aEEG as a useful tool for neuromonitoring in critically ill children – Current evidence and knowledge gaps

Nora Bruns | Ursula Felderhoff-Müser | Christian Dohna-Schwake

Department of Paediatrics I, University Hospital Essen, University of Duisburg-Essen, Essen, Germany

Correspondence
Nora Bruns, Department of Paediatrics I, University Hospital Essen, University of Duisburg-Essen, Hufelandstr. 55, 45147 Essen, Germany. Email: Nora.Bruns@uk-essen.de

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Abstract
Aim: Amplitude-integrated electroencephalography (aEEG) is used in children beyond neonatal age, but systematic investigations have been lacking. This mini-review summarised aEEG studies on children aged one month to 18 years, evaluated the usefulness of aEEG and identified knowledge gaps or limitations.

Methods: We searched the PubMed database for articles published in English up to September 2020, and 23 papers were identified.

Results: aEEG was frequently used to compensate for the absence of continuous full-channel EEG monitoring, particularly for detecting seizures. Interpreting background patterns was based on neonatal classifications, as reference values for older infants and children are lacking. It is possible that aEEG could predict outcomes after paediatric cardiac arrests and other conditions. Gaps in our knowledge exist with regard to normal values in healthy children and the effects of sedation on aEEG background patterns in children.

Conclusion: The main application of aEEG was detecting and treating paediatric seizures. Further research should determine reference values and investigate the potential to predict outcome after critical events or in acute neurological disease. It is likely that aEEG will play a role in paediatric critical care in the future.

Keywords
amplitude-integrated electroencephalography, outcomes, paediatric, sedation, seizures

1 | BACKGROUND

The neurological assessment of paediatric intensive care patients continues to be challenging for nurses and physicians. Evidence that electrocortical activity in this patient group needs to be continuously monitored is growing.1-3 However, the gold standard, which is continuous full-channel electroencephalography (EEG), is rarely available and time-consuming to provide.4 An easy-to-use alternative is amplitude-integrated electroencephalography (aEEG), which is a simplified, time-compressed EEG with a reduced set of electrodes. The interpretation is based on the evaluation of trends, but also allows staff to assess the raw EEG curve.

aEEG was originally developed as a cerebral function monitor for adult patients after resuscitation,5 but it has mainly been investigated and applied in newborn infants with seizures and hypoxic ischaemic encephalopathy.6,7 A further, mainly scientific, use is to predict neurological long-term outcomes in preterm infants.8 In line with its original purpose, aEEG is increasingly used for monitoring...
brain activity in adults after cardiac arrests. Paediatric intensive care staff also use aEEGs, but clinical guidelines are lacking and its scientific evaluation in such patients is less advanced than for neonatology and adult medicine.

Due to their importance in neonatology, aEEG devices are widely used in children's hospitals and are also available to paediatric intensive care staff, which has led to their increasing use in this field. Even though more trend parameters exist for EEG, aEEG is still the default feature of cerebral function monitors, making it particularly relevant for paediatric intensive care physicians. This paper reviews the literature on using aEEG for critically ill children beyond neonatal age. It elaborates its usefulness and the current knowledge gaps with regard to these patients.

2 | METHOD

We conducted two searches in the PubMed database in September 2020. The first query consisted of the search string (amplitude-integrated EEG) OR (aEEG OR amplitude-integrated electroencephalogram*), with the age filters set for one month to 18 years. The second query consisted of the same search string plus AND (child* OR pediatr) without age filters set.

After we discarded the duplicates, we screened the titles and abstracts for eligibility. Articles had to be published in English and deal with aEEG in children who were older than one month and up to 18 years of age. We assessed the full texts of the selected papers and verified they met the inclusion criteria. Eight papers were excluded at this stage (Figure 1). One eligible paper did not show up in the PubMed search but was previously known to the authors. We finally included 23 articles (Table 1). This paper also provides examples of tracings from children treated on our paediatric intensive care unit with aEEG to demonstrate possible aEEG findings in toddlers and children (Figures 2 and 3).

