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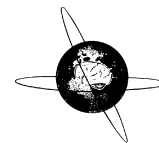
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Research paper

Evaluation of SEPs in asphyxiated newborns using a 4-electrode aEEG brain monitoring set-up



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ABSTRACT

Objective: To evaluate the reliability of recording cortical somatosensory evoked potentials (SEPs) in asphyxiated newborns using the 4-electrode setup applied in routine long-term amplitude-integrated EEG (aEEG) brain monitoring and to assess the number of averages needed for reliably detecting the cortical responses.

Methods: We evaluated median nerve SEPs in 50 asphyxiated full-term newborns. The SEP interpretation (present or absent) from the original recordings with 21-electrodes and approximately 600 trials served as the reference. This was compared to SEP classification (absent, present, or unreliable) based on a reduced (300 or 150) number of averages, and to classification based on only four electrodes (F3, P3, F4, P4).

Results: Compared to the original classification, cortical SEPs were uniformly interpreted as present or absent in all 50 newborns with the 4-electrode setup and 600 averages. Reducing number of averages to 300 still resulted in correct SEP interpretation in 49/50 newborns with 21-electrode setup, and 46/50 newborns with 4-electrode setup.

Conclusions: Evaluation of early cortical neonatal SEPs is reliable from the 4-electrode setup commonly used in aEEG monitoring. SEP is discernible in most newborns with 300 averages.

Significance: Adding SEP into routine aEEG monitoring offers an additional tool for early neonatal neurophysiological evaluation.

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1. Introduction

Treatment of neonatal hypoxic-ischaemic encephalopathy (HIE) with therapeutic hypothermia significantly improves later outcomes (e.g. [Tagin et al., 2012](#)), but at the same time delays early prognostication possibilities with amplitude-integrated EEG (aEEG) ([Bonifacio et al., 2015](#); [Csekó et al., 2013](#); [Hallberg et al.,](#)

[2010](#); [Massaro et al., 2012](#); [Thoresen et al., 2010](#)) leaving no apparent alternative bedside methods for early outcome prediction.

Somatosensory evoked potentials (SEPs), traditionally recorded using only a few scalp electrodes, are known to be highly predictive of outcome during the first days ([de Vries, 1993](#); [Gibson et al., 1992](#); [Scalais et al., 1998](#); [Suppiej et al., 2010](#); [Swarte et al., 2012](#)) or even hours ([Eken et al., 1995](#)) of life in asphyxiated neonates treated in normothermia. In general, in these settings normal SEPs predict favorable and bilaterally absent SEPs unfavorable outcome. These earlier studies did, however, report a few neonates with bilaterally absent SEPs and a good outcome ([Gibson et al., 1992](#); [Suppiej et al., 2010](#); [Swarte et al., 2012](#)). Though extremely rare, such cases have possibly discouraged wider use of SEPs in outcome prediction after perinatal asphyxia. Recent studies recording SEPs concomitantly with whole-scalp EEG, however, reported no “false bilaterally absent” SEPs and suggested that SEPs

Abbreviations: aEEG, amplitude-integrated electroencephalography; EEG, electroencephalography; HIE, hypoxic-ischaemic encephalopathy; NICU, neonatal intensive care unit; SEP, somatosensory evoked potential; SI, primary somatosensory cortex; TH, therapeutic hypothermia.

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do offer an additional method for early outcome prediction at bedside not only in normothermic but also in hypothermia-treated neonates (Nevalainen et al., 2017a,b).

At the same time, the availability of neonatal SEPs is generally limited to office hours even in the few hospitals where they are offered. Consequently, use of SEPs in acute circumstances such as perinatal asphyxia is virtually non-existent. On the contrary, aEEG brain monitoring is widely used and available at any time. Even though the aEEG electrodes - commonly placed at P3, P4, F3, and F4 - are not located right over the sensorimotor area [vs. CP3 and CP4 electrodes recommended for median nerve SEPs (Cruccu et al., 2008) and applied by most of the previous neonatal studies], they are still located bilaterally anterior and posterior to the central sulcus and thus bipolar montages between these electrodes catch the tangentially oriented dipolar source at area 3b of the primary somatosensory cortex (SI) in the central sulcus which produces the earliest cortical SEP (named N1 or N20 in the literature, see e.g. Allison et al., 1989, 1991; Lauronen et al., 2006). Thus, the earliest cortical SEP components (SI response) could be recordable by complementing routine aEEG with median nerve stimulation.

