microstructure	Fractional anisotropy corpus callosum				•			•			•
			Fractional anisotropy posterior Limb of the internal capsule				•						•
			Fractional anisotropy centrum semiovale										•
			Apparent diffusion coefficient corpus callosum										•
			Apparent diffusion coefficient posterior limb of the internal capsule										•
			Apparent diffusion coefficient centrum semiovale										•
		Cortical measurements	Cortical surface area		•							•	
			Cortical sulcation		•								
			Gyrification index				•					•	
		Linear measurements on MRI	Bipartiel width					•					
			Interhemispheric distance/fissure					•	•				
			Transcerebellar diameter					•					
			Cerebellar height						•				
			Cerebellar width						•				

(*continued on next page*)

Table 2 (*continued*)

		Natalucci et al. (2013)	Benders et al. (2015)	Wikström et al. (2017)	Tataranno et al. (2018)	Hüning et al. (2018)	De Wel et al. (2021)	Failla et al. (2022)	Tarocco et al. (2022)	Vesoulis et al. (2022)	Winkler et al. (2023)
Qualitative	Kidokoro subscores					●[e]			●[e]		
	Maturation score	●[c]									

EEG = electroencephalogram, MRI = magnetic resonance imaging.

[a] Types of spontaneous activity transient (SAT) parameters: number SAT events in a time interval (Benders et al., 2015; Tataranno et al., 2018), percentage of SAT events in a time interval (De Wel et al., 2021; Benders et al., 2015).

[b] Types of inter-burst interval (IBI) parameters: duration of IBI (Benders et al., 2015; De Wel et al., 2021), number of IBIs in a time interval (Wikström et al., 2017; Tataranno et al., 2018).

[c] Including subscores.

[d] Including volumetric growth.

[e] An adapted Kidokoro scoring system was used.

3.7. *Potential confounders affecting EEG-MRI associations*

Out of the ten studies included, eight (80%) conducted confounder adjustments in their statistical analysis (Benders et al., 2015; De Wel et al., 2021; Failla et al., 2022; Natalucci et al., 2013; Tataranno et al., 2018; Vesoulis et al., 2022; Wikström et al., 2017; Winkler et al., 2023). While the specific confounders varied across these studies, possible confounders affecting EEG-MRI associations included GA at birth, PMA at MRI scanning, morphine administration, birth weight (or birth weight z-score), Apgar score, white matter injury score, minor punctate MRI lesions, the number of postnatal morbidities, days on mechanical ventilation, and postnatal head circumference growth.

Furthermore, to mitigate the influence of interindividual variation in brain size, several studies also corrected regional volumetric measurements against total or intracranial volume (Tataranno et al., 2018; Vesoulis et al., 2022; Wikström et al., 2017).

4. Discussion

This systematic review provides a comprehensive overview of the existing literature regarding the associations between EEG and MRI measurements in preterm infants. We included ten studies, which showed large heterogeneity in the selection and timing of EEG and MRI measurements. Consistent findings among the reviewed studies were the associations of increased EEG discontinuity and higher Burdjalov maturity scores with better brain maturation on MRI. However, due to the diverse application of other EEG parameters in these studies, establishing consistent associations for these parameters proved challenging.

In the studies we reviewed, discontinuity was the most frequently analyzed EEG parameter. Four studies consistently reported that less discontinuity, quantified as shorter IBIs and higher SATs, was related to improved brain maturation, indicated by enhanced measurements in total brain volume, cerebellar volume, fractional anisotropy of the corpus callosum, cortical surface, cerebellar width, or gyrification index (Benders et al. 2015; De Wel et al. 2021; Tataranno et al. 2018; Wikström et al. 2017). These findings are supported by developmental and cellular research (Andescavage et al., 2017; Kostović & Judaš, 2010). Burst-like EEG patterns are a result of migration of thalamocortical axons into the cortical plate and the start of synaptogenesis, during the third trimester (Kostović & Judaš, 2010). The third trimester is also a period of rapid brain growth (Andescavage et al., 2017). This might explain the discontinuity-brain association.

The Burdjalov score is a widely used scoring system designed for visually scoring various aspects of aEEG recordings, including continuity, cycling, the amplitude of the lower border, and bandwidth (Burdjalov et al., 2003). Four reviewed studies employed the Burdjalov (sub)scores, with three of them linking higher Burdjalov (sub)scores to better brain maturation, indicating its potential to be a good marker for brain maturation abnormalities identified at TEA. In other literature, the Burdjalov score was also found to be useful for indicating brain injury and predicting neurodevelopmental outcomes (Bruns et al., 2017; El Ters et al., 2017; Ralser et al., 2017). Nevertheless, as a visual assessment method, the Burdjalov scoring system is subject to inter-rater variability, time-consuming to use, and requires specific training to achieve proficiency. Moreover, GA at birth and PMA at EEG monitoring are not considered in this scoring system. Therefore, there is a need to develop novel, automated methods in future research to make the scoring process more objective and efficient.

In addition to the two most frequently analyzed EEG parameters, several other qualitative and quantitative EEG parameters, including spectral content, connectivity, amplitude, and seizure burden, were also used in the reviewed studies. However, each of these parameters was only used in a single study, making it difficult to compare results and draw reliable conclusions.