3 | RESULTS

3.1 | Use of aEEG in paediatric intensive care units

Our review showed that the number of scientific studies and case reports on the use of aEEG in children beyond the neonatal period is increasing. In addition to reports on seizures, research suggests that the background pattern may have diagnostic value.

We do not know how common the use of the aEEG actually is in older infants and children. A telephone survey carried out in East England found that only one of the 17 hospital general paediatric wards used aEEG and another had access to conventional EEG on-call during weekends. According to an online survey of paediatric intensive care units (PICUs) in Germany, about half of the 43 units who took part had access to conventional EEG during on-call periods and weekends and 93% had access to aEEG devices. Of these PICUs, 64% used aEEG on infants and children with altered mental states. The respondents particularly appreciated how aEEG could detect non-convulsive epileptic states, that they could start using it without contacting the EEG service and that it offered the possibility of continuous recording. The different results between the English and German surveys may have been caused by selection bias in the German online survey or by differences in resources between the two countries. Another possibility is that usage had actually increased, as the English survey was conducted four years before the German study.

3.2 | Interpretation of recordings

aEEGs are interpreted by recognising patterns that reflect long-term trends in amplitude height. Generally, the assessment focuses on the background pattern, seizures and sleep–wake cycling. Clinical information, such as the patient’s age, sedation or circulatory instability, must be taken into account when interpreting the tracings. Reference values of the upper and lower margins only exist for neonates and infants up to 3.5 months of age. No common references or classifications exist for older infants and children. For that reason, researchers and clinicians often use the neonatal Hellström–Westas classification for infants, children and even adults. This includes visually assessing the background patterns, seizures and sleep–wake cycling. It is easy for clinicians to learn how to perform aEEGs, even if they are not EEG experts. One study found that, after a short training period, PICU personnel performed well when it came to detecting severely altered background patterns using the Hellström–Westas classification (kappa 0.71, 95% confidence interval 0.57–0.85), but moderate changes were more difficult to identify. Another study explored whether medical students improved how they interpreted trends in a modified aEEG when it came to identifying wakefulness, sleep and encephalopathic patterns compared to conventional EEG. The study found that their performance improved significantly. Other studies showed that interrater agreement between EEG experts on the aEEG background pattern was good in preterm and term infants. Interrater agreement has not been investigated in paediatric aEEGs but is likely to be equally
good. Further research is urgently needed to determine physiological background patterns, age-specific reference values and the factors that affect aEEG backgrounds.

### 3.3 Seizures

Seizures in full-term neonates and older children are typically seen as abrupt rises in the upper and lower margins of the aEEG band for the duration of the incident. Several case reports and case series have illustrated the usefulness of aEEG in children with seizures.\(^{15,24-29}\) aEEG has helped to detect subclinical seizures, continuously monitor seizure activity and guide anticonvulsant therapy in patients aged between one month and 16 years.\(^{24,25,27-29}\) Underlying conditions included acute encephalopathy, bacterial meningitis, head injuries and epilepsy.\(^{24,25,27-29}\) Epileptogenic areas were identified by a conventional EEG in an 11-year-old non-critically ill patient with frontal lobe epilepsy and then monitored with aEEG for days, allowing clinicians to detect frequent seizures and titrate treatment.\(^{26}\) In a series of patients with genetic epilepsy, the seizure pattern showed a specific triphasic shape that differed from the typical seizure patterns usually observed in an aEEG.\(^{30}\)

