NEONATAL SEIZURE DETECTION

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1.0 Background

Neonatal seizures occur in around 10% of all pre-term live births, making them the most common neurological emergency in the Neonatal Intensive Care Unit (NICU), both nationally and worldwide[1]. Although the underlying causes and subsequent effects of neonatal seizures on long-term outcome are not entirely understood, studies have shown that seizures are a risk factor for neurodevelopment sequelae such as cognitive impairment, moderate-severe brain injury, and epilepsy.[2] Specifically, in cases of hypoxic–ischemic encephalopathy (HIE) where there is a shortage of oxygenated blood to the brain, neonatal seizures have been linked to severe brain injury and a high risk of epilepsy.[3]

Detecting these seizures in the NICU is an ongoing clinical challenge. Although common symptoms include random eye movements, tightening of the muscles, or jerking movements of the body, these movements are often quite subtle. Thus, it is difficult to distinguish between clinically relevant and normal behavior in the neonate while relying on visual observation alone. Furthermore, the vast majority of seizures in neonates are non-convulsive and cannot be detected without physiological signal monitoring.[4] Upon detection, treatment of these seizures is usually through administration of antiepileptic drugs (AEDs) such as phenobarbital, phenytoin, and lorazepam, which can mitigate the adverse effects of the seizure.

Currently, conventional electroencephalography or cEEG is the most commonly used method to detect seizures. In this noninvasive monitoring system, a technician connects multiple electrodes to a patient's scalp in order to measure underlying electrical signals from the brain. Although the number of electrodes average around 25, they can go as high as 256 in attempts to get a more accurate signal.[5] An alternative to this monitoring method is amplitude integrated EEG or aEEG. Usually using only two or four EEG channels, aEEG performs data preprocessing steps such as band-pass filtering and semi-logarithmic time compression to create a simpler signal that is easier than the cEEG to analyze. Although this process of filtering

makes it more difficult to detect certain types of seizures, the ease of use and interpretation often overcome this enhanced accuracy, which is why the use of aEEG in the NICU has been rising over the last few years.

In both cases, the output from the monitoring system must be continually observed and evaluated if there is hope for seizure treatment in real-time. With the conventional EEG specifically, a trained neurologist is necessary to properly analyze the electrode readings. Neonatologists, such as our client Dr. Zachary Vesoulis, would prefer to have an automatic seizure detection algorithm that could alert clinicians if and when a seizure is occurring and would remove the need for constant monitoring of EEG output.

2.0 Need Statement

There is a need for an accessible monitoring system to alert clinicians in neonatal intensive care units (NICU) about the health status of seizure-prone neonates for potential life-saving intervention.

3.0 Project Scope

There is a need for an accessible monitoring system to alert clinicians in the NICU about the health status of seizure-prone neonates for potential life-saving intervention. This system will employ a limited channel-EEG to provide a less expensive alternate to current, commercialized software. A device that fulfills this need will include different responses based on the severity of the situation to guide the clinician towards an apt response. In addition, it will have an accessible device interface and be safe for use with infants. We propose to deliver, by the end of April 2019, a system that can both reliably detect seizures in neonates utilizing data from a limited-channel EEG and alert clinicians of an ongoing seizure with distinct and non-chaotic signals appropriate for the NICU. The prototype will include a user manual for detailed instructions on the reproduction and operation of the system.

4.0 Design Specifications

Given that neonatal seizures have been shown to link to negative outcomes later in life, the primary concern for our device is sensitivity, or how well the device does at correctly recognizing seizures. Secondary to this concern is the specificity of the device, or how well it performs at recognizing the absence of a seizure. Additionally, it is imperative that our device is safe for use in the NICU. This includes stipulations such as minimal wiring or electrodes that do not damage the neonate's skin during use. The device must also be simple enough for any trained clinician to use with minimal set-up time and with little prior experience analyzing EEG traces. The output of the device must be secure and only accessible by clinicians who are monitoring the care of patients. Lastly, the cost of the device must be low enough that it can be afforded by both large hospitals in the US and hospitals in lower income areas with less access to the latest, most expensive monitoring technology. These specifications among others are shown in **Table 1**.

Table 1. Design specifications for the brain monitoring and seizure detection device.

