Neonatal quantitative electroencephalography and long-term outcomes: a systematic review

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PUBLICATION DATA

Accepted for publication 8th November 2021.

Published online 21st December 2021.

ABBREVIATIONS

Bayley-III	Bayley Scales of Infant and Toddler Development, Third Edition
BSID-II	Bayley Scales of Infant Development, Second Edition
IBI	Interburst interval
PCA	Postconceptional age

AIM To evaluate quantitative electroencephalogram (EEG) measures as predictors of long-term neurodevelopmental outcome in infants with a postconceptional age below 46 weeks, including typically developing infants born at term, infants with heterogeneous underlying pathologies, and infants born preterm.

METHOD A comprehensive search was performed using PubMed, Embase, and Web of Science from study inception up to 8th January 2021. Studies that examined associations between neonatal quantitative EEG measures, based on conventional and amplitude-integrated EEG, and standardized neurodevelopmental outcomes at 2 years of age or older were reviewed. Significant associations between neonatal quantitative EEG and long-term outcome measures were grouped into one or more of the following categories: cognitive outcome; motor outcome; composite scores; and other standardized outcome assessments.

RESULTS Twenty-four out of 1740 studies were included. Multiple studies showed that conventional EEG-based absolute power in the delta, theta, alpha, and beta frequency bands and conventional and amplitude-integrated EEG-related amplitudes were positively associated with favourable long-term outcome across several domains, including cognition and motor performance. Furthermore, a lower presence of discontinuous background pattern was also associated with favourable outcomes. However, interpretation of the results is limited by heterogeneity in study design and populations.

INTERPRETATION Neonatal quantitative EEG measures may be used as prognostic biomarkers to identify those infants who will develop long-term difficulties and who might benefit from early interventions.

Adverse events during early brain development can damage this organ and may cause long-term adverse outcomes.[1–3] Reliable prognostic biomarkers are needed to identify those infants who will develop long-term neurological difficulties. Cranial ultrasound and magnetic resonance imaging are commonly used in clinical practice for the early detection of brain abnormalities. However, structural brain abnormalities do not fully explain the observed heterogeneity in long-term outcomes,[4] thus shifting attention towards studying brain function with electroencephalography (EEG).[5,6] Neonatal EEG is characterized by a dominant frequency that resides in the delta frequency band, in contrast to adults who show dominant frequencies around 10Hz.[7–9] In infants, higher frequencies, including theta, alpha, and beta oscillatory activity, are predominantly present during transient specific waveforms, such as delta brushes or sharp temporal theta bursts, and are not part of the background pattern as they are in adults.

Both conventional and amplitude-integrated EEGs are used for qualitative assessments.[10] However, the interrater reliability of qualitative interpretation is often suboptimal.[11] Computer-assisted EEG analysis of conventional and amplitude-integrated EEGs can detect disruptions that are not always apparent by visual assessment.[12] Therefore, quantitative EEG techniques, such as amplitude-integrated EEG amplitudes and conventional EEG power spectrum analysis, have gained interest.[7] There are indications that associations between neonatal quantitative EEG measures and long-term outcomes exist;[13,14] however, the prognostic utility of early quantitative EEG measures in infants at risk of adverse long-term brain functioning is unclear. This systematic review aimed to evaluate quantitative EEG

 DOI: 10.1111/dmcn.15133

measures as predictors of long-term neurodevelopmental outcome in infants with a postconceptional age (PCA) below 46 weeks, including typically developing infants born at term, infants with heterogeneous underlying pathologies, and infants born preterm, to identify biomarkers for more accurate prognoses and indications for early interventions.

What this paper adds

- Neonatal quantitative electroencephalogram (EEG) measures were associated with long-term outcomes across multiple studies.
- Higher amplitude-integrated EEG amplitudes, more continuous patterns, and higher absolute powers were associated with favourable long-term outcomes.
- Neonatal quantitative EEG measures might provide new prognostic information in neonates at risk.