To establish a novel clinical routine that would be widely available in neonatal intensive care units (NICUs), we set out to study whether SI SEPs can be reliably detected in asphyxiated newborns using only the four scalp electrode locations (P3, P4, F3, and F4) routinely applied in aEEG brain monitoring. We also assessed in real life settings of the NICU how many averages are typically needed for a reliable interpretation of cortical SEPs as compared to a “ground truth” obtained using an excess number of averages and high number of electrodes.

2. Patients and methods

2.1. Participants

The study group consists of a systematic retrospective collection of 50 newborns (23 females, gestational age (GA) between 36 + 7 and 42 + 2 weeks) treated for asphyxia/HIE at the tertiary level NICU of the Helsinki University Hospital during years 2011–2014. The predictive values of EEG, SEPs, and VEPs (evaluated from 21 EEG electrodes) in these same newborns have been previously published (Nevalainen et al., 2017b). Of the 50 newborns 28 met the cooling criteria applied in our hospital (defined in Azzopardi et al., 2008) and consequently underwent whole-body therapeutic hypothermia with target temperature 33–34 degrees for 72 h as part of their treatment strategy. As all neurophysiological recordings were performed for clinical indications, 15 of the 28 were still under hypothermia during the EEG and SEP recording. The Ethics Committee for Pediatrics, Adolescent medicine, and Psychiatry, Hospital District of Helsinki and Uusimaa, approved the study protocol.

2.2. EEG and SEP: measurement and data analysis

We applied a study routine developed in our hospital where 21-electrode EEG and SEPs are recorded simultaneously (Nevalainen et al., 2015, 2017a,b). The recordings were performed according to clinical need between 15 h and 10 days postnatally (39 of the 50 newborns were recorded within the first four postnatal days). Details of data collection and SEP stimulation in the same cohort have been previously published (Nevalainen et al., 2017b). In short, EEG was collected at 2000 Hz using a NicoletOne system (Cardinal Healthcare/Natus, USA; acquisition bandwidth 0.053–500 Hz) and 21-electrode EEG caps (sintered Ag/AgCl electrodes; Waveguard, ANT-Neuro, Germany). During the EEG recording, each median nerve was stimulated at the wrist with surface electrodes and a

portable electrical peripheral nerve stimulator (Micromed Energy Light stimulator; Micromed, Italy). The current was individually adjusted to just above the motor threshold.

We averaged the SEPs offline in BESA[®] software (BESA GmbH, Germany). The spontaneous EEG data during the median nerve stimulation were first visually inspected and periods with seizures were discarded from the averages. Epochs from –100 ms to 800 ms relative to stimulus were then averaged without further filtering. To reduce artifacts, due to e.g. large movement, epochs with amplitude over 200 or 300 μ V (depending on the individual amplitude level of the brain activity) were discarded. In addition to averages of the entire data (mean number of averages after artifact rejection 640), we calculated sub-averages of the first approximately 3 and 6 min (mean number of averages after artifact rejection 160 and 310, respectively). These will be referred to as 600, 300 and 150 averages. For each set of averages the odd and even stimuli were separately averaged to evaluate reproducibility of the responses (see the Supplementary Figure).

Supplementary data associated with this article can be found, in the online version, at <https://doi.org/10.1016/j.cnp.2018.06.003>.

SEP interpretation was based on a consensus review by two neurophysiologists (authors PN and LL) who classified the early SEPs to be present, absent or unreliable (due to low signal-to-noise ratio) using the following setups: i) 21-electrode standard longitudinal bipolar montage with voltage maps and possibility of remontaging using the 600 averages (results previously published in Nevalainen et al., 2017b) and the reduced number of 300 and 150 averages, and ii) 4-electrode bipolar montage (including F4-P4, F3-P3, P3-P4, F3-F4, F3-P4 and F4-P3 derivations) without voltage maps using the 600 and 300 averages. In case of disagreement, the consensus was reached by discussion. The percentage of SEPs classified in line with the original SEP classification based on 21-electrode setup with 600 averages was then calculated for each reduced setup.

To classify the newborns according to their EEG background activity, we used the previously published EEG scores (Nevalainen et al., 2017b) based on criteria by Murray et al., (2009): grade 4 = inactive trace (background activity <10 μ V or severe discontinuity meaning interburst interval (IBI) >60 s), grade 3 = severe abnormality (discontinuous activity, IBI 10–60 s, severe attenuation of background patterns, no sleep-wake cycle), grade 2 = moderate abnormality (discontinuous activity during some parts of the recording, IBI <10 s, severe voltage depression, or clear asymmetry/asynchrony), grade 1 = mild abnormality (continuous background pattern with slight abnormalities: e.g., mild asymmetry, or mild voltage depression), and grade 0 = normal.

