Neonatal EEG at scalp is focal and implies high skull conductivity in realistic neonatal head models

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Abstract

The potential improvements in spatial resolution of neonatal EEG used in source localization have been challenged by the insufficiencies in realistic neonatal head models. Our present study aimed at using empirical methods to indirectly estimate skull conductivity; the model parameter that is known to significantly affect the behavior of newborn scalp EEG and cause it to be markedly different from that of an adult. To this end, we used 64 channel EEG recordings to study the spatial specificity of scalp EEG by assessing the spatial decays in focal transients using both amplitudes and between-channels linear correlations. The findings showed that these amplitudes and correlations decay within few centimeters from the reference channel/electrode, and that the nature of the decay is independent of the scalp area. This decay in newborn infants was found to be approximately three times faster than the corresponding decay in adult EEG analyzed from a set of 256 channel recordings. We then generated realistic head models using both finite and boundary element methods along with a manually segmented magnetic resonance images to study the spatial decays of scalp potentials produced by single dipole in the cortex. By comparing the spatial decays due to real and simulated EEG for different skull conductivities (from 0.003 to 0.3 S/m), we showed that a close match between the empirical and simulated decays was obtained when the selected skull conductivity for newborn was around 0.06–0.2 S/m. This is over an order of magnitude higher than the currently used values in adult head modeling.

The results also showed that the neonatal scalp EEG is less smeared than that of an adult and this characteristic is the same across the entire scalp, including the fontanel region. These results indicate that a focal cortical activity is generally only registered by electrodes within few centimeters from the source. Hence, the conventional 10 to 20 channel neonatal EEG acquisition systems give a significantly spatially under sampled scalp EEG and may, consequently, give distorted pictures of focal brain activities. Such spatial specificity can only be reconciled by appreciating the anatomy of the neonatal head, especially the still unossified skull structure that needs to be modeled with higher conductivities than conventionally used in the adults.

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Introduction

Recent advances in developmental neuroscience as well as in medical care of preterm and ill infants have significantly increased the interest in functional brain assessment. Brain activity in babies is most reliably recorded with neonatal EEG. It is now known, however, that the conventional recording configuration with only 6–10 electrodes (André et al., 2010) does hardly suffice to distinguish brain lobes from each other, making its spatial information content severely compromised (Grieve et al., 2004; Odabaee et al., 2013 see also Zwienen et al., 1991). A better spatial parcellation has been recently attempted by devising various means to record high density EEG (hdEEG) from the neonatal head in the laboratory environment (Fifer et al., 2006; Grieve et al., 2008; Odabaee et al., 2012; Roche-Labarbe et al., 2008), and even in the neonatal intensive care units (Stjerna et al., 2012; Vanhatalo et al., 2008; Welch et al., 2013).

Increasing the number of recording electrodes leads to clear theoretical benefits, including recognition of cerebral activities that may, otherwise, go unnoticed or unlocalized. Most importantly, higher electrode number (ie. increased spatial sampling) opens a possibility for genuine...
Recent studies have showed that neonatal/infant scalp EEG has a very high spatial content, or spatial pattering (Grieve et al., 2004; Odabaee et al., 2013). Those works confirm the idea that adding more electrodes would add non-redundant information, however they also show implicitly that spatial smearing of scalp EEG is substantially lower in the neonates (Odabaee et al., 2013) than in the adults (Freeman Walter et al., 2003; Srinivasan et al., 1998a,b). This notion has far reaching implications: The salient low spatial smearing in the neonatal EEG means that the conductive pathways from the cortex (the generator) to the scalp electrodes need to be significantly different in babies compared to adults. An obvious difference is the head geometry where tissue layers are thinner in newborns. The shorter cortex–electrode distance is, by itself, unlikely to explain the observed differences in spatial smearing which in the adults is commonly considered to arise from the poorly conductive skull layer.

Histological comparison of cranial tissues in infants and adults showed that the skull layer undergoes a significant development from the soft and relatively wet, unossified skull matrix (Silau et al., 1995) to a hard and relatively dry (ossified) adult skull bone. It is very conceivable that this histological difference would imply higher skull conductivity and hence less spatial smearing in the neonates. It is not known, however, what skull conductivity values would be plausible in the neonatal EEG source localization. While electric impedance tomography has been developed to provide potential alternative paradigm for empirical estimation of in vivo tissue conductivities in humans (Esler et al., 2010; Turovets et al., 2008), we are not aware of any experimental configurations how conductivity of live human neonatal skull could be measured directly. Skull conductivities have been studied in animal neonates (Pant et al., 2011), but those results cannot be used for human because of the marked differences in the cranial histology in the early development. Studies with EEG source localization of human neonatal EEG (Despotovic et al., 2012; Roche-Labarbe et al., 2008) have avoided the issue by simply adopting conductivity values from prior adult literature, however the lack of empirical reference makes interpretation of those results difficult.