METHOD

This review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement[15] and was registered at PROSPERO (no. CRD42020189084).

Study selection

Inclusion criteria were: infants with a PCA below 46 weeks during EEG recording; acquisition of resting state amplitude-integrated or conventional EEG; quantitative analysis of EEG data; standardized follow-up after at least 2 years; analyses of associations between quantitative EEG measures and long-term outcome assessments; and peer-reviewed and original research.

PubMed, Embase, and Web of Science were searched up to 8th January 2021. The search strategy employed is shown in Appendix S1 (online supporting information). In addition, experts (CJS and JD) were consulted and the reference lists of the articles included in this review were searched.

Figure S1 (online supporting information) shows the selection process. Title and abstract screening was performed by two independent reviewers (CvtW and VJG). Interrater agreement was assessed with Cohen's kappa.[16]

Data extraction and synthesis of results

Piloted forms were used for data extraction (Appendix S2, online supporting information). In case of uncertainty, two reviewers (CvtW and VJG) discussed the eligibility of study content for this review. Studies were grouped into one or more of four outcome categories: cognitive outcome; motor outcome; composite scores (i.e. a combination of items dichotomized into unfavourable and normal outcome groups); and other standardized outcome assessments.

Risk of bias

Risk of bias at the study level was assessed by two independent reviewers (CvtW and TvR) by using a modified version of the Checklist for Case Series developed by the JBI,[17] with one additional item addressing methodological quality of EEG acquisition, as described previously[17] (Appendix S3, online supporting information). JBI scores were reported.

RESULTS

The search yielded 1740 unique records; 105 studies were selected for full-text screening. Twenty-four studies met the inclusion criteria and all studies were identified as case series. Table S1 (online supporting information) provides a list of studies excluded from the review and the reasons for exclusion. Interrater agreement for title and abstract screening was moderate (κ=0.44).[18] Absolute JBI scores and the answers of two independent reviewers on the JBI items per study can be found in Table S2 (online supporting information). Table S3 (online supporting information) provides an overview of the study characteristics. Gestational age ranged from 22 to 42 weeks and PCA from 22 to 45 weeks. Five out of 24 studies (partly) investigated a group of typically developing infants born at term. Most of the studies investigated the population of infants born preterm (n=17) and infants with hypoxic ischaemic encephalopathy (n=3). Forty-eight per cent of infants were male. More detailed information on gestational age, age during EEG, birthweight, sex, data quality and/or artefact handling, drug administration, and sources of funding are found in Table S4 (online supporting information). Mean age at follow-up varied from 2 to 8 years and 77% of children were below 3 years of age at follow-up. Most of the studies used the Bayley Scales of Infant Development, Second Edition (BSID-II; n=10) and Bayley Scales of Infant and Toddler Development, Third Edition (Bayley-III; n=4) and/or Griffiths Scales of Babies Abilities (n=3) as the long-term outcome assessments. Table S5 (online supporting information) provides descriptions of long-term outcome assessments.

Descriptions of quantitative EEG measures are provided in Table S6 (online supporting information). Sixteen studies analysed conventional EEG data and eight studies analysed amplitude-integrated EEG data. Quantitative EEG measures were mostly related to conventional EEG-based power spectrum analysis (n=11), followed by measures related to the amplitudes of amplitude-integrated EEG data (n=7) and conventional EEG data (n=1), including automated quantification of discontinuous background patterns (n=4). Other measures based on conventional EEG data included functional connectivity (n=4) and network (n=3) measures.

Cognitive outcome

Sixteen studies investigated the associations between neonatal quantitative EEG measures and long-term cognitive outcomes. Five studies did not report significant findings after covariate adjustment.[19–23] Significant results are summarized in Figure S2a (online supporting information).