We also classified the background based on the 4-electrode data (using both the spontaneous 4-electrode EEG and the aEEG trace) using a criteria modified from the above full EEG criteria. We expected grade 1 and 2, where the difference is mainly quantitative, to be difficult to differentiate based on the 4-electrode data and hence category 1 was left out. The 4-electrode background categories were then defined as follows: Grade 4 and 3 same as above, grade 2 = moderate abnormality (discontinuous activity during some parts of the recording, IBI <10 s, clear voltage depression, or asymmetry/asynchrony), grade 0 = no clear abnormality. Infants with full EEG grade 1 were, thus, expected to fall into either grade 2 or grade 0 of the 4-electrode categories.

3. Results

3.1. 21-Electrode SEPs

21-electrode SEP classifications based on the 300 averages were in line with the original classification (600 averages) in all but one

Table 1
The uniformity of SEP classification between the different reduced setups and the original 21-electrode, 600-average classification. The misinterpreted (mi.) or unreliable (ur.) SEPs are shown with respect to the EEG background category. The numbers depict the number of newborns falling into each category. The type of misinterpretation is marked by the superscript letters: a) original classification bilaterally present, reduced classification unilaterally absent, and b) original classification bilaterally absent, reduced classification unilaterally absent. Gr = grade.

Setup		In line with original classification n (%)	Misinterpreted and unreliable SEPs with respect to EEG grade									
Electrodes	Averages		Gr4 (n = 9)		Gr3 (n = 8)		Gr2 (n = 16)		Gr1 (n = 15)		Gr0 (n = 2)	
			mi.	ur.	mi.	ur.	mi.	ur.	mi.	ur.	mi.	ur.
4	600	50 (100%)	-	-	-	-	-	-	-	-	-	-
21	300	49 (98%)	-	-	1 ^a	-	-	-	-	-	-	-
4	300	46 (92%)	-	-	-	2	-	1	-	1	-	-
21	150	42 (84%)	-	1	2 ^{a,b}	3	1 ^a	1	-	-	-	-

newborn that originally had bilaterally present SEPs, but was classified as having unilaterally absent SEPs based on the 300 averages. This newborn had grade 3 EEG background. When only 150 averages were used, in five cases SEPs were classified unreliable due to low signal-to-noise ratio (SNR) and in three cases SEPs were misinterpreted (in two the originally bilaterally present SEPs were classified unilaterally absent and in one the originally bilaterally absent SEPs were classified unilaterally absent). Five of these eight cases had EEG grade 3, one had EEG grade 4, and two had EEG grade 2 (Table 1).

3.2. 4-Electrode SEPs

The full-average 4-electrode SEPs were always classified in line with the original SEPs (Fig. 1). As the traces with 150 averages were often misinterpreted/unreliable even from the 21-electrode data, we only evaluated the traces with 300 averages using the 4-electrode setup. They were in line with the original classification in 46/50 newborns. In the other four the SEPs were classified as unreliable (see the Supplementary Figure for an example). Two of the four infants had grade 3, one had grade 2, and one had grade 1 EEG background.

3.3. 4-Electrode EEG background grading

As it seemed that success in SEP interpretation with the 4-electrode setup and reduced number of averaged depended of the EEG background, we further assessed how well the EEG background could be graded using the 4-electrode setup. The grading was the same in all newborns that were originally classified into EEG grade 0, grade 2, grade 3, or grade 4 categories. Of the 15 newborns that had full EEG grade 1 background, seven were classified to grade 0 and the other eight to grade 2 based on the 4-electrode set-up.

4. Discussion

Our data suggest that in asphyxiated newborns cortical SEPs can be reliably evaluated from the four electrodes at locations that are typically used for long term brain monitoring in the aEEG (or cerebral function monitoring, CFM) paradigm if an excess number of averages (i.e. 600 or more) is used. Evaluation of the subaverages showed that approximately 300 trials (i.e. 5 min of artefact free data with 1 Hz stimulation rate) provided a sufficient signal-to-noise ratio for a reliable SEP assessment in most, but not all newborns. Thus, in cases where there is uncertainty of SEP interpretation, a higher number of averages, a full-EEG setup, or both should be used to be able to confidently classify the SEPs for outcome prediction.

