Amplitude-integrated electroencephalography applications and algorithms in neonates

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Amplitude-Integrated Electroencephalography Applications and Algorithms in Neonates: A Systematic Review

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\section*{ABSTRACT} Amplitude-integrated electroencephalography (aEEG) is a simplified method for long-term, continuous, and bedside monitoring of brain activity. While conventional Electroencephalography (EEG) is the gold standard of assessing brain function, aEEG is easy to operate and allows bedside interpretation of brain activity by health care providers without extensive knowledge of neurophysiology. aEEG is increasingly applied in neurological monitoring in neonates, especially in the neonatal intensive care unit (NICU). To a growing extent, researchers and clinicians are convinced that aEEG provides valuable clinical information and can be used to assess the severity of neonatal encephalopathy. Meanwhile, to digitalize the aEEG transformation process and automate the interpretation process, different algorithms have been proposed in the last decades. This paper provides a comprehensive review of aEEG for neonatal monitoring from both clinical and technological perspectives. The paper first reviews the clinical applications of aEEG and discusses the merits and demerits of neonatal aEEG monitoring in terms of the assistance of the treatment and prognosis of cerebral diseases like hypoxic-ischemic encephalopathy (HIE), seizure and so on. And then furthermore, the algorithms to transform EEG into aEEG and the algorithms for aEEG interpretation like the automatic classification of aEEG tracing, automatic seizure detection of aEEG, etc. are reviewed.

\section*{INDEX TERMS} Amplitude-integrated electroencephalography, cerebral function monitoring, automatic seizure detection.

\section*{I. INTRODUCTION} The conventional electroencephalography (EEG) is the gold standard for seizure detection and treatment, and grading the severity of encephalopathy \cite{1}–\cite{6}. In the neonatal EEG test, a minimal nine electrodes are required to be arranged over the scalp by a specific technician. Interpretation of these EEG recordings requires a neurophysiologist or pediatric neurologist with expertise in neonatal EEG. The complex mounting of EEG equipment, the limited diagnostic period and the time-consuming (visual) interpretation of the EEG hamper long-term brain monitoring, especially in a critical care environment like the neonatal intensive care unit (NICU).

In contrast to EEG, the technology of amplitude-integrated EEG (aEEG) offers a simplified method for continuous (days) monitoring to track the dynamic cerebral activities. It is derived from a limited-channel EEG, normally, from one channel with two symmetric parietal electrodes (P3, P4) or two channels with additional one pair of symmetric electrodes (C3, C4) and one reference electrode on the forehead. The positions of the recording electrodes are according to the international 10–20 system. Then, aEEG is calculated from the EEG by asymmetric bandpass filtering, rectifying, smoothing, and compression using piecewise...
semilogarithmic transformation. By attaching single- or double-channel EEG electrodes on the scalp, aEEG minimizes skin disruption and discomfort to neonates and allows a long-term, continuous, bedside monitoring of brain activity. Meanwhile, aEEG is relatively easy to interpret by doctors and nurses with limited expertise in neurophysiology.

aEEG was developed by Maynard et al. in 1969, firstly called Cerebral Function Monitor (CFM), used to study cerebral activity in resuscitated patients with suspected brain damage [7]. It was originally developed as a bedside monitor for adult intensive care. As the technology of aEEG evolved, the use of aEEG has spread from adults to both term and preterm neonates in the next few decades [8], [9]. Nowadays, the technology of aEEG is widely applied for brain monitoring in infants, e.g., seizure detection and treatment [10]–[17], assessment of the severity of hypoxic-ischemic encephalopathy (HIE) in full-term infants [18]–[23] or to track brain maturation in preterm infants [24], [25]. Early changes in background aEEG activity and the presence of sleep-wake cycling have shown to be useful in predicting the neurodevelopment outcome of neonates with HIE [26]–[28]. While the predictive values of aEEG in neonates with therapeutic hypothermia in the existing works seem discrepant. Same observations have been found in neonatal seizure; specifically, some studies showed strikingly similar results, while some studies presented almost completely different conclusions. To illustrate, several authors [10], [15] have presented a sensitivity of 80% for seizure detection, while others [17] report a sensitivity of only 30%. To fully understand why the results remain controversial, what are the factors may result in these conclusions, and what are the potentials and limitations of the aEEG for these applications, a review of aEEG for clinical applications is required.

As for the technique behind the clinical applications, aEEG was initially generated by filtering, rectifying, smoothing, and compressing the EEG signal using a purely analog prototype as proposed by Liu et al. [36], and the aEEG tracing was written on heat sensitive paper. This kind of device was later replaced by multi-functional devices that can record and display aEEG tracing and raw-EEG simultaneously. Table 1 lists several aEEG devices. CerebraLogik [29], Brainz [30] and Unique+ [31] are devices that can provide aEEG, real-time EEG and/or continuous measurement of impedance. Recently, besides the aforementioned devices that integrate analogy circuits/units to acquire the aEEG directly, digitalized aEEG transformation procedure that transfers EEG into aEEG using a purely digital prototype has attracted widespread attention. With the development of the digital aEEG system, it provides the opportunity towards a quantitative approach of aEEG interpretation. In recent years, different algorithms have been proposed to digitalize the aEEG transformation process or to automate the interpretation process [32]–[41]. With the development and utilization of the novel digitalized aEEG transformation procedure, a quantity of automatic aEEG interpretation algorithms like the machine learning methods for the aEEG tracing classification [34]–[39], the algorithms for the automatic seizure detection [40], [41] have been proposed.

This paper aims at reviewing aEEG in neonates from both clinical and methodological perspectives. From the clinical perspective, we review two major clinical applications of aEEG. First, as the perinatal management and the prognostic value of diagnostic tools may have changed after the worldwide implementation of therapeutic hypothermia in infants with HIE, we review and discuss the prognostic value of aEEG for infants treated with therapeutic hypothermia. Second, the sensitivity and specificity among existing studies for neonatal seizures are reviewed and the potentials and limitations of aEEG are discussed. From methodologies perspective, the algorithms processing aEEG are discussed with a focus on the available algorithms for transforming raw EEG into aEEG and the methodologies for automating aEEG interpretation process.

The rest of this review paper is organized as follows. In Section II, a systematic search strategy is applied to obtain the relevant aEEG applications research from both clinical and methodological perspectives. Meanwhile, clinical applications of aEEG are reviewed in Section III, and the signal processing technique for aEEG are presented and reviewed in Section IV, followed by a brief discussion in Section V. At last, a conclusion in Section VI ends the review.

**II. METHOD**

In this section, to perform a systematic review of aEEG from both clinical and methodology perspectives, the literature research strategy is introduced. Meanwhile, the screening...
procedure and inclusion and exclusion criteria are also presented. At last, the corresponding search results by applying the literature research strategy and inclusion and exclusion criteria are presented.