A higher minimum amplitude, based on amplitude-integrated EEG, in infants born preterm might be related to higher precursor literacy skills.[24] Middel et al. reported

seemingly contradictory results, describing both negative and positive associations between cognitive outcomes (verbal IQ, selective attention, and long-term verbal memory) and amplitude-integrated EEG amplitude centiles (5th, 50th, and 95th) in infants born preterm.[25]

Higher absolute power in the delta, theta, and alpha frequency bands, calculated over conventional EEG data, was favourable for long-term cognitive performance and language development in infants born extremely preterm and preterm.[26] Studies investigating the association of relative power with long-term outcome showed contradictory results. Nghiem et al. and Pham et al. investigated EEG data derived from the same cohort of infants born at term exposed to dioxin.[27,28] Pham et al. showed that, during quiet sleep, conventional EEG-based relative delta power in the occipital area of the left hemisphere was negatively associated with language performance at 26 months of age.[28] By contrast, both the study by Nghiem et al., where EEG data were analysed during active sleep in infants born at term, and the study by Castro Conde et al., where infants born at term who were small for gestational age and infants born preterm with birthweight appropriate for gestational age were investigated, showed that language performance at 2 years of age was positively associated with relative delta power.[27,29] Furthermore, language performance at 2 years of age was negatively associated with relative alpha power in infants born preterm and at term.[27,29] These studies had high JBI scores.

Connectivity studies based on conventional EEG data showed that alpha and theta coherence might be negatively associated with language in infants born at term[27] and that beta coherence was a discriminator for five groups based on outcome.[30] Another study investigating burst characteristics using conventional EEG data in infants born extremely preterm showed that higher scaling slopes, lower sharpness, and lower symmetry of bursts predicted better cognitive outcomes.[31]

Motor outcome

Eight studies investigated the associations between motor outcome and neonatal quantitative EEG measures (Fig. S2b, online supporting information). One study reported no significant findings.[25] An amplitude-integrated EEG-based study showed that higher minimum and maximum amplitudes in interburst intervals (IBIs) during the extremely preterm period are related to better motor outcome (BSID-II).[32] Conventional EEG-based absolute power in the delta, theta, alpha, and beta frequency bands was positively associated with two motor scores (BSID-II and Peabody Developmental Motor Scales, Second Edition) in infants born extremely preterm and preterm.[26] Relative delta power, based on conventional EEG, in the left occipital area in infants born at term during active sleep was negatively associated with motor outcome (Bayley-III), whereas relative alpha power in the left parieto-occipital and right temporo-occipital areas showed a positive association.[28] Castro Conde et al. showed a positive association between relative delta/alpha power ratio (i.e. relatively higher power in the lower-frequency bands) and motor outcome (Bayley-III) in infants born at term small for gestational age and infants born preterm appropriate for gestational age,[29] whereas El Ters et al. showed that it was favourable to have a spectral edge frequency at 90% above 9.2Hz (indicating higher power at higher frequencies) in infants born extremely preterm.[33] Nghiem et al. reported an association between relative alpha power during active sleep in infants born at term at electrode position Fp2 and fine motor skills (Bayley-III); however, the direction of the association was unclear.[27]

Higher symmetry and lower sharpness of bursts, based on the conventional EEG data of one channel, in infants born extremely preterm was associated with better motor performance, as assessed with the BSID-II.[31]

Composite scores

Eight studies used composite scores for long-term outcome assessment (Fig. S2c, online supporting information). The definition of composite scores differed per study (Table S3, online supporting information). All studies reported significant results. Amplitude-integrated EEG-based studies showed that a higher amount of discontinuous background pattern in infants with hypoxic ischaemic encephalopathy born at term[34] and lower minimum and maximum amplitudes in infants born preterm and at term-equivalent age[35] might have high positive predictive values (>87%) for adverse long-term outcomes. IBI duration and percentage in infants born extremely preterm was positively associated with adverse long-term outcomes,[36] as was lower total absolute power between 23 and 31 weeks of PCA.[26]