Early outcome prediction with clinical assessment is complicated in asphyxiated newborns due to the rapidly changing neurological state during recovery from HIE. Brain monitoring with

aEEG/EEG is widely used as an additional bedside method for outcome prediction after perinatal asphyxia. Although a normal or only mildly abnormal EEG background is predictive of a good outcome already during the first postnatal day (Hamelin et al., 2011; Murray et al., 2009; Pressler et al., 2001), an inactive aEEG/EEG after perinatal asphyxia is only predictive of a poor outcome if it fails to recover within 24 h in normothermic (e.g. Murray et al., 2009; Pressler et al., 2001) or within 36–48 h in hypothermic newborns (Bonifacio et al., 2015; Csekó et al., 2013; Hallberg et al., 2010; Massaro et al., 2012; Thoresen et al., 2010). Thus, there is still a need for an additional early bedside prognostication tool particularly during the first two postnatal days when treatment decisions are made.

SEPs have potential for contributing to the early bedside prognostication. Earlier studies in normothermic HIE newborns, using set-ups with only few recording electrodes, showed in general excellent predictive abilities of SEPs during the first days (de Vries, 1993; Gibson et al., 1992; Scalais et al., 1998; Suppiej et al., 2010; Swarte et al., 2012) or even hours (Eken et al., 1995) of life. However, a few unexplainable cases with absent SEPs and a favorable outcome were reported (Gibson et al., 1992; Suppiej et al., 2010; Swarte et al., 2012), which may have somewhat discouraged a more widespread use of SEPs in outcome prediction after birth asphyxia. In our previous work with a complete scalp-EEG coverage no falsely absent SEPs (Nevalainen et al., 2017b) were detected, however, suggesting that strict control of the technical factors make recording of SEPs reliable, giving consequently reliable data for outcome prediction.

An important advantage of SEPs in the era of modern intensive care is their resistance to mild hypothermia, which has been demonstrated in adult cardiac arrest patients treated with therapeutic hypothermia (Sandroni et al., 2014) and recently also in asphyxiated newborns undergoing hypothermia (Nevalainen et al., 2017a,b).

To expand the use of neonatal SEP, there is, however, a need for a practical SEP methodology that would be widely applicable in the NICU at any time. Recording SEPs with the aEEG monitor that is already available at the bedside could indeed offer such a widely available and easy-to-apply methodology. In this regard, the present data are encouraging as they show that the four aEEG electrode locations suffice for detecting the cortical SEPs when a sufficient number of averages is used. Our results, thus, complement the previous studies in hypothermia-treated newborns, which applied a full EEG montage (Nevalainen et al., 2017a,b).

We also confirmed that the grade of EEG background abnormality could be determined from the reduced four aEEG electrodes similarly as from the whole head EEG with the precision needed for the prognostication - that is separating inactive (grade 4), burst-suppression (grade 3), and continuous EEG background (grade 0–2) (Nevalainen et al., 2017b). Previously, background classification based on aEEG and EEG was compared by Toet et al. (2002). They, however, used different classification systems