A. LITERATURE RESEARCH STRATEGY

To realize a quantitative and qualitative systematic review, which includes both clinical and methodologies applications of aEEG in neonates, a search of CINAHL, PubMed/MEDLINE, ScienceDirect, SpringerLink, and IEEE Xplore database was performed in January 2019. The search strategies for these databases involved two themes: aEEG and neonates. The search terms aEEG, amplitude integrated electroencephalography, cerebral function monitor, amplitude integrated EEG, neonate, infant, and newborn were used to extract relevant studies. For example, for PubMed/MEDLINE database, the specific search strategy was: (aEEG OR “amplitude integrated electroencephalography” OR “cerebral function monitor” OR “amplitude integrated EEG”) AND (neonat” OR infant OR newborn). Relevant articles in the past eighteen years (2000.01-2019.01) were collected. Only papers in English and published in full text were included in the review process.

B. SCREENING PROCEDURE AND INCLUSION AND EXCLUSION CRITERIA

The screening procedure consisted of three steps. Firstly, duplicates were removed. Secondly, the initial screening was performed on reviewing the title and abstract. Studies were excluded by applying the following exclusion criteria: 1. No neonate target population; 2. No aEEG technology was involved; 3. Reviews, case reports, case series, study protocol, editorial, commentary, pilot study, and letter; 4. Books of conference proceeding. Finally, the full text was checked for the inclusion criteria. Regarding the inclusion criteria, this paper aimed at reviewing from both clinical and methodological perspectives. As the prognostic value of aEEG for infants treated with hypothermia would be reviewed, only studies with a study aim of therapeutic hypothermia were included. Neonatal seizures can be classified as clinical only seizures and electrographic seizures [42], [43]. A clinical only seizure refers to a sudden paroxysm of abnormal clinical changes that do not correlate with a simultaneous EEG seizure activity. While electrographic seizures are abnormal, paroxysmal encephalographic events that differ from background activity and evolve in morphology, frequency, and spatial distribution on EEG [44]. Electrographic seizures can be further divided into electroclinical seizures (also called clinically evident seizures) and electrographic-only seizures (also named subclinical seizures). Electroclinical seizures can be of any duration, including very brief events such as myoclonic seizures. By contrast, an electrographic-only seizure is defined as a sudden, repetitive, evolving and stereotyped event of abnormal electrographic pattern with the amplitude of at least 2 mV and a minimum duration of 10 s [45]. In this review, we included studies with aEEG and EEG monitoring for electrographic seizures detection in neonates. While for the detection of other seizures, namely, clinical only seizures that do not correlate with a simultaneous EEG activity, were excluded in this review. From a methodological perspective, an explicit review of aEEG transformation procedure has been provided. Also, the methodologies for automating aEEG interpretation process have also been explored and reviewed. Therefore, the inclusion criteria are described as follows: 1. For clinical applications, studies for evaluating the prognostic value of aEEG in neonates with HIE treated with hypothermia were included. 2. For clinical applications, comparative EEG studies for assessing the utilization of aEEG for electrographic seizures (electroclinical and electrographic-only seizures) monitoring, detecting, and managing were involved. 3. For methodological applications, algorithms for transforming EEG to aEEG were included. 4. For methodological applications, studies with algorithms for automatic aEEG interpretation were involved.

C. SEARCH RESULTS

After performing electronic searches of the aforementioned databases, 1034 articles were obtained. Among these studies, 748 studies remained after removing duplicates. Subsequently, from the abstract and title review by applying the exclusion criteria, 457 papers were excluded, and 291 papers were retained for the consideration. After the application of the inclusion criteria, 235 papers were excluded, and 26 papers remained. Two articles were added after cross-referencing the papers. Thus, a total of 28 papers was finally included in the systematic analysis, which mainly involves 9 articles for the clinical application of aEEG in neonates with HIE treated with hypothermia, 9 articles related to aEEG application for electrographic seizure monitoring, detecting and managing, 3 articles regarding aEEG transformation algorithms, 5 articles for automatic normal and abnormal aEEG tracings classification algorithms, and 2 articles for automatic seizure detection algorithms.

III. CLINICAL APPLICATIONS OF aEEG

In this section, the clinical applications of aEEG have been reviewed and discussed, which mainly involve neonates with HIE treated with hypothermia by assessing the aEEG background pattern or sleep cyclicity and electrographic seizure analysis using aEEG.

A. aEEG IN NEONATES WITH HYPOXIC-ISCHEMIC ENCEPHALOPATHY

Neonatal HIE remains one of the leading causes of neonatal mortality and long-term disability worldwide. It results from severe hypoxia before, during or after birth, and 42% of asphyxiated infants suffering from HIE [46]. Moderate to severe HIE may result in neurological sequelae, including cognitive and neurodevelopment problems with disabilities [47], [48] or death [49]. In 1999, aEEG was suggested as a simple clinical tool for early assessment of neonates with HIE [50]. It has been further confirmed by other studies
in [19], [51], [52]. Meanwhile, the systematic reviews on the prognostic value of aEEG on neonates with HIE have been performed in [53], [54], which also demonstrated the predictive value of aEEG for assessing the HIE. Thus, the review of the predictive or prognostic value of aEEG for assessing HIE is not included in this review. This review mainly focuses on reviewing the prognostic value of aEEG for infants with HIE treated with therapeutic hypothermia.

Recently, several randomized clinical studies have proven that a reduction in brain/body temperature (therapeutic hypothermia) significantly decreased mortality and improved neurodevelopmental outcomes in neonates with HIE [55]–[59]. The predictive value of early aEEG recordings on the neurodevelopmental outcome of infants with HIE who were either cooled (received the therapeutic hypothermia) or maintained at normothermia has become a hotspot of research [18]–[20], [60]–[63]. Several studies have confirmed that early aEEG background activity, recorded within 6 h after birth, is a strong predictor of neurodevelopmental outcome at 18 months in infants who have asphyxia and were treated with normothermia [18]–[20]. For infants who are treated with hypothermia, the predictive value of aEEG is less clear. Thus, in this paper, the predictive value of aEEG for infants with HIE treated hypothermia is reviewed and discussed. Table 2 summarizes the relevant work from hypothermia-treated HIE infants [22], [28], [62], [64], [65]. The persistent abnormal aEEG background pattern at 6 h, 12 h, and 24 h had a PPV of 36.4%, 36.4%, and 40%, respectively. The persistent abnormal aEEG time courses in infants with HIE treated with hypothermia is not predictive of an adverse outcome. In [22], a sequential rise of the PPV has been observed and the highest predictive value of 92% at 60 h is reached. The abnormal aEEG background pattern for longer than 60 h provides a reliable prediction of adverse outcome in hypothermia-treated HIE infants. In [64], [65], fluctuations of PPV/odd ratios have been observed. The distinct results and conclusions may mainly due to the considerable heterogeneity of these studies regarding inclusion criteria, mode of cooling, onset, the specifications of aEEG technique (e.g., the recording channels of aEEG, durations of aEEG recordings, the recording devices, etc) and long-term follow-up. To further give a fair assessment of the aEEG predictive value of a short-term or long-term outcome in with hypothermia-treated HIE infants, observational cohort study with neurodevelopmental follow up, standard inclusion criteria, standard aEEG specifications, and treatment policy are needed.