Network studies revealed that lower clustering coefficient and weight dispersion between 28 and 32 weeks of PCA, reflecting less ordered network organization, were associated with better outcomes in groups with and without intraventricular haemorrhage.[37] A support vector machine model based on 94 quantitative EEG measures derived from an independent EEG data set of neonates with hypoxic ischaemic encephalopathy born before 29 weeks' gestational age and who were medically stable during EEG recordings, was used to predict the PCA in infants who underwent serial EEGs between 26 and 38 weeks of PCA.[38] A lower predicted PCA than the true PCA was significantly associated with adverse neurodevelopmental outcome.[39] Infants born extremely preterm with higher scaling slopes, lower sharpness, and lower symmetry of bursts, based on conventional EEG measurements of one channel during the extremely preterm period, had favourable outcomes at 2 years of age.[31]

Other standardized outcomes

Eight studies investigated the associations between a variety of long-term outcome assessments and neonatal quantitative EEG measures (Fig. S2d, online supporting information). One study reported no significant associations.[25] Minimum and maximum amplitudes during IBIs, based on amplitude-integrated EEG data, in infants born

extremely preterm were both positively associated with better outcome; increased duration of IBIs might be associated with higher disability.[32] Furthermore, in infants born at term with tuberous sclerosis complex, conventional EEG-based regularity and range EEG asymmetry, reflecting discontinuous patterns, were higher in children at 2 years of age with more autism spectrum disorder traits.[21]

Higher absolute power during quiet sleep in infants born at term within higher frequencies might be related to both higher socioemotional competence and lower autism spectrum disorder risk scores in males but not females at 2 to 3 years of age.[40] Conventional EEG-based relative delta power in the frontal and parietal areas of the left hemisphere in infants born at term was positively associated with duration of face fixation, reflecting communicative abilities, around 2 years of age.[28] Cainelli et al. found that relative alpha power in infants born preterm during active sleep at certain electrode positions was positively associated with visual and auditory attention at 6 years of age and that relative beta power was positively associated with visual attention.[23] Relative beta power in the parietal area of the right hemisphere in infants born at term was negatively associated with the duration of face fixation at 26 months of age.[28] Sleep-induced connectivity changes in posterior networks comprising mostly occipital cortices in the alpha and beta frequency bands correlated significantly with visual performance in infants born extremely preterm and at term.[41] Two network studies showed that higher EEG complexity, a measure that reflects whether an EEG signal is random or has a certain order, might be positively associated with favourable outcomes, namely lower risk of later epilepsy and fewer autism spectrum disorder traits.[21,42]

Summary of results

Figure 1 shows an overview of the neonatal quantitative EEG measures related to a long-term favourable outcome. There is substantial heterogeneity across the studies included in this review in terms of study design. Multiple studies showed that neonatal amplitude-integrated EEG-based amplitudes and discontinuous patterns and conventional EEG-based absolute power across the total power spectrum can predict long-term outcome at the group level in several domains. The results of studies investigating relative power are contradictory. Single studies showed associations between a spectral edge frequency at 90%, several network and connectivity measures, burst characteristics and predicted age differences, and long-term outcomes.

DISCUSSION

This systematic review aimed to investigate the potential of neonatal quantitative EEG measures to serve as biomarkers for long-term outcomes. Twenty-four studies were identified, with most focusing on infants born preterm. The population born preterm is at risk for adverse outcomes even in the absence of detectable structural brain abnormalities, resulting in a need for prognostic tools in addition to neuroimaging.[43] The results of this review show that several quantitative EEG measures can predict long-term outcome at the group level.