Specification	Metric	Description
Sensitivity	99%	Seizures detected divided by total number of seizures
Specificity	80%	False seizures detected divided by total number of seizures
Frequency Sampling	> 240 Hz	The frequency rate at which signals from the neonate's brain are sampled
Device Responsivity	< 10 seconds	Delay between initiation of a seizure and device alert
Operating Time	24 hours	This device will operate over multiple neonatal sleep-wake cycles
Device Setup Time	< 10 minutes	Non-expert clinicians should be able to set up system with ease
Production Cost	$200 (USD)	Cost-effective device based on integration with NICU equipment
Device Size	9 cm x 6.5 cm x 2.5 cm	The device will be easily storable and portable for rapid, efficient use

5.0 Existing Solutions

5.1 Currently in Use in NICU

The current, wide-regarded "gold standard" system for monitoring seizures in neonates is through conventional, or continuous-video, EEG (cEEG). This technique requires a skilled technician to set up the international 10-20 electrode placement system, making sure to use appropriate electrodes for the infant's delicate skin (**Figure 1**).[6] Following this, trained neurologists read and interpret the signal, manually scanning for any seizure events. In addition, they have video recordings of the patient that can be observed alongside the EEG.[7] In locations where this is possible, it proves to be very precise and accurate. However, this solution also presents a wide variety of challenges in terms of accessibility. Without access to either the electrodes or specialists, a neonatal unit would not be able to effectively utilize this technique, especially not on a large scale. Even for locations with the access, there is rarely an opportunity for perfectly continuous bedside monitoring. Consequently, the signals would not always be analyzed in real-time, therefore removing the possibility for real-time treatment. Ant-Neuro developed an electrode cap, waveguard™ original, which slides directly on the patient's head to place 23 electrodes at once (Waveguard, ANT-Neuro, Enchede, The Netherlands).[8] Although this could potentially provide a solution to the issue of extensive set up time, it would cause too much skin damage for use with neonates.

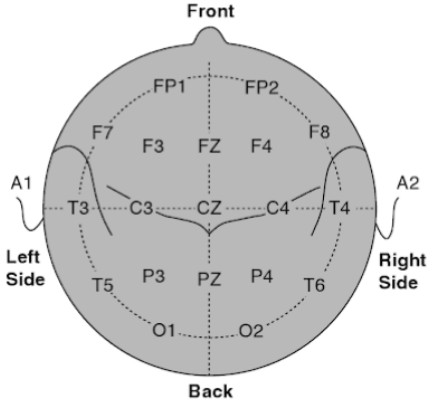

Figure 1. International Electrode Placement Diagram for cEEG use.

Amplitude-integrated electroencephalogram (aEEG) has been used as an alternative method to overcome some of the limitations of the cEEG.[9] This technique, also referred to as cerebral function monitoring, allows less trained neonatologists to be able to setup a limited electrode array (often 2 or 4 electrodes). The use of less electrodes also produces a safer and

less intrusive experience. These factors make this a more accessible system in care units across the world.

One device in particular, the BrainZ BRM3 EEG patient monitor, uses two pairs of biparietal electrodes placed in the P3, P4, C3, and C4 positions along with a ground electrode for cross cerebral and unilateral analysis (Natus Medical, San Carlos, CA).[10] To remove artifacts from factors such as movement and interference, the device includes a band-pass filter that attenuates signal activity below 2 Hz and above 15 Hz.[11] It displays the raw EEG waveform, the post-processing aEEG parameter, and the signal quality (**Figure 2**).[12] With little training, bedside clinicians are able to read the simplified signals and their trends over many hours by monitoring the background and rhythmic activity.[13] Another device, the Olympic CFM 6000 developed by Lectromed Ltd. UK has also proven effective as an aEEG. It uses a slightly different method for modifying the raw signal.[14] For example, its use of a 2-20 Hz band-pass filter highlights that there is a range of parameters for which the aEEG can operate.