Being able to display the long-term trend of cerebral activity makes it possible to identify seizures in aEEG tracings. In a retrospective analysis in our PICU, aEEG helped staff to detect epileptic states more frequently than clinical observation on its own or intermittent conventional EEG.\(^{14}\) Nevertheless, there are pitfalls in interpreting suspicious sections, because artefacts can cause seizure-like patterns. Prospective studies on the ability of staff to detect seizure activity after short-term training have yielded varying results. Nurses who received short-term blended learning only agreed moderately with aEEG specialists when it came to detecting seizures in infants and children with a low incidence of seizures.\(^{16}\) More encouraging results were obtained by a study on seizure detection by brief training neurophysiologists without prior aEEG experience.\(^{31}\) That study found that using an eight-channel aEEG, without access to raw EEG, yielded a low false-positive rate for seizure identification, of 0.05 false positives per hour, and sensitivity was good (81.5%).\(^{31}\) Similarly, after short training, critical care providers detected seizures with a sensitivity of 77% and specificity of 65%.\(^{32}\) While the negative predictive value was good (88%), the false-positive rate was high, with a positive predictive value of 46%.\(^{32}\) When a study compared a modified aEEG with a colour density spectral array to conventional EEG, medical students performed equally well in both.\(^{21}\) Another study that compared automated seizure detection by commercially available software packages to experts yielded heterogenous results.\(^{33}\) While the experts recognised 74% of the seizures in an aEEG and 77% in colour density spectral array, the software ranged between 37% and 92%. These false-positive rates were generally lower for the experts than for the software and differed greatly between different software packages.\(^{33}\)

In a prospective study that evaluated the implementation of aEEG for seizure detection in a PICU, 101 patients underwent quantitative EEG monitoring, including aEEG and colour density spectral array.\(^{34}\)

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**FIGURE 1** Study selection flow chart, according to the PRISMA guidelines

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Records identified by PubMed search (n = 633)

Records after duplicates removed (n = 514)

Records identified from another source (n = 1)

Records screened (n = 515)

Records excluded (n = 484)

Full-text articles assessed for eligibility (n = 31)

Full-text articles excluded (n = 8)*

Studies included in review (n = 23)

Reasons for exclusion:

- Article not in English (n = 2)
- Review article (n = 2)
- Only neonates (n = 3)
- Not about aEEG (n = 1)
| Year | Authors         | Study type          | Objective                          | Main findings                                                                 |
|------|-----------------|---------------------|------------------------------------|-------------------------------------------------------------------------------|
| 2009 | Okumura et al   | case report         | seizure monitoring                 | Identification of subclinical seizures and monitoring of anticonvulsive treatment by aEEG |
| 2010 | Komatsu et al   | case report         | seizure monitoring                 | Cluster of subclinical seizures revealed by aEEG and monitoring of anticonvulsive treatment |
| 2010 | Ishikawa et al  | case report         | seizure monitoring                 | A channel with ictal findings in continuous EEG converted into aEEG for continuous monitoring of seizures and efficacy of anticonvulsive treatment |
| 2010 | Steward et al   | interventional study| seizure detection                  | Median sensitivity of seizure identification by neurophysiologists without access to raw EEG was 83% in colour spectral density array and 82% in aEEG, low false-positive rate |
| 2011 | Okumura et al   | case reports        | seizure monitoring and guidance of treatment | Identification of subclinical seizures by aEEG and monitoring of anticonvulsive treatment during refractory status epilepticus in two children |
| 2011 | Zhang et al     | comparative study   | physiological background patterns   | Establishment of reference values for upper and lower amplitude in neonates and infants up to 3.5 months of age |
| 2012 | McKeever et al  | observational study | monitoring of anaesthesia depth     | Rise of the upper and lower amplitudes induced by anaesthesia, with larger differences in older children |
| 2014 | Mc Keever et al | observational study | monitoring of anaesthesia depth     | No correlation of the minimal alveolar concentration of sevoflurane with the mean amplitude in children under two years |
| 2014 | Igarashi et al  | case series         | seizure monitoring and guidance of treatment | Recognition and treatment of non-convulsive seizures in three unconscious infants with head injury |
| 2015 | Kobayashi et al | observational study | EEG trend interpretation and seizure detection by non-experts | Creation of trend figures including information on amplitude and frequency conventional EEGs; higher rate of correct answers identifying state of consciousness from trend figures compared to raw EEGs; no differences for seizure identification |
| 2016 | Kalra et al     | telephone survey, case series | aEEG use in paediatric wards | No use of aEEG in paediatric wards except for the investigators’ unit; confirmation of suspected seizures by aEEG when conventional EEG was unavailable |
| 2016 | Latal et al     | observational study | outcome prediction after heart surgery | Prediction of intelligence quotients at four years from postoperative aEEG background and sleep–wake cycling |
| 2017 | Schettler et al | case report         | seizure monitoring and guidance of treatment | Diagnosis and treatment of seizures |
| 2017 | Du Pont-Thibodeau et al | observational study | seizure detection by non-experts | Seizure recognition in aEEG and colour spectral density array by critical care medicine providers offers reasonable sensitivity and negative predictive values |
| 2018 | Jiang et al     | observational study | outcome prediction in anti-NMDAR encephalitis | Correlation of parietal bandwidth with outcome after 12 months in adolescent and young adults with anti-N-methyl-D-aspartate receptor encephalitis |