The development of the neonatal EEG pattern follows a predictable route, including the evolution from discontinuous to continuous background patterns.[44,45] Bursts during discontinuous background patterns in the early phases are vital endogenous drivers for activity-dependent brain wiring before the onset of sensory-driven ongoing cortical activity.[46] Qualitative EEG research has shown that longer IBIs have strong predictive value for adverse short- and long-term outcomes in infants with hypoxic ischaemic encephalopathy[10,35,47] and other underlying neuropathologies.[48] Consistent with these findings, the results from this review indicate that those infants with shorter IBIs and lower IBI percentages had better outcomes[36] and that higher minimum and maximum amplitude-integrated EEG amplitudes, which possibly reflect shorter IBIs, increased burst length, and/or overall higher amplitudes, were also favourable.[24,32,35] These findings reflect that better maturation of the background pattern in the preterm period and around term age in infants with and without encephalopathy or tuberous sclerosis complex, based on conventional, amplitude-integrated, and quantitative EEG measures, predicts better long-term outcomes.[21,24,25,32,35] This is supported by the findings of Stevenson et al., who showed that brain maturational delays in infants born extremely preterm in the neonatal phase, as indicated by the predicted age difference between true and predicted PCA derived from a support vector machine model, were related to long-term adverse outcomes.[39]

The results of conventional EEG absolute power analyses were consistent with the findings of amplitude-integrated EEG amplitude-related measures; in infants born extremely preterm, preterm, and at term, higher absolute power in several frequency bands was related to favourable long-term outcomes, as were higher amplitude-integrated EEG amplitudes.[26,40] However, absolute amplitude values cannot be compared between the studies included in this review because different amplitude-integrated EEG systems have different amplitude values.[49] Furthermore, EEG measures predominantly depend on the magnitude of individual pyramidal cell current dipoles as well as the degree of neural synchronization over a patch of the cortex. However, as shown in non-human primates, differences in neural synchronization alone can change EEG amplitudes without changes in the amplitudes of local field potentials (i.e. neural activity recorded by electrodes placed in the tissue with the generating cells).[50] It is therefore unclear if the observed favourability of higher amplitudes in the neonatal EEG is linked to increased magnitudes of current dipoles, increased synaptic and/or neural density, or increased neural synchronization.

Although multiple studies have described a close relationship between PCA and functional connectivity and network measures,[13,51–55] only a few studies exploring the associations between these measures and long-term neurodevelopmental outcome were identified in this review.

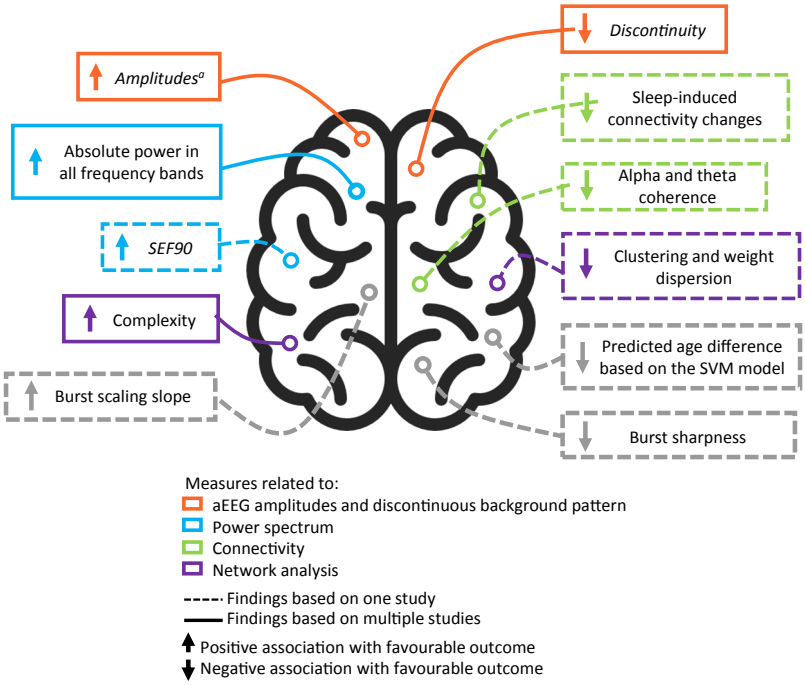

Figure 1: Patterns of quantitative electroencephalogram (EEG) measures associated with favourable long-term outcomes. [a]Text in italics identifies quantitative EEG measures that are based on amplitude-integrated EEG (aEEG) data. SVM, support vector machine; aEEG, amplitude-integrated EEG.