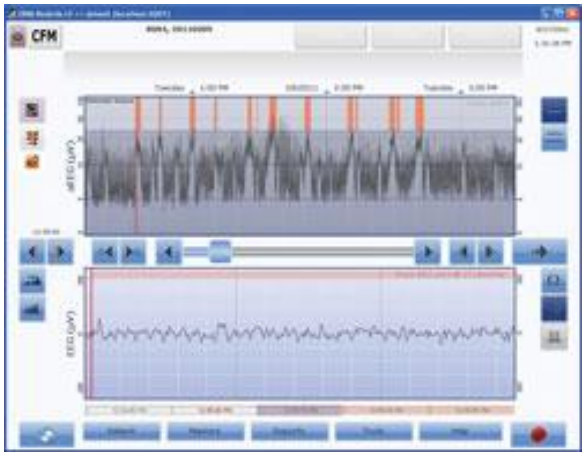

Figure 2. BrainZ BRM3 interface.

In both devices, experienced neonatologists were able to effectively use the aEEG with both high selectivity and specificity. However, Rakshasbhuvankar et al. summarized that this was not the case for all commercial devices (See Appendix).[15] Overall, with the increase in accessibility comes a tradeoff in efficiency. Low amplitude, fleeting, and seizures localized in positions far from the electrodes are difficult to detect. In addition, with the simplified signals comes a higher degree of artifacts to the system, leading to neonatologists often recording a higher degree of false positives. Ultimately, this device is used as an indicator that a proper EEG recording should be performed with corresponding experts.

Building from the BrainZ BRM3, the CFM Olympic Brainz™ Monitor and the corresponding RecogniZe™ software serve to detect seizure events in real time (**Figure 3)**.[16] This device, developed by Natus Newborn Care, again uses up to three channels in addition to a clinician-friendly display that allows for review of areas with potential seizures. Through its automated detection, it yields a high sensitivity (78%) with few false positives.[17] Still, it experiences the same faults one would have from manual reading the aEEG. For example, only 1 in 5 seizures that last less than 30 seconds are found by traditional cEEG, and it is even rarer for this system to notice such an event. However, the longer the duration of the seizure, the more accurate the software will be. This is necessary as high-risk cases often require immediate intervention.[18] Furthermore, over-treatment is a non-issue; Lawrence et al. evaluated the device and found that with just informal, minimal training, "physicians were able to accurately use this algorithm to differentiate seizures from false-positives."[19] Ultimately, the device provides a safe alternative to other current methods.

Figure 3. CFM Olympic Brainz™ Monitor for NICU.

Without a constant need for bedside monitoring, this device is more accessible than its predecessors. However, although there is an improvement, it is both expensive ($25,000 - $30,000) and non-portable.[20] The wheels aid in mobility, but it is still overall a large and bulky device. A more accessible device would be both portable and incorporable with existing technologies in the NICU.

5.2 Seizure Detection Algorithms

Along with needing accessible hardware, a robust software component is also necessary for any seizure-detection device in the NICU. Although they haven't been used specifically with the aEEG yet, there are several other seizure detection strategies along with RecogniZe™. Different algorithms feature different assumptions and processes that affect the final parameters such as responsivity, sensitivity, and specificity. The following solutions are not usable in real-

time monitoring, but they do have strong potential to be useful to neurologists and neonatologists if they are able to distinguish seizure events rapidly.

The first method is a machine learning technique using a Random Forest Classifier. Using EEG data from 100 channels, each with a duration of 23.6 seconds, Mursalin et al. implemented an Improved Correlation-based Feature Selection (ICFS) method followed by a Random Forest Classifier to accurately determine over 97% of seizures in each of their cases (**Figure 4**).[21] This Random Forest approach allows for multiple, flexible pathways leading to different outcomes. By extracting prominent features, these paths continually develop and lead to accurate event classification. Another approach is to use Support Vector Machines (SVMs) rather than the Random Forest. This method examines the variance between different features and uses this to isolate different outcomes that it categorizes. Following this structure, Kumar et al. created an algorithm that was over 95% accurate over largely the same set of cases.[22]

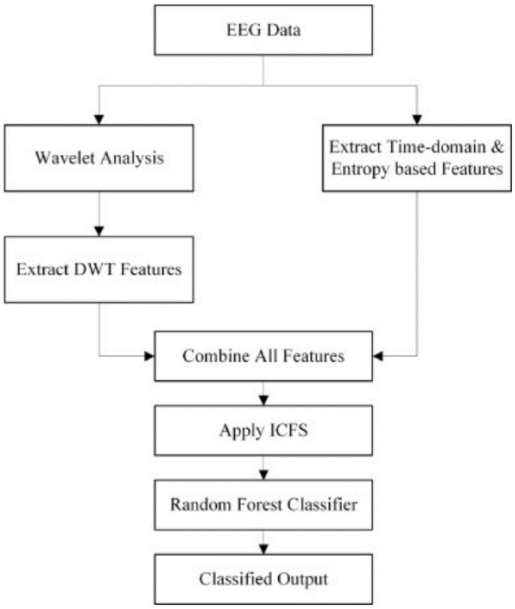

Figure 4. ICFS and Random Forest Classifier approach block diagram.