Specifically, regarding the spectral content of the EEG, one reviewed study reported negative correlations between relative spectral power in all frequency bands with multiple brain volumes and cerebellar width, and positive correlations with interhemispheric fissure (De Wel et al., 2021). These results partially contrast with the relationship between PMA and spectral power, as reported in previous studies (Niemarkt et al., 2011; Tolonen et al., 2007). Furthermore, inconsistent directions were also observed in the relationships between relative spectral power and long-term neurodevelopmental outcomes (van 't Westende et al., 2022). Given these inconsistencies, the relative spectral power appears to be a less reliable parameter for assessing brain maturation.

Of note, most of the included studies (9/10) focused on extremely to very preterm infants (born before 32 weeks of gestation). The exception was the study by Benders et al. (2015), which included infants born between 25.6 and 35.6 weeks of gestation. However, the average GA at birth reported in this study was 29.3 weeks (SD = 2.5 weeks), indicating most of their study population was born extremely or very preterm. Therefore, the findings discussed in this review are largely applicable to extremely to very preterm infants.

Extremely to very preterm infants usually experience numerous essential medical interventions and various visual, auditory, and somatosensory stimuli during their stay in the NICU, indicating that multiple confounding factors can influence EEG and MRI measurements. To address this issue, it is important to control for confounders in the analysis to mitigate their influence. Out of numerous potential confounders, several are particularly important and should be considered in the investigation of EEG-MRI relationships, including GA at birth (André et al., 2010), PMA at MRI scanning (Volpe, 2019), the presence of brain injury (Ramenghi et al., 2007; Ranasinghe et al., 2015), and the administration of medications affecting brain activity (Bell et al., 1993; Norman et al., 2013; Tataranno et al., 2020; ter Horst et al., 2004). Unfortunately, the medication administration is less considered in the studies investigated in this review, introducing possible bias in the findings. Specifically, six studies included the administration of morphine or other sedatives as a confounding factor (Benders et al., 2015; De Wel et al., 2021; Failla et al., 2022; Natalucci et al., 2013; Wikström et al., 2017; Winkler et al., 2023), one excluded EEG sequences of patients with sedative medications other than morphine at the time of monitoring (Natalucci et al., 2013), and only one excluded infants with any medications potentially affecting brain activity (Tataranno et al., 2018).

The quality assessment revealed several issues that challenge the generalizability of the findings of the reviewed studies. The major issue is the lack of essential information being reported. For example, Tarocco et al. (2022) and Wikström et al. (2017) did not report the female-to-male ratio of their study population, despite the potential differences in EEG signals between female and male preterm infants (Griesmaier et al., 2014). Moreover, only four studies reported the descriptive statistics regarding EEG and MRI measurements (Failla et al., 2022; Hüning et al., 2018; Vesoulis et al., 2022; Wikström et al., 2017), with the majority focusing only on the association results. Additionally, differences in EEG data acquisition (e.g., the number of electrodes or channels used) and the lack of standardized calculations for EEG parameters, added to the heterogeneity across studies.

The most significant limitation is that the heterogeneity among the reviewed studies makes it challenging to summarize all reported results and to provide a clear overview of the existing findings. This heterogeneity also made it impossible to perform a *meta*-analysis of the investigated results. Additionally, language restrictions might have excluded valuable insights from non-English publications.

Several promising avenues for future research warrant mention. First, most of the reviewed studies (6/10) focused only on early EEG monitoring within the first postnatal days. While early monitoring offers the potential for predicting brain development from a very early stage, recent research has indicated that EEG recordings taken around 35 weeks of gestational age may have stronger predictive value for neurodevelopmental outcomes than those conducted immediately after birth (Lloyd et al., 2021). Future studies could benefit from exploring a combined approach, involving both early postnatal EEG monitoring and subsequent weekly recordings throughout the NICU stay. Secondly, there are no individual EEG parameters to accurately predict MRI brain development. It is needed for future studies to examine the combined predictive value of multiple types of EEG parameters. Lastly, establishing standardized guidelines for clinical EEG use in the NICU is crucial. Given the wide range of EEG parameters available, it is essential for clinicians to understand which parameters are clinically relevant and how to effectively utilize them at the bedside.

5. Conclusion

In summary, this study systematically reviewed existing literature investigating the relationship between early life EEG parameters and brain MRI measurements in preterm infants. The studies we reviewed showed heterogeneity in both EEG and MRI measurements utilized. Among the various EEG parameters studied, discontinuity and the Burdjalov maturity scores were most frequently assessed. It was consistently observed that reduced discontinuity and higher Burdjalov scores correlate with improved brain structural maturation. This consistent association underscores their value as important markers for connecting functional brain activity with structural brain development. Our findings shed light on the clinical relevance of specific EEG parameters, thus aiding in their more effective application in clinical practice.

CRediT authorship contribution statement

Roos F. Meijer: Conceptualization, Methodology, Validation, Formal analysis, Investigation, Data curation, Writing – original draft, Writing – review & editing, Visualization. **Xiaowan Wang:** Conceptualization, Methodology, Validation, Formal analysis, Investigation, Data curation, Writing – original draft, Writing – review & editing, Visualization, Supervision. **Inge M. van Ooijen:** Methodology, Writing – review & editing, Visualization, Supervision. **Bauke van der Velde:** Writing – review & editing. **Jeroen Dudink:** Writing – review & editing. **Manon J.N.L. Benders:** Writing – review & editing, Supervision. **Maria Luisa Tataranno:** Conceptualization, Methodology, Resources, Writing – review & editing, Supervision, Project administration.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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