This study was set out to define suitable range of values for neonatal skull conductivity by combining empirical measures of spatial spreading in the neonatal EEG with forward simulations using realistic neonatal head models. We aimed to answer two questions: First, what is the extent of spatial correlations in the neonatal EEG signal? Second, by comparing this information to forward simulations with a realistic neonatal head model, what levels of skull conductivity could explain such spatial correlation in the neonatal scalp EEG?

**Methods and materials**

The study consists of two complementary parts, one empirical and the other based on simulations. The empirical part uses high density EEG (hdEEG) recordings to analyse spatial decays in signal amplitudes and correlations in the neonatal and adult EEG. The simulation part uses a realistic newborn head model to compute scalp potentials (forward solution) generated by discrete cortical dipoles mimicking cortical sources of focal transients in the real EEG. The simulations were computed for different skull conductivities to work out which conductivity values were plausible in the neonatal EEG source localization. The simulation part allows us to test how conductivity of live human neonatal skull could be measured experimentally, as well as the possibility of forward simulations with a realistic neonatal head model.

**Subjects and hdEEG recording**

Four hdEEG recordings were acquired from four different newborns at term age in the Department of Children’s Clinical Neurophysiology (Helsinki University Central Hospital) using a Full-band EEG (Vanhatalo et al., 2005) acquisition system with sampling rate of 256 Hz or 512 Hz (Cognitrace; ANT B.V., Enschede, The Netherlands, www.ant-neuro.com). We used a 64 channel hdEEG caps tailored for neonates (Waveguard, ANT B.V., Enschede, The Netherlands, www.ant-neuro.com; see also Stjerna et al., 2012). A video clip showing an EEG recording of this kind can be seen by following the link www.nemo-europe.com/en/educational-tools.php. Informed consent was obtained from the parents prior to recordings. This study was approved by the Ethics Committee of the Hospital for Children and Adolescents, Helsinki University Central Hospital.

The four adult EEG recordings used in this study were kindly provided by Dr. German Gomeq-Herrero. They were recorded with a 256-channel EEG system (Geodesic Inc, www.cgi.com) for unrelated studies in VU University of Amsterdam, The Netherlands.

**Analysis of spatial amplitude decay**

Focal transients are a common and salient occurrence in both normal and abnormal neonatal EEG (André et al., 2010; Castro Conde et al., 2004; Okumura et al., 2003). They are characterized by a short and relatively sharp appearance and spatial distribution that is consistent with an underlying cortical origin. In this study, focal transients were marked by a board certified EEGer (S.V.) using the ASA review software, and further analysis was performed using MATLAB. The electrode with the highest amplitude peak at the marked location was chosen as the reference electrode, and all potential values from other electrodes were plotted as a function of distance from this reference electrode. Notably, reference electrode in this context means the electrode that was plotted at location zero in the spatial decay graphs (see Figs. 1 and 2), and it is not to be confused with the recording reference which in our study was grand average. This procedure was repeated for all focal transients, which yielded a total of 110 transients (group 1 n = 38; group 2 n = 21; group 3 n = 51). Finally, a linear regression was computed over the nearest 5 cm (for newborns) or 10 cm (for adult) from the index electrode. Electrodes whose amplitudes were found to be >90% of the reference value were excluded from further analysis in order to mitigate the effects of noise and other artifacts (see also Discussion).
Analysis of spatial correlation decay

Spatial decay of linear correlations between electrodes were computed using 2 min long scalp EEG segments to see how rapidly these correlations decay as function of distance from the reference electrode. This decay was taken as a measure of spatial smearing of scalp EEG. This approach, however, cannot distinguish between signal spread due to conductive tissue layers and multiple local sources from that generated by a large cortical source. However, results from previous studies strongly favor the interpretation that the relative differences between neonates and adults are mainly attributed to spatial smearing via volume conduction (Grieve et al., 2003; Nunez et al., 1999; Odabaee et al., 2013).

It is known that temporal frequencies correlate inversely with the size of cortical generator (Freeman et al, 2003). Since we wanted to limit our analysis to cortical activities that likely encompass relatively small cortical areas, we removed slow events from the EEG in the following way. A median filter was applied using a window length of 120 samples (~230 ms in data sampled at 512 Hz), which was seen to cover about half of focal transients analyzed elsewhere in our work. We then subtracted the median low pass filtered data from the original trace (see also Vanhatalo et al., 2003). The advantage of this approach compared to a conventional low pass filtering, is that it removes the low frequencies without introducing the typical “filter ringing” that would confound any subsequent analysis based on instant amplitudes.