However, the findings of these studies were promising since all except one[20] showed significant associations between a variety of connectivity and network measures and long-term outcomes.[21,27,30,37,42] Interestingly, Tokariev et al. showed that investigating the location of changes in functional connectivity might be relevant since functional connectivity in the visual occipital region in infants born extremely preterm and at term was positively associated with higher visual performance after 2 years.[41]

Several potential factors may have influenced the results of the studies included in this review. Drug exposure may have influenced the results since it may have affected several features of early brain function reflected in the EEG.[19,56,57] For example, phenobarbital and morphine might promote discontinuous background patterns.[58–60] However, the effects of drug exposure on neonatal brain activity are difficult to investigate because of the possible bias introduced by the clinical reasons behind administering these drugs. Another factor not taken into account in all of the studies included in this review is sex. Brito et al. showed that sex was an important factor for the relationship between autism spectrum disorder risk scores and absolute power at higher frequencies since this association was only present in males.[40] In addition, previous research showed that a spectral edge frequency at 90% and relative powers differed between males and females.[61,62] Furthermore, vigilance state, including quiet, active, and intermediate sleep, affects quantitative EEG analysis,[14,63,64] a factor that was considered in only seven of the 24 studies included in this review.[22,23,27,28,37,40,41]

A major limitation of this review is the lack of a quantitative synthesis (meta-analysis), which was impeded by heterogeneity in study design. The studies included in this review investigated different study populations, for example, infants born preterm, infants with asphyxia, or infants with tuberous sclerosis complex. In addition, EEG settings and analyses were substantially different across studies, including differences in the number of electrodes, reference electrodes, and quantitative EEG measures used. This precludes determination of the best quantitative EEG measures as prognostic biomarkers, indicating the need to standardize neonatal EEG acquisition and analysis.

A wide range of long-term outcome assessments were used, even within single outcome categories. Assessment designs were diverse, including neurological examinations, parental questionnaires, and standardized batteries. For example, cognition was assessed by nine different outcome assessments (Bielefelder screening, Wechsler Preschool and Primary Scales of Intelligence, Wechsler Intelligence Scale for Children, NEuroPSYchological Assessment, BSID-II and Bayley-III, Kaufman Assessment Battery for Children, Rey Auditory Verbal Learning Test, Behavior Rating Inventory of Executive Function, and Stanford–Binet Test) across 16 studies. In addition, age at follow-up varied widely and there was a lack of standard definitions as to what should be regarded as an adverse outcome. Since we investigated associations, the definition of adverse outcome might not have influenced the interpretation of the observed trends. Nonetheless, heterogeneity in definitions impedes the insight into clinical relevancy of the results of

the current review, which should be considered during interpretation. Another limitation was the lack of large high-quality studies. Furthermore, a risk of bias should be taken into account when interpreting the results because at least 21 of 24 studies had no consecutive and/or complete inclusion of patients. Moreover, different guidelines exist for conducting systematic reviews, each with their own strengths and weaknesses. For example, when compared to the AMSTAR checklist,[65] a limitation of the PRISMA guideline is that a single reviewer is allowed to perform data extraction, which might increase the risk for subjective influences in the extracted data.[15] The strengths of this review are its systematic design and assessment of risk of bias.