**B. aEEG FOR ELECTROGRAPHIC SEIZURES IN NEONATES**

Neonatal seizures are paroxysmal, repetitive and stereotypical epileptic events observed in newborns [66]. The incidence of seizures in neonates is around 1.5% [67]. They may occur because of several causes, e.g., hypoxic-ischemic encephalopathy, intracranial hemorrhage or infarction, meningitis or metabolic encephalopathies [68]. Repetitive and long-term seizures may affect brain development [69]. Conventional EEG is considered as the gold standard for measuring cerebral electrical activity and diagnosing seizure activity. However, EEG monitoring is highly resource-intensive, which requires expensive equipment, available technologists, and clinical neurophysiologists who are well trained in neonatal EEG interpretation [70].

In contrast, aEEG offers a simplified and continuous bedside monitoring opportunity. Unlike recognition of seizures on conventional EEG, which requires extensive neurophysiologic training; the interpretation of aEEG is relatively straightforward for clinicians or nurses with limited expertise in neurophysiology as it is mainly based on simple pattern recognition [71]. Thus, aEEG, with or without raw EEG trace, has been increasingly used for the detection, monitoring, and management of neonatal seizures. Fig. 1 illustrates an example of repetitive seizure activity. The abrupt rises in lower margin amplitude are very suggestive of electrographic seizure activity. The simultaneous raw EEG shows the repetitive spiky amplitude changes. However, it worthwhile to mention that the accuracy of seizure detection on aEEG also depends on the degree of expertise and familiarity with aEEG readings of clinicians, e.g., more seizures can be detected if the clinician is more experienced [11]; misinterpretation of the aEEG can lead to false diagnosis of seizure activity, such as movement artifacts [15], diaphragm spasm [72], etc. Meanwhile, as the aEEG recordings are derived from only
one or two compressed EEG channels, concern has arisen that some seizure activities may be underestimated, especially if the seizures durations are short or the seizure is focal or multifocal and distant from the catchment area of the applied electrodes [14], [17]. Therefore, the sensitivity and specificity among these studies and the potentials and limitations

<table>
<thead>
<tr>
<th>Authors (Years)</th>
<th>No. of recordings</th>
<th>Specifications of aEEG (Channels, With/without EEG, recording devices)</th>
<th>Inclusion criteria and treatment policy</th>
<th>Start time and duration of recordings</th>
<th>Follow up age (months)</th>
<th>Outcomes</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thoresen et al. (2010) [63]</td>
<td>74 infants (31 infants: NT; 43 infants: TH)</td>
<td>Single-channel aEEG (P3-P4) using needle electrodes; without EEG; Lectromed &amp; Olympic CFM 6000.</td>
<td>Infants who met the CoolCap entry criteria; whole-body cooling at 34.5 °C or head cooling at 33.5 °C.</td>
<td>Within 6 h; 6 to 166 hours.</td>
<td>18.</td>
<td>At the age of 3 to 6 h, PPV (abnormal aEEG pattern): 84% for NT; 59% for TH.</td>
<td>Early aEEG patterns can be used to predict the outcome for infants treated with normothermia but not hypothermia. The presence of sleep-wake cycling of aEEG by 120 hours of age can be considered as a predictor of normal outcome. Early aEEG did not add to the predictive value of death and disability among infants with moderate or severe HIE. aEEG loses its positive predictive value after therapeutic hypothermia implementation. aEEG provides a reliable prediction of outcome from the 48h hour during hypothermia in HIE infants.</td>
</tr>
<tr>
<td>Takenouchi et al. (2011) [28]</td>
<td>31 infants (31 infants: TH)</td>
<td>Single-channel aEEG; with raw EEG; Olympic CFM 6000.</td>
<td>Infants with moderate to severe HIE; head cooling at 34.5 °C.</td>
<td>Within 6 h; 72 hours during TH and 3 to 5 days after TH.</td>
<td>18 or later.</td>
<td>At the age of 120 h, PPV (aEEG sleep-wake cycling): 68% for TH.</td>
<td></td>
</tr>
<tr>
<td>Shankaran et al. (2011) [60]</td>
<td>108 infants (57 infants: NT; 51 infants: TH)</td>
<td>Single-channel aEEG (C3-C4) using gold disk cup electrodes; with raw EEG; Moberg neonatal EEG monitor.</td>
<td>Infants born after 36 weeks gestation with severe acidosis and/or birth asphyxia; whole-body cooling.</td>
<td>Within 9 h; NA.</td>
<td>18 to 22.</td>
<td>At the age within 9 h, PPV (abnormal aEEG pattern): 62% for NT; 51% for TH.</td>
<td></td>
</tr>
<tr>
<td>Ancora et al. (2013) [62]</td>
<td>16 infants (16 infants: TH)</td>
<td>NA; without EEG; Olympic CFM 5330.</td>
<td>Infants born after 36 weeks gestation with moderate-severe HIE; head cooling.</td>
<td>Within 24 h; recording during TH.</td>
<td>17.3±6.3.</td>
<td>At the age of 6 h, 12 h and 24 h, PPV (abnormal aEEG pattern): 36.4%, 36.4% and 40% respectively for TH.</td>
<td></td>
</tr>
<tr>
<td>Czekó et al. (2013) [22]</td>
<td>70 infants (70 infants: TH)</td>
<td>Single-channel aEEG; without EEG; Olympic CFM 6000.</td>
<td>Infants with moderate-severe HIE; whole-body cooling between 33 and 34°C.</td>
<td>Within 6 h; 72 hours during TH.</td>
<td>18 and 24.</td>
<td>At the age of 6 h, 24 h, 48 h and 60 h, PPV (abnormal aEEG pattern): 50%, 65%, 82% and 92%.</td>
<td></td>
</tr>
<tr>
<td>Azzopardi et al. (2013) [21]</td>
<td>314 infants (156 infants: NT; 158 infants: TH)</td>
<td>NA; without EEG; NA.</td>
<td>Infants born after 35 weeks gestation with HIE; whole-body cooling between 33 and 34°C.</td>
<td>Within 6 h; several hours.</td>
<td>18.</td>
<td>At the age within 6 h, PPV (abnormal aEEG pattern): 59% for NT; 51% for TH. PPV (abnormal aEEG voltage): 63% for NT; 55% for TH. At the age within 12-18, 24-30, and 36-42 h, PPV (aEEG background patterns): 62%, 66% and 50%.</td>
<td>A lower PPV in infants treated with hypothermia, probably due to a neuroprotective effect of cooling. During hypothermia, aEEG measurements are early predictors of long-term outcome after HIE.</td>
</tr>
<tr>
<td>Lemmers et al. (2013) [64]</td>
<td>48 infants (39 infants: TH; 9 infants: excluded.)</td>
<td>Single-channel or two-channel aEEG; without EEG; Olympic 6000 or Brainz BRM.</td>
<td>Infants with HIE; whole-body cooling at 33.5 °C.</td>
<td>Started from admission; 4 days.</td>
<td>18.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Padden et al. (2015) [61]</td>
<td>38 infants (21 infants: NT; 17 infants: TH)</td>
<td>Two-channel aEEG (C3-C4, P3-P4); with raw EEG; BRM2 Brain Monitor.</td>
<td>Infants born after 36 weeks gestation with moderate or severe HIE; whole-body cooling between 32.5 and 33.5°C.</td>
<td>Within 72 h; 72 hours during TH.</td>
<td>NA.</td>
<td>PPV (abnormal aEEG pattern): 75% for NT; 43% for TH.</td>
<td>Early aEEG has a limited predictive of hypothermia.</td>
</tr>
<tr>
<td>Niezen et al. (2017) [65]</td>
<td>42 infants (39 infants: TH; 9 infants: excluded.)</td>
<td>Single-channel aEEG (P3-P4) using needle electrodes; without EEG; Olympic CFM 6000 &amp; Lectromed Multitrace 2.</td>
<td>Infants with HIE; whole-body cooling at 33.5 °C.</td>
<td>At 6 h, 12 h, 24 h, 48 h, 72 h after birth; 5 hours during TH.</td>
<td>30.</td>
<td>At the age of 6 h, 12 h, 24 h, 48 h, 72 h, odds ratios (aEEG background pattern): 7.7, 24.4, 13.3, 14.0, 11.7.</td>
<td>aEEG during therapeutic hypothermia has a predictive value.</td>
</tr>
</tbody>
</table>