(Continues)
The diagnoses of the seizures were retrospectively confirmed by a neurophysiologist. The sensitivity and negative predictive value were 100%. However, the high false-positive rate was 52% and this presented similar challenges to previous studies. Treatment was initiated after a median time of 25 min and ranged from five minutes to more than three hours. Treatment was initiated after a median time of 25 min and ranged from five minutes to more than three hours. To conclude, seizure recognition by non-experts was possible and showed high sensitivity. The high false-positive rates displayed in the studies that we reviewed highlight the need for suspected seizures to be confirmed by raw EEG reviews by experts. The rate of seizures missed in children, due to the reduced number of electrodes used, has not been investigated. This is a limitation, especially for the detection of focal seizures. Neonates have a high proportion of focal seizures, and one study showed that only about 68%-85% of those detected by full-channel EEG were also detected by aEEGs. The present data support the use of aEEG for seizure detection and treatment when continuous full-channel EEG is unavailable. However, the method should only be used in conjunction with expert raw EEG reviews and cannot replace intermittent full-channel EEGs.

### 3.4 Predicting outcomes

One of the most important aspects to guide care after a critical event is estimating the outcome. The evolution of aEEG background patterns predicts outcomes in newborn infants with hypoxic ischaemic encephalopathy and in adults after a cardiac arrest. Normal background patterns and normalisation are associated with better outcomes than failure to normalise. Preterm infants with normal or normalisation of background patterns within the first 72 h of life achieved better development at two years of age than those who displayed a persisting pathological background. The aEEG background improved postoperatively in a study of young infants undergoing cardiac surgery due to congenital heart disease. A lack of sleep–wake cycling was associated with severe...
The same research group found that preoperative and postoperative aEEGs correlated with neurological development at one year of age. Abnormal preoperative background patterns, and the absence of postoperative sleep–wake cycling, independently predicted poorer motor and cognitive outcomes. In another study on young infants undergoing cardiac surgery with cardiopulmonary bypasses, abnormal postoperative background patterns, and a lack of return to sleep–wake cycling, predicted poorer intelligence quotients at four years of age. However, no such association was found for motor outcomes.

One study looked at 30 patients, of up to three years of age, after they had a cardiac arrest and found that the aEEG background correlated with the neurological outcomes when they were discharged from the PICU. The aEEG recordings were divided into three-hour sections, evaluated using the Hellström–Westas classification and transformed into a 24-hour summary score according to the background pattern. The scores were significantly associated with neurological outcomes and a cut-off value discriminated between favourable and poor outcomes. In addition, the evolution of the background pattern was examined. This showed that only one patient with a pathological background had a favourable outcome and only one patient with a normal background showed an unfavourable outcome. This was in line with the findings in a mixed patient population, where pathological background patterns and adverse evolutions of background were associated with poor outcomes. In adolescents and young adults with anti-N-methyl-D-aspartate receptor encephalitis, a greater parietal aEEG bandwidth predicted poorer neurological outcomes after 12 months.

Although evidence is still sparse, these results show that pathologies of different aetiologies may affect aEEG bandwidth. Long-term outcomes after cardiac surgery have been associated with perioperative aEEG patterns. The post-resuscitation summary score offers the possibility to stratify the severity of brain injuries in cardiac arrest patients. In the long term, this could further promote the use of aEEGs in paediatric intensive care medicine and facilitate clinical studies on neuroprotective strategies and post-cardiac arrest care.