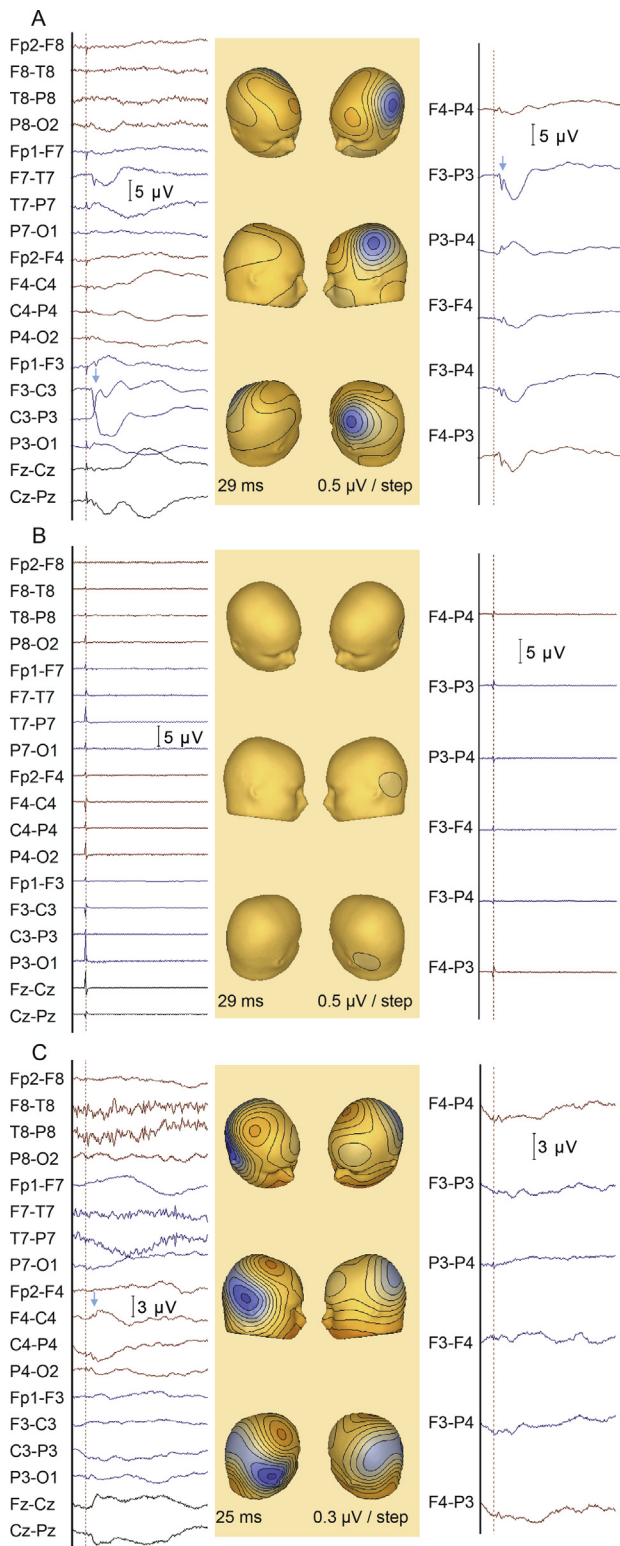


Fig. 1. Evaluation of SEPs with the 21-electrode longitudinal bipolar montage with voltage maps (left column) vs. the four-electrode montage without voltage maps (right column). A) and B) show the full 600-average traces to right median nerve stimulation in one newborn with normal SEP (A) and one newborn with absent SEP (B) that were classified similarly with 21 and 4 electrodes. C) Shows the reduced 300-average traces to left median nerve stimulation from a newborn in whom the SEP could be classified as present from the 21-electrode data but was classified as unreliable from the four-electrode recording. The blue arrows point out the SEP response where present. The timescale for the SEP traces is from -50 to 450 ms relative to stimulus (shown by the dotted line).

for EEG and aEEG and were not able to show exact correspondence between traces classified for example as burst-suppression, although in general they did show a good correspondence between aEEG and EEG for normal traces and severely abnormal traces.

A current limitation of the presented EEG-SEP protocol is the need for offline averaging, which does not allow observation of the averaged SEPs while collecting the data. Therefore, the optimal number of averages for reliable interpretation must be known beforehand. A previous study in healthy newborns reported attenuation of SEP amplitudes with increasing number of averages (Bongers-Schokking et al., 1989). Our current data from sick newborns suggest SEP evaluation to be more reliable with a higher number of averages. This apparent discrepancy may be at least partly explained by the different recording conditions, such as the unavoidably higher noise level in the NICU, which necessitates a higher number of averages yielding a better signal-to-noise ratio for SEP detection. Particularly, the combined effect of reducing the number of electrodes and the number of averages resulted in an increasing number of unreliable SEPs compared to only reducing the number of averages. This finding is interesting in the sense that it may explain some of the previously reported “false absent” SEPs which have been recorded with only few scalp electrodes (e.g. Suppiej et al., 2010; Swarte et al., 2012), and often also with fewer averages (Swarte et al., 2012). As the sufficient number of averages to gain reproducible SEPs varies from case to case, technical advances in standard aEEG/EEG recording software are mandatory for enabling online averaging of evoked responses, which will enable determining a sufficient number of averages individually at bedside and will significantly reduce the recording time.

It must be noted, that instead of the subdermal needles often used in aEEG monitoring, in this study we used surface electrodes. Although the different properties of the different electrodes types (e.g. different surface areas) may affect the recorded data, we believe that the main findings of this study are not dependent on the exact electrode type.

5. Conclusions

Our data showed that the presence/absence of the early cortical neonatal SEPs can readily be determined using the 4-electrode bifrontoparietal montage routinely used for long term aEEG brain monitoring. In most newborns, 300 averages suffice for reliable SEP assessment but in cases of uncertainty a larger number of responses and/or a full EEG setup may be necessary. These results encourage further studies jointly recording SEP with aEEG data which would enable acute and longitudinal SEP assessment effortlessly during aEEG monitoring after perinatal asphyxia.

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Declarations of interest

None.

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