HIE: hypoxic ischemic encephalopathy; PPV: Positive Predictive Value; NA: Not Available; TH: Therapeutic Hypothermia; NT: Normothermia Treatment.
of aEEG seizures need to be further discussed. In Table 3, the comparative studies of aEEG and EEG detection analysis of seizures are presented.

These studies were mainly performed in term and moderately preterm infants and the results are summarized as follows.

- The sensitivity of neonatal seizure detection varies in each study. A relatively lower sensitivity of individual seizure detection (each seizure onset and duration detection) is obtained in comparison with the sensitivity of patients with seizure detection (seizure occurrence detection in each patient) [11], [13], [17]. Around or even more than 30% individual seizures can be expected to be identified by aEEG [11]–[14], [17], [73], [74]. Around or even more than 80% patients with seizure can be identified by aEEG [13], [15]–[17], [74].
- More seizures can be detected if the observer/clinician is more experienced, or if the duration of the seizure is longer, or the amplitude of the seizure is larger, or the frequency of the seizure is repetitive [12], [16], [17].
- Using aEEG in combination with the raw EEG signal outperforms only using aEEG [12], [73].
- Using multi-channel aEEG for the neonatal seizure detection can achieve higher sensitivity in comparison to using a single channel aEEG [12], [13], [73].
- The number of detected seizures using aEEG is significantly different when the electrodes are placed in different positions. The central area may be considered as the optimal position for aEEG electrodes [13], [14], [73].

Compared to EEG, aEEG has relatively poor sensitivity for individual seizure detection, which may vary mainly due to the following factors: 1) The neonatologists’ level of expertise in aEEG interpretation. 2) Misdiagnosed or false positive detected seizures, which may due to the artifacts, i.e., movements that have seizure-like patterns in the aEEG tracing [15]. 3) Shorter seizures, focal, multifocal or global seizures often go unnoticed using aEEG due to low time resolution and the position of the electrode in use. 4) Some of the unique characteristics of seizures, like spatial evolution, which makes seizures identifiable on EEG but not on aEEG.

In conclusion, to detect the seizure onsets (e.g., the duration/frequency of seizure activities), aEEG cannot be equivalently considered as EEG. Thus, solely using aEEG for seizure detection, diagnosis, or management is insufficient. It may be used as the preliminary screening and the simultaneous EEG signal can be used for the further confirmation of the suspicion of seizure activity.

IV. SIGNAL PROCESSING TECHNIQUE FOR aEEG

Present clinicians mainly focus on observing aEEG patterns in three aspects: minimum and maximum voltage (upper and lower borders of the output trace), pattern, and sleep-wake cycling cyclicity. Although observing the amplitude of aEEG provides valuable information, more information hidden in the aEEG can be extracted using statistic methods, signal processing methods, or other methods.

In this section, the digital methods to transform EEG to aEEG are reviewed, followed by the review of the automatic classification methods for distinguishing normal and abnormal aEEG tracings. At last, automatic seizure detection methods are presented and discussed.

A. EEG TO aEEG TRANSFORMATION

Initially, the analogy aEEG device, namely CFM, was proposed by Maynard et al. [7], calculating aEEG from EEG by a specific bandpass filter, semilogarithmic amplitude compression, rectification, smoothing (peak-to-peak detection) and time compression, as the procedure shown in Fig. 2. The bandpass filter was designed with a passband of 2–15 Hz to minimize artifacts from sweating, movements, muscle activity, and electrical interference. Then the rectification is performed by inverting negative signal amplitude into positive values. Next, an amplitude envelope of the signal is computed for the peak-to-peak detection. The peak-to-peak amplitude of the processed signal bursts is transferred to the upper border of the aEEG trace, and the peak-to-peak amplitude of the inter-burst processed signal is transferred to the lower border of the aEEG trace. Thus, aEEG can represent changes in the background activities of the EEG amplitudes. Finally, the signal is time-compressed and written out at a slow speed of 6 cm/h on the paper.
### TABLE 3. Amplitude-integrated electroencephalography for neonatal seizure detection.