Next, linear (Pearson) correlation was computed between the 2 min (61,440 samples) EEG segments from every electrode pair, and correlation coefficient was plotted as a function of distance between the electrodes. To assess the general nature of the spatial decay, we fitted quadratic, cubic and linear functions to the different plots. We found that the inter-electrode correlation decays can be adequately approximated by a linear function over the closely spaced neighbors (see Fig. 2A), hence a linear approximation was adopted. Finally, the slope of the linear regression of these linear approximations was computed as a measure of the scalp EEG spatial decay.

Statistical testing

As most data was clearly non-normally distributed (see Fig. 2B), we used nonparametric tests in all analysis. Comparison between individuals and groups was performed using analysis of variance with Kruskall–Wallis test. Any significant findings were followed by post hoc pairwise comparison with non-parametric Mann Whitney U test, which was also used for all pairwise group comparisons. Statistical significance was considered if p < 0.01 was observed.

Head model generation

A magnetic resonance image (MRI) was acquired with a Philips 3 T scanner in Helsinki University Central Hospital from a full-term healthy baby. Each slice was 240 × 256 pixels with a pixel resolution of 1 × 1 mm, and slice thickness of 0.9 mm. From the full image stack, 176 slices covering the cranium were segmented manually into 5 compartments (scalp, skull, CSF, brain, eyes) by a clinician using FSL software.
were down sampled to sparser grids: scalp, inner skull and outer skull to 2562 vertices (5120 faces) and brain surface to 4322 vertices (8640 faces). The brain surface (that corresponds to outermost cortical surface) was used as a source space (with a distances between sources are about 3 mm). Forward operator for this three-shell model was computed using Symmetric Boundary Element Method in the OpenMEEG software (Gramfort et al., 2010).

Tissue conductivities

The purpose of this work was to define plausible range of conductivities in the neonatal skull, which is the only conductive layer that undergoes substantial developmental change with respect to its histological, and hence conductive properties. We adopted the conductivities of other tissue compartments (brain 0.33 S/m, CSF 1.79 S/m, scalp 0.33 S/m) directly from the prior literature (Despotovic et al., 2013; Ramon et al., 2006; Roche-Labarbe et al., 2008). Using a single conductivity value for skull compartment is seen as inadequate in adults due to their spatial heterogeneity and low conductivities in the first place, however our present results suggest orders of magnitude higher conductivity for neonatal skull making potential heterogeneity practically irrelevant in the baby head models. Our forward solutions were then computed with three different skull conductivities that ranged from the very poorly conductive estimate of adult skull to a high conduction similar to scalp (ie. 0.0033 S/m, 0.033 S/m, and 0.33 S/m). It would be histologically plausible to assume that the soft and well vascularized neonatal skull tissue (Ernst et al., 2011; Silau et al., 1995) might have conduction properties comparable to scalp.

Forward solutions and their analysis

Forward solutions (scalp potentials in each scalp points, n = 90649; see Fig. 3E) with FEM were computed for radial sources placed in a parietal position into three different depths (8 mm, 13 mm and 16 mm) from the scalp surface, and the procedure was repeated for all three skull conductivity values (ie. total of nine runs). Source depth was varied because the cortex-scalp distance is variable as shown in our present analysis (Fig. 3C) and the prior study of Beauchamp and colleagues (Beauchamp et al., 2011). We have also previously shown that spatial frequency of neonatal EEG depends on the source depth (Odabaee et al., 2013). The source space in BEM is at the brain surface, so we searched for locations near our FEM source (parietal) that were at about depths of 10–13 mm from the scalp surface.

We defined the highest (peak) value of scalp potentials, and then plotted all other scalp potential values as a function of distance from the peak value (see Fig. 3E). As the amplitude decay was found to be linear as was the case in the empiric data (see above), we fitted a linear regression line over the nearest 5 cm from the peak. The slope of this line was used to generate the graph that compares conductivities and source depths (Fig. 3F) as well as to finally compare these results to empirical findings from above.