### 3.5 aEEG during anaesthesia

Sedatives affect aEEG values in neonates and adults by lowering the amplitudes or causing depressed background patterns. Minimum and maximum amplitudes of parietal aEEG became higher after induction in children undergoing anaesthesia with inhaled gases and opioids, and these changes were age-dependent and less pronounced in younger infants. However, the electronically measured mean aEEG amplitude in children under two years of age did not correlate with the alveolar sevoflurane concentrations in another study. From our own experience, children’s background patterns can be continuous, in spite of continuously administered sedatives. However, we observed one infant who had a burst suppression pattern that was caused by a severe midazolam overdose. The patient took more than a week to re-establish a continuous background (Figure 3C and 3D).

Existing studies demonstrate that changes in aEEG occur during anaesthesia and help to discriminate between children who are
awake and anaesthetised. However, they do not support the use of aEEG to monitor the depth of anaesthesia. On the other hand, many children admitted to PICUs receive sedative treatment. Analgesedation has been shown to lower the median aEEG amplitude and increase the burst suppression rate in adults who have had cardiac arrests.43 Given the effects of sedation on neonates and adults, comprehensive knowledge about sedative-induced aEEG changes is relevant for paediatric critical care providers and further research is needed into this.

3.6 Limitations and outlook

aEEG has several limitations due to the underlying technique. A major concern is the reduced set of channels, as this causes loss of information from brain areas not covered by electrodes. While aEEG enables clinicians to carry out long-term trend monitoring, its short-term evolution is difficult to assess due to the compressed time scale. The height of amplitudes may be altered by artefacts, medication, state of consciousness and other clinical conditions. Various studies have addressed these concerns in neonates, but we know need to know whether these findings also apply to older infants and children.

Scientific articles that have evaluated the use of aEEG in older infants and children are still scarce. The number of papers on aEEG in preterm infants and newborn infants was similar 10 and 20 years ago. Today, there are an exhaustive number of papers and aEEG has become standard care for newborn infants after birth asphyxia. With increasing evidence on continuous neuromonitoring, studies on aEEG in children are likely to increase in the coming years. In particular, predicting outcomes is of major interest and will probably be comprehensively investigated. In this context, reference values for infants and children who are older than three months of age are urgently needed to distinguish physiological and pathological patterns.
As scientific and clinical experience grow, aEEG is likely to find a place in bridging the time to full-channel EEG and the rapid assessment of unresponsive children. Coma, seizures, traumatic brain injuries and post-resuscitation management are some of the clinical settings where this technique may be helpful.

To address the loss of information, due to the reduced number of channels, intermittent EEG and continuous aEEG monitoring could be combined to identify seizure foci via EEG. aEEG electrodes could be placed above seizure foci to enable long-term monitoring of these areas. Even when continuous full-channel EEG is available, additional trend monitoring may help to identify sections where seizures are suspected and to direct expert reviews of the raw EEG to these sections.

4 | CONCLUSION

Only a few studies have systematically investigated the use of aEEG in older infants and children. The existing studies, case reports and case series indicate that aEEG is useful in critically ill children. Identifying seizures and monitoring antiepileptic treatment are the most frequent indications for aEEG use. Excluding seizures works well for non-experts, but verifying suspected seizures requires experts.

Retrospective analyses suggest that the aEEG background changes in paediatric patients with several diseases. A particularly interesting study predicted outcomes after paediatric cardiac arrest and stratified the severity of brain injury based on a score.

Despite these encouraging results, being able to correctly interpret aEEGs in children is crucial. The major limitations of paediatric aEEG use are the lack of knowledge about physiological background patterns and the need for expert reviews of raw EEGs to confirm suspected seizures. Prospective trials need to address a number of urgent questions. We need to identify normal aEEG background amplitudes at different ages, how sedation affects aEEG backgrounds and whether aEEGs can reliably predict outcomes after critical events or acute cerebral insults. In short, we need to know whether patients benefit from aEEGs.

CONFLICTS OF INTEREST

The authors have no conflict of interest to declare.

ORCID

Nora Bruns https://orcid.org/0000-0003-3809-1887

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