<table>
<thead>
<tr>
<th>Authors</th>
<th>Recordings</th>
<th>Dataset</th>
<th>Inclusion Criteria</th>
<th>Study Cases (Age)</th>
<th>Included Seizures</th>
<th>Results</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shellhaas et al. (2007)</td>
<td>aEEG (C1, C4), EEG (FP1, FP2, T3, A1, O2, C3, F3, C4, Pz)</td>
<td>Infants with or without seizures.</td>
<td>140 infants (CA: 34 to 50 weeks)</td>
<td>EO</td>
<td>Individual seizure detection (Sen: 12-38%; Spc: PPV: NPV: NA). Patients with seizure detection (Sen: 22-57%; Spc: PPV: NPV: NA).</td>
<td>More seizures can be detected if the clinician is more experienced, or the duration, amplitude, frequency of the seizures is longer, lager and more repetitive, respectively. Using aEEG in combination with the EEG signal, analyzed by skilled clinician, provides acceptable sensitivity compared with simultaneous EEG.</td>
<td></td>
</tr>
<tr>
<td>Shah et al. (2008)</td>
<td>aEEG (C3, C4, P3, P4, FP1, FP2, T3, A1, O2, C3, F3, C4, Pz)</td>
<td>Infants with clinical seizures.</td>
<td>21 infants (term)</td>
<td>EO</td>
<td>Individual seizure detection: 1. aEEG plus raw signal (Sen: 76%; Spc: 78%; PPV: 78%; NPV: 78%). 2. 1-channel aEEG (Sen: 41-56%; Spc: 66-85%; PPV: 55-79%; NPV: 66-85%). 3. 2-channel aEEG (Sen: 27-44%; Spc: 83-98%; PPV: 72-92%; NPV: 83-98%).</td>
<td>Seizure detection rate is slightly better with multichannel aEEG compared with single-channel aEEG.</td>
<td></td>
</tr>
<tr>
<td>Wusthoff et al. (2009)</td>
<td>aEEG (FP3, FP4, C3, C4, FP5, FP6, T3, A1, O2, C3, F3, C4, Pz, Fz)</td>
<td>Infants with seizure.</td>
<td>121 infants (CA: 34 to 50 weeks)</td>
<td>EO</td>
<td>Individual seizure detection using C3-C4 channel (Sen: 73%; Spc: PPV: NPV: NA). Individual seizure detection using FP3-FP4 channel (Sen: 46%; Spc: PPV: NPV: NA).</td>
<td>Less seizures are detected when the electrodes are placed on the forehead compared to the central positions.</td>
<td></td>
</tr>
<tr>
<td>Evans et al. (2010)</td>
<td>aEEG (C3, C4, P3, P4, FP1, FP2, T3, A1, O2, C3, C4, F3, C4, Pz, Fz)</td>
<td>Infants require EEG monitoring.</td>
<td>44 infants (GA: 31 to 39 weeks)</td>
<td>EO</td>
<td>Individual seizure detection: 1. aEEG (Sen: 44.4%; Spc: PPV: NPV: NA). 2. aEEG plus raw single-channel EEG (Sen: 85.7%; Spc: PPV: NPV: NA).</td>
<td>Seizures may over-diagnose by aEEG due to the movement artifacts.</td>
<td></td>
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<tr>
<td>Zhang et al. (2011)</td>
<td>aEEG (C3, C4, P3, P4, FP1, FP2, T3, A1, O2, P3, C3, C4, Cz)</td>
<td>Infants with seizure.</td>
<td>62 infants (GA: 38. 6+1.6 weeks)</td>
<td>EO</td>
<td>Individual seizure detection: 1. aEEG interpreted by neuropathologist (Sen: 49.4%; Spc: PPV: NPV: NA). 2. aEEG interpreted by a neonatologist (Sen: 37.5%; Spc: PPV: NPV: NA). Patients with seizure detection: Both the neurologist and the neonatologist (Sen: 100%; Spc: PPV: NPV: NA).</td>
<td>Combination of aEEG with raw EEG offers more accurate diagnosis of seizures than only use aEEG.</td>
<td></td>
</tr>
<tr>
<td>Frenkel et al. (2011)</td>
<td>aEEG (P3, P4, Pz)</td>
<td>Infants at high risk of neurological insults.</td>
<td>38 infants (GA: 24 to 32 weeks)</td>
<td>EO</td>
<td>Individual seizure detection: 1. aEEG interpreted by neurologists (Sen: 71.8%; Spc: PPV: NPV: NA). 2. aEEG interpreted by a neonatologist (Sen: 95.4%).</td>
<td>The sensitivity of seizure detection is related to the clinician’s experience.</td>
<td></td>
</tr>
<tr>
<td>Mastrangelo et al. (2013)</td>
<td>aEEG (C3, C4, T3, T4, FP1, FP2, T3, A1, O2, C3, C4, Cz)</td>
<td>Infants with suspected seizures.</td>
<td>28 infants (GA: 39. 4+1.6 weeks)</td>
<td>EO</td>
<td>Individual seizure detection: 1. aEEG interpreted by neurologists (Sen: 33.7%; Spc: NA; PPV: 53.2%; NPV: NA). Patients with seizure detection (Sen: 86%; Spc: 75%; PPV: 46.1%; NPV: 95.4%).</td>
<td>aEEG may not be reliable for individual seizure detection.</td>
<td></td>
</tr>
<tr>
<td>Rakhashabhuvankar et al. (2017)</td>
<td>aEEG (C3, C4, P3, P4, Pz)</td>
<td>Infants with clinical or suspected seizures, or moderate HIE.</td>
<td>35 infants (GA ≥ 36 weeks)</td>
<td>EO and EC</td>
<td>Individual seizure detection (Sen: 33.7%; Spc: NA; PPV: 53.2%; NPV: NA). Patients with seizure detection (Sen: 86%; Spc: 75%; PPV: 46.1%; NPV: 95.4%).</td>
<td>aEEG may not be reliable for individual seizure detection.</td>
<td></td>
</tr>
</tbody>
</table>

HIE: hypoxic ischemic encephalopathy; GA: Gestational Age; CA: Conceptional Age; Sen: Sensitivity; Spc: Specificity; PPV: Positive Predictive Value; NPV: Negative Predictive Value; NA: Not Available; EO: Electrographic-only seizures; EC: Electroclinical seizures.
The basic principle of the aEEG procedure did not change over time, while the sequence of the aEEG procedure and the details of the procedure differ in different studies. In 2008, Hellström-Westas et al. presented a more detailed aEEG process [75]. The raw EEG goes through an asymmetric band-pass, which strongly attenuates activity below 2 Hz and above 15 Hz. Then the processed signal is semilogarithmic amplitude-compressed and displayed 0-10 mV linearly and 10-100 mV semi-logarithmically. After that, the signal is rectified, smoothed with a time constant of 0.5 s, time-compressed and displayed at a slow speed of 6 cm/h or 30 cm/h. El-Dib presented the aEEG transformation by applying the semilogarithmic compression after smoothing [76]. Recently, novel aEEG systems are continuously enriching the market, but these commercial devices provide similar but not identical aEEG outputs [33]. The aEEG modules embedded in these devices may differ from different manufacturers. However, both the aforementioned researches and commercial devices, the details of the aEEG procedure weren’t disclosed.