In addition to those methods, Persyst has patented a 12 EEG System Integration software using quantitative EEG (QEEG) based on the rhythmicity spectrogram of EEG signals (Persyst Corp, Rochester, M).[23] The rhythmicity spectrogram is a visual representation of the time, frequency, and power and through this quantitative comparison, they obtained an accuracy rate of nearly 90% with a maximum of two false positives over the course of a day. Their separately patented artifact removal technology makes it possible for them to have such a robust system.[24]

5.3 Signal Integration Systems

It was previously mentioned that cEEGs often employ a video monitoring system. This is an example of two different signal feedbacks being used to determine seizure events. Some seizure detection algorithms and systems include other bodily signals to produce a more accurate analysis. These additional signals add robustness to the detection algorithm and allow for novel approaches. Although the following solutions have not yet been implemented in the NICU, they have proven to be effective in other cases showing that they have the potential to serve in this new capacity.

As discussed in the last section, SVMs are an effective tool for detecting seizures through multiple EEG signal features. In 2015, Mporas et. al included ECG features in their approach to seizure detection and their algorithm worked with about 90% accuracy.[25] With their unique approach, the detection algorithm has the potential to integrate nicely into the NICU given that ECG is already monitored for all of the patients. Given the goal of accessibility, this extra signal may be able to compensate for those not received from limited electrodes. However, there exists the possibility that the additional signal magnifies the rate of false alarms.

The Angelcare® AC517 Baby Breathing Monitor with Video is widely used in household where the infant is at risk for seizures (**Figure 5**).[26] The sensor pad that the baby rests on detects motion and will alert the guardians if there is abnormal movement exceeding a threshold value.[27] In addition, the wireless device features a reviewable video with audio. In the NICU, the heart rate of each patient is already monitored, so it would be redundant to track motion as well if it's for the same purpose. However, in the case of seizure detection, the baseline activity level that the pad registers could be used in conjunction with the aEEG to alert clinicians.

Figure 5. Angelcare® AC517 Baby Breathing Monitor with Video. The device includes multiple displays for guardians to interact with.