Standardization of amplitude-integrated and conventional EEG acquisition is required to increase comparability across future studies and establish and implement normative neonatal quantitative EEG ranges where gestational age, PCA, age, drug exposure, sex, and vigilance states are taken into account. Bearing in mind current clinical practice guidelines that recommend the use of 8 to 12 electrodes[66] and limitations regarding EEG set-ups within neonatal care units, we believe that, if possible, at least 21 electrodes should be used for a conventional EEG set-up for research purposes because high-density EEGs are needed for sufficient spatial resolution due to the high conductivity of the neonatal skull.[67] Registration length should cover a total sleep cycle with active and quiet sleep periods. Therefore, a minimum registration length of 3 hours is recommended for amplitude-integrated and conventional EEG recordings.[68] In addition, we advise obtaining conventional EEG data instead of amplitude-integrated EEG data because amplitude-integrated EEG data can be derived from conventional EEG recordings. In the neonatal EEG, the higher oscillatory frequencies predominantly reside in transient waveforms, which poses a problem for the interpretation of quantitative EEG results in higher-frequency bands. For frequency band definition, we propose to at least investigate the delta (0.5–4Hz) and total frequency range separately (0.5–30Hz). Theta (4–8Hz), alpha (8–13Hz), and beta (13–30Hz) frequency bands might also be distinguished since several studies in this review showed that analysing these frequency bands can be fruitful; however, these should be interpreted with care because their meaning in the neonatal phase is yet to be elucidated.

The findings by Stevenson et al. delineate the value of serial EEGs since single-recording deviations of the developmental trajectory and overall changes in trajectories were revealed.[39] Serial EEGs increase the capacity to distinguish between transient and chronic EEG abnormalities.[69,70] Therefore, we recommend that future researchers should consider investigating serial EEG recordings. We suggest EEGs should be recorded at weekly intervals because of the fast evolution of the background pattern and the transient waveforms that appear and disappear on a weekly basis.[8] For cross-sectional study designs, we recommend recording EEGs around PCAs of 35 weeks, as suggested by Cainelli et al.[23] Around 35 weeks, the neonatal EEG becomes continuous and power increases at higher frequencies, making it an interesting and dynamic time point for investigating maturation of brain activity in infants born preterm.[23]

CONCLUSIONS

Based on the findings of this systematic review, we conclude that there are significant associations between neonatal quantitative EEG measures and long-term outcomes, indicating that quantitative analysis of the neonatal EEG has the potential to be clinically significant. Multiple studies showed that amplitude, background pattern, and power spectrum-related measures are associated with long-term outcomes in several domains, including the cognitive and motor domains. Our findings underscore that quantitative EEG analysis has the potential to improve neonatal care since it can provide new prognostic information in infants at risk. However, inference is limited by heterogeneity in populations and study designs. There is a definite need for more explorative studies to identify the most relevant quantitative EEG measures for prognostication in clinical practice.

ACKNOWLEDGEMENTS

We thank Dr V Bekker-Chernova for her help with the translation of one of the full-text articles included in this review. Jeroen Dudink acknowledges the financial support of EU H2020 MSCA-ITN-2018: INtegrating Functional Assessment measures for Neonatal Safeguard (INFANS), funded by the European Commission under grant no. 813483.

CONFLICT OF INTEREST

The other authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

Data sharing not applicable - no new data generated, or the article describes entirely theoretical research.

SUPPORTING INFORMATION

The following additional material may be found online:

Appendix S1: Search strategy.

Appendix S2: Data extraction form.

Appendix S3: Assessment of risk of bias.

Figure S1: Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram.

Figure S2: Results of the studies included in this review.

Table S1: List of excluded studies based on full-text screening

Table S2: Answers of two independent reviewers on a modified version of the Checklist for Case Series developed by the JBI

Table S3: Sample characteristics, study quality, EEG settings, qEEG measures, EEG paradigms, and long-term outcome assessment(s)

Table S4: Additional sample characteristics and study information

Table S5: Description of outcome measures

Table S6: Descriptions of quantitative EEG measures

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