In recent years, different methods for transforming EEG into aEEG [32]–[34], which obtained by applying the aforementioned search strategy, is presented in Table 4. In 2010, Li et al. proposed a novel aEEG transform algorithm, which applied Box-Cox transformation instead of the semi-logarithmic compression process [34]. The raw EEG signal was filtered by a bandpass filter and then smoothed and time-compressed. Finally, the amplitude was compressed by Box-Cox transformation and displayed at a speed of 6 cm/h. The Box-Cox transformation was used as the approximation of the traditional semilogarithmic compression. However, the design of the filter wasn’t disclosed, and the transformed aEEG tracing was not provided and compared with the existing commercial devices. Furthermore, the novel aEEG transformation algorithm hasn’t been validated and applied for clinical research.

In 2013, Zhang and Ding [32] presented a detailed aEEG transformation algorithm which follows the principle of the original CFM [7]. The aEEG transformation went through a procedure as follows: asymmetrical filtering, rectifying, smoothing (envelope detection, segmentation, and terminal point extraction), time compression, and amplitude compression. A flat band-pass filter using Parks-McClellan algorithm, which has an asymmetrical gain with a slope of 12 dB per decade in the frequency range of 2-15 Hz is designed. Then, to obtain rectified EEG signals, absolute value evaluation is adopted. Meanwhile, to characterize the tendency of EEG amplitude changes, a 5th order Butterworth filter was used to detect the EEG envelope, followed by a smoothing, time and amplitude compression process. Finally, aEEG is displayed. Fig. 3 presents a detailed aEEG transformation procedure using the algorithm proposed by Zhang and Ding [32]. However, the impact of different filters design and smoothing algorithms were not investigated and included.

In 2017, Werther et al. investigated different aEEG systems and aEEG emulations, specifically on filters design and peak detection algorithms [33]. The emulating process of aEEG including band-pass filter, rectification, and peak detection are explained in details. Different band-pass filters and the different duration of a rectangular moving window in the smoothing for peak detection are analyzed. Good concordance between the existing commercial devices (Olympic, NicoletOne), and aEEG emulations that implemented an asymmetric bandpass filter, rectification, and a rectangular moving window durations of 0.5–3 s for peak detection have been found. Even the existing commercial aEEG systems and aEEG emulations have similar outputs, but there are not identical same.

In the aEEG transform procedure, the basic principles of the aEEG algorithm did not change over time. Fig. 4 presents
the frequency-response curves of several different filters that are available in the research field. It mainly involves a simulation of the original CFM filter proposed by Maynard et al. [7], a Parks-McClellan filter proposed by Zhang and Ding [32], and a Butterworth bandpass filter. However, the details of the procedure are not disclosed for most of the existing commercial devices or standardized for the researches, especially for the filter design and peak detection algorithms. Thus, for the existing commercial devices or the automatic aEEG transformation methods, the outputs are not the same. The impact of the different filters design and peak detection algorithms have been investigated in [33]. While the effect of the difference in shape and amplitude of these outputs on the aEEG interpretation need to be further explored. Meanwhile, we hope the aEEG device manufacturers would disclose the details of the aEEG algorithm soon. Clinicians, engineers, and manufacturers would cooperate and a standardized aEEG algorithm could be established for the further sophisticated aEEG analysis.

B. CLASSIFICATION OF NORMAL AND ABNORMAL aEEG TRACINGS

To give an accurate interpretation of aEEG, the classification of aEEG tracings is normally considered as the fundamental step. According to the explicit aEEG pattern classification criterion proposed by Tsuchida et al. [44], aEEG tracings can be classified into the following categories: Continuous activity (C), Discontinuous activity (DC), Burst-Suppression Amplitude activity (BSA), Low Voltage activity (LV), and Inactive-flat activity (FT). These patterns can also be roughly classified into Normal tracings (C, DC) and Abnormal tracings (BSA, LV, FT). In clinical, the classification is normally performed by neonatologists manually. While the manual classification of aEEG tracings is a subjective and low-efficiency process. To simplify the aEEG tracings classification, different algorithms for automatic classification have been proposed [35]–[39]. A total of 5 papers were obtained using the search strategy, as listed in Table 5.

These existing automatic aEEG tracings classification methods can be roughly classified into two directions. The first follows the principles of the expert system, which generates decisions by reasoning through human knowledge or experience. In [35], Dempster–Shafer theory was used to model an expert system for classifying the normal and abnormal aEEG tracings. A set of heuristic rules for making the decisions are generated based on the previous prior knowledge concluded in [34]. The second method applies machine learning models for the classification, which usually learns models between features and corresponding aEEG tracing classes by interaction with a set of training data and uses the learned models for classifying the remaining tracings. A typical machine learning model mainly involving the signal acquisition, signal pre-processing, feature extraction, and classification has been widely used in the automatic aEEG tracing classifications [36]–[39]. In the feature extraction step, different features are extracted. Here we concluded all the features used in [36]–[39] and classified these features into the following categories:

- **Amplitude features.** The observation of the amplitude of aEEG tracings plays a crucial role in the manual clinical aEEG interpretation process. The features which can represent the amplitude information of aEEG tracings like mean, maximum, and minimum value [38], [39], standard deviation [39], lower/upper border amplitude [36], [37], [39], and bandwidth [36] are extracted.

- **Statistical features.** For aEEG classification, criteria of clinical diagnosis demonstrated that data distribution played an important role in the classification of aEEG [75], [77]. Thus, a set of histogram features which can reveal the distribution of aEEG amplitude were extracted [37]–[39]. These histogram features can be used to represent histogram information directly due to the diversity of aEEG data distribution.

- **Non-linear features.**
  - Approximate entropy (ApEn). It was initially proposed by Pincus in 1991 [78] and has been predominantly used in the analysis of EEG signals [79]–[81]. As a nonlinear quantification method, it reflects the nonlinear and non-stationary properties of signals and evaluates the chaotic degree of the signal. Since 2012, ApEn has been attempted to utilize in aEEG tracing classification [35], [37], [38].
  - Permutation entropy (PE). PE was proposed by Bandt and Pompe in 2002 [82]. It can be used to measure the complexity of nonlinear time series [83], [84], and it has been widely applied to EEG records [85], [86]. Recently, it has been applied on aEEG in [39].

At present, to quantify the complexity of time series, non-linear dynamic features involving various entropies and dimensions have been widely applied for diverse physiological signals [87]–[91]. ApEn, as a representative measure, quantifies the irregularity of a time series without any requirement of prior knowledge. It provides a finite sequence formulation of randomness, via proximity to equidistribution and maximal irregularity. Specifically, a high value of ApEn indicates random and unpredictable variation, whereas

![Frequency Response Curves of Different Filters](image-url)
TABLE 5. Automatic normal and abnormal aEEG tracings classification methods.