6.0 Project Logistics

6.1 Gantt Chart

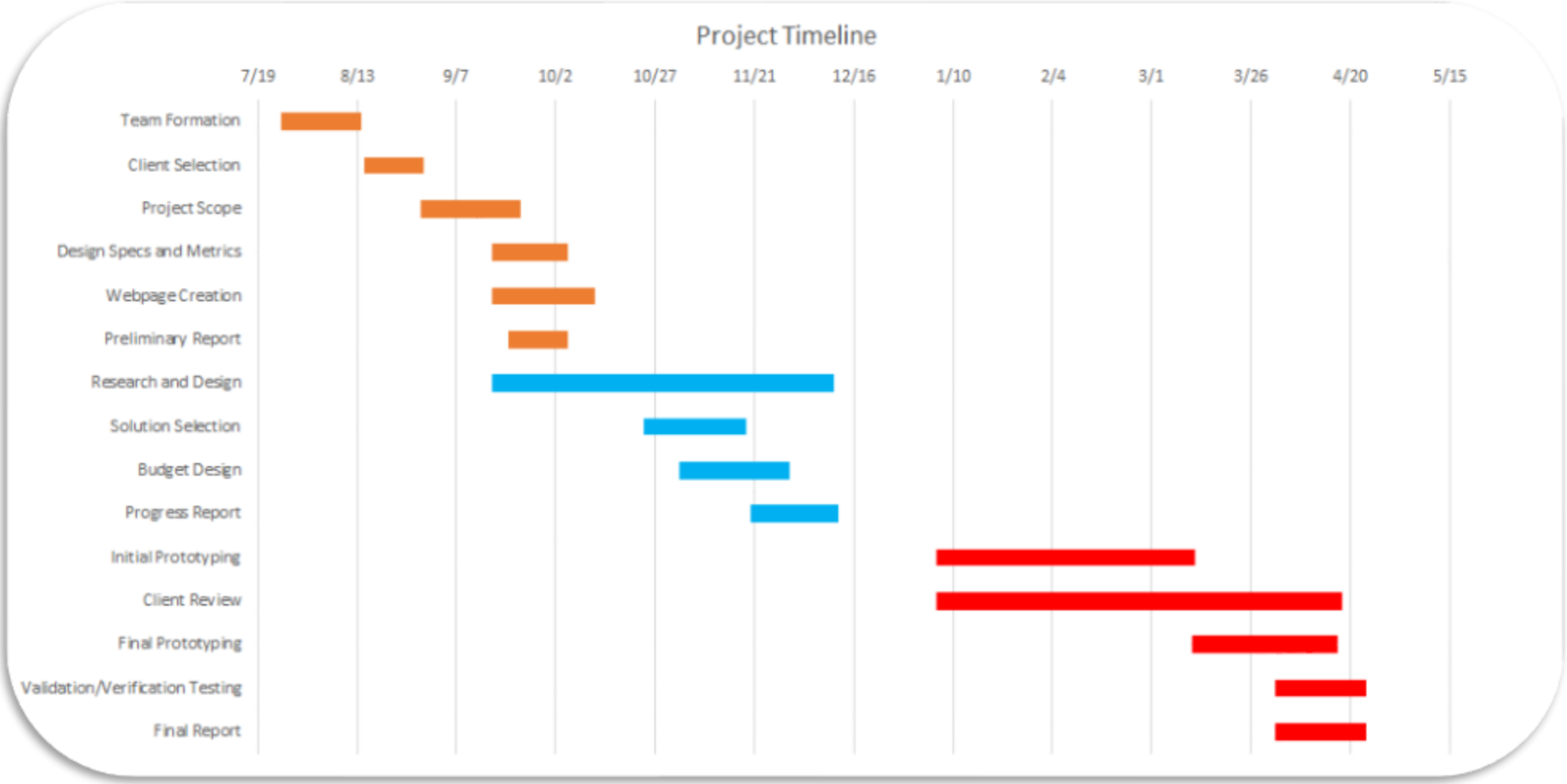

Figure 6. Gantt Chart detailing team responsibilities over both the Fall 2018 and Spring 2019 semesters.

6.2 Organization of Team Responsibilities

Table 2. Breakdown of how the project tasks are spilt up between the two group members.

Responsibilities	Kyle	Tahj
Report Writing	X	X
Point Person for Client Contact	X	
Web Page Upkeep		X
Literature Search and Clinical Relevance	X	X
Lead Software Designer		X
Signaling and Systems Analyst	X	
Electronics and Machine Design	X	
Cataloguing of Results	X	X
Preliminary Presentation		X
Progress Presentation	X	
V&V Presentation		X
Final Presentation and Poster	X	X

7.0 Conclusion

Seizures are one of the most common neurological problems that affect pre-term babies in the NICU. Although current solutions for monitoring neonatal brain activity exist (cEEG, aEEG), there is a need for automated seizure detection algorithm that will help streamline the process and make it easier to detect and react to neonatal seizures in areas where continuous monitoring is difficult. The purpose of this project is to create a device that will aid clinicians in the monitoring of neonatal brain state, alert them to any ongoing seizures, and most importantly, improve the care and long-term outcome of babies in the NICU.

8.0 Appendix

Table 3. Summary of different aEEG approaches and results from 2002-2013. (Table retrieved from Rakshasbhuvankar et al. 2015)[13]

Important characteristics of included studies.