<table>
<thead>
<tr>
<th>Authors (Year)</th>
<th>Dataset</th>
<th>Extracted Features</th>
<th>Classifier</th>
<th>Accuracy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yang et al. (2012) [35]</td>
<td>103 aEEG recordings (63 Normal Tracings and 40 Abnormal Tracings)</td>
<td>● Approximate Entropy</td>
<td>Revised Dempster–Shafer Theory</td>
<td>93.90%</td>
</tr>
<tr>
<td>Liu et al. (2012) [36]</td>
<td>103 aEEG recordings (63 Normal Tracings and 40 Abnormal Tracings)</td>
<td>● Lower margin amplitude of the whole tracing; ● Upper margin amplitude of the whole tracing; ● Bandwidth (Upper margin amplitude-Lower margin amplitude).</td>
<td>Domain Adaptation (1. Training Set: 16 recordings; 2. Training Set: All the dataset)</td>
<td>84.4% 93.2%</td>
</tr>
<tr>
<td>Wang et al. (2013) [37]</td>
<td>282 aEEG recordings (209 Normal Tracings and 73 Abnormal Tracings)</td>
<td>● Histogram features; ● Lower margin amplitude of each segmentation; ● Upper margin amplitude of each segmentation; ● Mean value of each segmentation; ● Approximate entropy. Total 3 features were extracted.</td>
<td>Random Forest (Training Set: 2/3 of the dataset; Testing Set: 1/3 of the dataset)</td>
<td>91.46%</td>
</tr>
<tr>
<td>Chen et al. (2014) [38]</td>
<td>282 aEEG recordings (209 Normal Tracings and 73 Abnormal Tracings)</td>
<td>● Basic features of each segmentation (minimum amplitude, maximum amplitude, mean value of amplitude and percentage of the lower margin values under 5µV); ● Histogram features; ● Approximate entropy. Total 115 features were extracted.</td>
<td>Random Forest (Training Set: 2/3 of the dataset; Testing Set: 1/3 of the dataset)</td>
<td>92.52%</td>
</tr>
<tr>
<td>Yang et al. (2016) [39]</td>
<td>276 aEEG recordings (217 Normal Tracings and 59 Abnormal Tracings)</td>
<td>● Mean value of the whole tracing; ● Standard deviation of the whole tracing; ● Histogram feature; ● Lower border; ● Permutation entropy. Total 5 features were extracted.</td>
<td>Gradient Boosting Decision Tree (5-fold cross validation)</td>
<td>93.12%</td>
</tr>
</tbody>
</table>

a low value of ApEn indicates regularity and predictability in a time series. It is nearly unaffected by low-level noise and provides informative features to highly discriminate the physiological signals, e.g., the discrimination seizure from non-seizure EEG signal [88], [91], the classification of normal and abnormal aEEG tracing [35], [37], [38]. PE, as an alternative complexity measure for time series, decomposes the original time series into a series of ordinal patterns describing the order relations between the present and a fixed number of equidistant past values at a given time [92]. Then it quantifies the degree of complexity of the original time series based on the appearance of ordinal patterns. Compared to other commonly used measures, PE has some particular advantages like conceptual simplicity, computational speed, robustness, etc. Apart from the ApEn and PE, other non-linear measures like, Shannon entropy [93], sample entropy [94], multiscale entropy [95], fractal dimensions [96], correlation dimension [97], and Lyapunov exponents [98], can also be used to measure the complexity of the time series and have not yet be explored to aEEG.

After feature extraction step, different classifiers were applied for the aEEG tracing classification, namely, Domain Adaptation [36], Random forest [37], [38], and Gradient Boosting Decision Tree [39]. Among these machine learning model-based methods, the classifier was directly applied after the feature extraction process. While a feature selection step can be considered between these two steps to select the relevant features and eliminate the redundant features of the dataset. By applying a feature selection step, it would be potentially optimized the parameters that need to be set-up in the subsequent classifier and reduces the possibility of overtraining effects and thus improves the performance of the classification. All methods obtained favorable results, which range from 84.4% to 93.9% accuracy. While it is complicated to evaluate the performance of these methods. All of these studies were verified on the private dataset, the generalization ability and reproducibility of these methods remains unclear. Meanwhile, different training sets were applied for the training process, thus comparing the performance of these methods depending on the accuracy is unfair. It is also worth noticing that for all the existing aEEG tracing classification methods, only off-line analysis was performed. In consideration of the practical use, an online scenario would be more applicable to the neonatologists.

C. AUTOMATIC SEIZURE DETECTION

Detection of seizures can be very challenging in neonates [99]–[101], since they are usually clinically subtle,
inconspicuous and difficult to differentiate from the normal behaviors of the inter-ictal periods or physiological phenomena. Especially after medication, seizures durations are often shorter and the symptoms of seizures are usually clinically silent. Numerous automatic seizure detection algorithms based on EEG have been proposed [87], [102]–[105]. Compared with EEG, aEEG has a relatively lower sensitivity for individual seizure detection. While detecting patient with seizures, aEEG reaches a comparable sensitivity in comparison with the gold standard, as described in Section III. Thus, aEEG is widely used as a bedside available screening tool for neonatal seizure detection. For automating the seizure detection process, only two studies were searched and reviewed [40], [41].

A seizure on aEEG is described as a transient rise in aEEG amplitude, upper and lower border, or sometimes only the upper border [75]. In [40], [41], the algorithms for seizure detection are mainly derived from the description of neonatal seizures on aEEG. In [40], to remove the artifacts from the raw aEEG signal, a pre-processing step is applied on aEEG firstly. It eliminates the signal where the corresponding impedance exceeds 20 kΩ. Then, the lower boundary is obtained by calculating the 10th percentile of the samples for each 10 s segment. Meanwhile, the reference boundary, which defined as a weighted average of the lower boundaries during the last 6 min, is obtained. Finally, a seizure is detected when the lower boundary was at least an empirically determined threshold (EDT) higher than the reference boundary for at least 60 s. To evaluate the performance of the proposed seizure detection algorithm, the classification results were compared with manual interpretation from two neurophysiologists, and the intraclass correlation coefficients reached 0.95 and 0.85, respectively. In [41], a middle line is calculated by averaging the lower boundary and upper boundary. Then, a reference line of onset (ReON) is calculated by averaging aEEG signal over the last 5 min for every 10 s. Meanwhile, a reference line of offset (ReOFF) is calculated by an average of the upper boundary over the last 5 min for every 10 s. Once, the lower boundary is higher than ReON indicating a starting point of a detected seizure. If the middle line is lower than ReOFF, it indicated an ending point of the detected seizure. An average sensitivity of 88.50% is obtained using the proposed automatic seizure detection method.

Existing automatic aEEG seizure detection methods are mainly inspired by the description of the seizure on aEEG. By comparing the lower boundary with a reference boundary, the seizures are detected. Although high sensitivities and low false positives are obtained in these algorithms, these algorithms still need to be systematically tested and validated by clinicians, e.g., the detection rate of individual seizures. Meanwhile, machine learning methods can also be investigated for aEEG seizure detection shortly. Furthermore, an accurate real-time seizure detection algorithm can be explored and expected to be integrated into the commercial device and alert bedside caregivers to potential seizures.