Author Year of publication Study design	Sample size (infants)	PMA weeks	Inclusion criteria	aEEG device	Index test	Duration of monitoring	aEEG montage	aEEG reporters	Results	Authors conclusions
Toet 2002 Prospective	33	≥36	Infants with suspected seizures and/or moderate HIE	CFM[a]	aEEG	30 min	P3–P4	Neonatologist	PWS detection: Sensitivity 80% Specificity 100% PPV – 100% NPV – 92%	aEEG useful to detect seizures.
Rennie 2004 Retrospective	40	24–42	Video EEG showing seizures + control	CFM[a]	aEEG	Not specified	P3–P4	Four non expert neonatologists	Seizure detection: Sensitivity 26, 31, 42, 52%[b] Specificity 71, 95, 100, 100%[b]	aEEG may miss half of the seizures.
Shelhaas 2007 Retrospective	121	34–50	cEEG with seizures	aEEG derived from original EEG trace	aEEG	23–145 min	C3–C4	Six neonatologists with variable interpretation expertise	PWS detection Sensitivity: mean 40% (range 21–57%), Seizure detection Sensitivity: mean 25% (range 12–38%)	Seizures difficult to detect on aEEG
Shah 2008 Prospective	21	Term	Infants with clinical seizures	BRM2#	aEEG with the raw trace	4.2–42 hr (18 hr median)	C3–P3 C4–P4	Experienced neonatologists	Seizure detection: Sensitivity 76% specificity 78% PPV – 78% NPV – 78% PWS detection: sensitivity:85%	Experienced neonatologist detected majority of seizures using aEEG.
Lawrence 2009 Prospective	34	≥36	Infants at risk for seizures	BRM3#	aEEG with the raw trace	1–88 hr (21 hr mean)	C3–C4 P3–P4	Experienced aEEG reader	Seizure detection: Sensitivity 76% False positive 3%	aEEG can be accurately interpreted & compares favourably with cEEG
Bourez Swart 2009 Prospective	12	Term	Seizures on cEEG HIE	EEG transformed to aEEG-Micromed software	aEEG	30 min	C3–C4, O1–O2, T3–T4, Fp1–Fp2	Two experienced neonatologists	**Single channel** PWS detection: Sensitivity 92% (95% CI 65, 99) Seizure detection: Sensitivity 30% (95% CI 22, 38) **Multichannel** PWS detection Sensitivity 100% (95% CI 76, 100) Seizure detection Sensitivity 39% (95% CI 31, 48)	Multi-channel aEEG identified all patients with seizures.
Evans 2010 Prospective	44	31–39	Infants requiring cEEG monitoring	aEEG derived from cEEG	aEEG	12–360 hr (median 24 hr)	C3–C4 O1–O2	Paediatric neurologist	Seizure detection: Sensitivity 80% (95%CI 69, 91) Specificity 50% (95% CI 36, 64)	aEEG over-diagnosed seizures.
Frenkel 2011 Retrospective	38	24–43	High risk infants with abnormal aEEG	CFM6000	aEEG with the raw trace	1–2 hr	P3–P4	Medical student (S), Fellow (F) and experienced neonatologists (N)	PWS detection Sensitivity: 80 (S), 90 (F), 90% (N)[b] Specificity: 43 (S), 86 (F), 93% (N)[b] Seizure detection: Sensitivity: 84 (S), 71 (F), 76% (N)[b] Specificity: 39 (S), 93 (F), 96% (N)[b]	aEEG has very high sensitivity and specificity with experienced users.
Zhang 2011 Prospective	62	Term	Seizures on cEEG	aEEG derived from EEG to trans-formed by fast Fourier system	aEEG with the raw trace	Mean 11.5 hr	C3–P3 C4–P4	Experienced electroencephalographers	**aEEG** PWS detection Sensitivity 17% Seizure detection Sensitivity: 44% **aEEG with raw trace** PWS detection Sensitivity: 70% Seizure detection Sensitivity: 85%	aEEG cannot serve as a substitute for cEEG
Mastrangelo 2013 Retrospective	28	Term	Suspected seizures in encephalopathic neonates	aEEG derived from EEG	aEEG	≥12 hr	C3–T3 C4–T4	Two paediatric neurologists (N1) and one neonatologist (N2)	Seizure detection: Sensitivity 49 (N1), 37.5% (N2)[b]	aEEG not reliable for detection of individual seizures.

[a] CFM (Lectromed, Devices Ltd, UK).
[b] Multiple values of sensitivity/specificity indicate values obtained with different readers, #BRM 2 and 3 (BrainZ Instruments, Aukland, New Zealand).
PMA – Post-menstrual age, aEEG – amplitude-integrated electroencephalogram, CFM – cerebral function monitor, PWS – "patients with seizures", EEG – electroencephalogram, cEEG – conventional electroencephalogram,, hr – hours, PPV – positive predictive value, NPV – negative predictive value, HIE – hypoxic ischaemic encephalopathy.

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