V. DISCUSSION

aEEG has been widely applied in the neonatal intensive care unit, and provides diagnostic and prognostic information in evaluating brain function of the neonates. The prognostic utility of early aEEG for neonates with HIE is well established. The background activity of aEEG tracings shows a strong predictive value of brain injury and later neurodevelopmental outcome in neonates with HIE. Meanwhile, aEEG is a useful adjunct tool to clinical criteria for assessing the degree of severity of HIE and in selecting patients for therapeutic hypothermia. However, the prognostic value has changed after the implementation of therapeutic hypothermia. The predictive value of early aEEG on long-term outcome is reduced in infants treated with cooling compared with non-cooled infants. It may because of the neuroprotective effect caused by the effect of the hypothermia treatment on the ongoing brain damage. Furthermore, the predictive role of aEEG in evaluating the short-term and long-term neurodevelopmental outcome of hypothermia-treated HIE infants varies in recent studies. These studies yielded these different observations mainly due to the following factors: 1. The heterogeneous in terms of the study population, e.g., gestational age and inclusion criteria for inducing hypothermia. 2. Variations in aEEG specifications and interpretations. The specifications of aEEG technique (e.g., the recording channels of aEEG, durations of aEEG recordings, the recording devices, etc.) have a direct impact on the recorded aEEG tracings. Werther et al. presented that commercial aEEG devices may have similar but not identical aEEG tracings, which may arise due to the filter design and peak detection methods embedded in the commercial devices [33]. Meanwhile, the electrode placement (the channel of the recordings), skin-electrode impedance, etc. also have impacts on the aEEG tracings [106]. These specifications of aEEG technique may indirectly affect the variety in the performance that uses aEEG for evaluating the outcome of the therapeutic hypothermia in HIE. In addition, different guidelines for interpreting aEEG tracings were applied in the existing studies. Al Naqeeb et al. classified the aEEG in term infants into three categories, namely, normal amplitude, moderately abnormal amplitude, and suppressed amplitude [50]. Hellström-Westas et al. classified aEEG patterns into five different categories, namely, continuous activity, discontinuous activity, burst-suppression amplitude activity, low voltage activity and inactive-flat activity [77]. The predictive values of aEEG are based on the interpretation of aEEG tracings. Thus, different aEEG interpretation guidelines may also influence the evaluation of the outcome of the therapeutic hypothermia in HIE. 3. The distinct therapeutic hypothermia methods including the start time of the hypothermia therapy and treatment modality. It was observed in [107], newborns with moderate HIE, starting hypothermia therapy within 6 h and between 6 to 12 h after HIE showed curative effects. While for the newborns with severe HIE, only starting hypothermia therapy within 6 h showed curative effects. Meanwhile, treatment...
modalities includes the methods of treatment (head cooling or whole-body cooling), the equipment of the treatment, methods for temperature maintenance, monitoring, and rewarming, the use of different target core temperatures and variable lengths of time for treatment [108], [109]. The follow-up time is various. Thus, to draw comprehensive conclusions, further large clinical studies that give fully considerations on the issues mentioned above are urgently required.

In previous studies, the diagnosis and quantification of neonatal seizures were interpreted on aEEG and EEG independently. The reliability of aEEG for seizure detection has been plagued by controversy. Although aEEG produces discernible transient rise in aEEG amplitude, upper and lower border of seizures, aEEG has relatively poor sensitivity for individual seizure detection and cannot be considered equivalent to the EEG monitoring. Solely using aEEG has significant limitations in the identification of seizures, which may principally because some of the unique seizures, like brief seizures, focal seizures, and seizures that small in amplitude that are recognizable on EEG but not on aEEG. While aEEG can reach a favorable sensitivity in detecting patients with seizure. With the advent technique of aEEG devices that allows the neonatologists and neurologists to access the aEEG and raw EEG signals simultaneously, the utilization of aEEG as a screening tool and calling up the corresponding raw EEG to reinforce the decision of suspicious seizures becomes possible. Thus, aEEG may be considered as a clinically useful alternative when EEG is not available or as a preliminary screening tool for neonatal seizure detection.

Besides the clinical applications of aEEG, automatic algorithms for aEEG have also been reviewed. From the engineering aspect, aEEG research may be restricted by the following perspectives. First, although the basic principles of the aEEG have been well defined, the standardized aEEG transformation procedure has not been established. Different aEEG device manufacturers applied different algorithms for the aEEG transformation, and the details of the applied algorithms are not disclosed. The outputs of existing commercial devices are not the same. Meanwhile, the relevant aEEG researchers explored different filters and smoothing algorithms according to their understanding. The obtained aEEG output usually compared with an existing commercial device in terms of the tracing shape. The differences in shape and amplitude of these outputs may indirectly affect the subsequent aEEG interpretation. Second, the automatic aEEG interpretation algorithms are verified on the private dataset. As far as we know, there is no public aEEG dataset available online. Thus, the generalization ability and reproducibility of these algorithms remains unclear. Public available dataset would potentially enhance the progress in this direction and provide a possible solution for the algorithm comparison and reproduction. Finally, all the existing automatic aEEG interpretation algorithms have not yet been externally validated by clinical experts. The applicability and reliability needed to be further explored and discussed.

It also worth mentioning that the review of aEEG in clinical applications, specifically, the predictive values of aEEG in hypothermia-treated HIE infants was limited by the heterogeneity of inclusion criteria, treatment policy (with or without medications), the specifications of aEEG technique, the interpretation guidelines of aEEG tracings, and the variability in interest and outcomes, etc. in the existing studies. With the number of related studies increases, comparison and validation on these studies, e.g. the impact of aEEG specifications, the impact of the specific hypothermia therapy treatment modality, etc. can be further analyzed.

VI. CONCLUSION

aEEG, as a simplified method of EEG recording that derived from one or two channels EEG, has emerged as a popular way to monitor neurological function in the NICU. The evidence on the prognostic ability of aEEG in hypothermia-treated HIE infants for the short-term and long-term neurodevelopmental outcome is various with the heterogeneous in the population, therapeutic hypothermia treatment policy, specifications of aEEG, etc. Further large clinical studies with standard inclusion, standard aEEG specifications, treatment policy, and long-term follow-up are urgently needed. Although aEEG produces discernible deflections of the large ictal spikes of seizures, solely using aEEG has significant limitations in the identification of seizures. aEEG may be considered as a clinically useful alternative when EEG is not available or as a preliminary screening tool for neonatal seizure detection. With the widespread use of aEEG, numerous automatic aEEG interpretation algorithms have been proposed in recent years, whereas these automated algorithms still require rigorous testing and validation before integration into aEEG devices.

REFERENCES


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