Results

Spatial amplitude decay

Inspection of the raw hdEEG data (Fig. 1B) shows that transients in the neonatal EEG often cover only a few electrodes, and that they can, hence, be assumed to have been generated by a focal cortical generator. All signal amplitudes at the given peak times were then plotted as a function of inter-electrode distance (Fig. 1D). Such graphs demonstrate clearly that the amplitudes decay rapidly within first few centimeters before becoming scattered further away due to the presence of unrelated ongoing activity in other cortical areas. The slope of the linear fit was thus taken as a proxy of spatial amplitude decay. The slope values within each subject (example shown in Fig. 1E) were found to be notably

(Smith et al., 2004). The same segmented image stack was used for generation of both head models as described below.

Finite element method (FEM)

A 3D FEM head model was generated using custom made scripts (cf. Ramon et al., 2006) from the segmented image stack where voxel resolution was 1 × 1 × 1 mm. The electrical conductivities of various tissues were obtained from the literature as detailed below. For a given dipole position, flux and potential distributions were computed using an adaptive FEM solver (Ramon et al., 2006). The scalp potentials were extracted for further analysis. For a typical FEM run, voxel sizes varied from 1 × 1 × 1 to 16 × 16 × 16 pixels. A detailed image of a FEM run voxels is shown in Fig. 3 where voxels near the dipole are of 1 × 1 × 1 pixel size, while voxels further away have varying size. The size of voxels was automatically adjusted in the FEM solver based on a preset L2 norm error limit on the normal and tangential fluxes at the voxel faces.

Boundary element method (BEM) head model

To generate BEM-based head model, Brainstorm software (Tadel et al., 2011) was used along with the previously segmented MRIs to construct 3D surfaces of the scalp, outer skull, inner skull and brain (see Fig. 3A). To reduce the computational load, the raw 3D surfaces
The slope values in different newborns showed no significant difference ($p = 0.52$; Fig. 1F). Moreover, comparison between electrode groups showed no significant differences between midline region (fontanel) and other brain regions covered with newborn skull tissue ($p = 0.21$ for comparison between groups). Taken together, these indicate that spatial decay of scalp amplitudes is by and large consistent across scalp areas as well as between individuals.

**Spatial correlation decay**

Plotting the linear correlations between electrodes as a function of inter-electrode distance in the neonatal EEG showed a clear decay to near zero within about the first five centimeters (an example subject is shown in Fig. 2A).

Inspection of a similar analysis in the adult (256 channel) hdEEG recordings showed that the slope of spatial decay in the adults is strikingly flatter, and the levels of correlation tend to be more scattered throughout the scalp (ie. at all distances). After inspecting a larger number of individual graphs (one example shown in Fig. 2A), it was concluded that the adult EEG data exhibits a relatively linear slope up to about 10 cm from the reference electrode. Hence, the linear regression fit in the adult data was performed for the nearest 10 cm from the index electrode.

The regression slopes were found to be consistent and without significant differences within the groups of neonates and adults (Fig. 2B). However, the slopes were generally about three times steeper in the neonates compared to adults (mean slope in adults 0.052; mean slope in neonates 0.17), and the difference between age groups was highly significant ($p < 0.001$).

**Forward model simulations**

Spatial decay of scalp EEG was next estimated from the realistic shape neonatal head model where EEG source was placed at varying depths in the parietal cortex. The distribution of scalp potentials has a clear peak above the source consistent with the radial source orientation. Comparison of different skull conductivities showed expectedly that the scalp potential becomes progressively smoother towards the lower conductivity. Indeed, with the skull conductivity adopted from the adult literature (0.0033 S/m), the scalp potential distribution from a single focal cortical source extended over half of the head which is different from the empirically observed focality in neonatal EEG signals.

Similar analysis using the BEM model (Fig. 4) showed that the plots of spatial amplitude decay have considerably less scatter, which is likely due to reduced noise in the relatively simple forward solution of BEM.
as shown in the Fig. 4, the results between FEM and BEM models were generally very comparable.

Consistent with the results from prior studies using a 4-layer spherical neonatal head model (Odabaee et al., 2013), we found a clear relationship between different source depths and the spread of scalp EEG potentials. The most superficial source (at 8 mm depth) produced a highly focal potential distribution, which became considerably broader as the source was placed deeper at 13 mm or 16 mm.

Comparison of empirical and simulation results

Our simulation work yielded a two dimensional relationship of spatial decays (Fig. 3F) of scalp EEG potentials as a function of the skull conductivity and the source depth. In order to determine empirically the range of plausible conductivity levels associated with neonatal skull, there is first a need to define an anatomically reasonable source depth. For that purpose, we computed cortex–scalp distances (Fig. 3C) that, together with a recent study by Beauchamp and colleagues (Beauchamp et al., 2011) suggest that the surface of cortex is at around 6–10 mm from the scalp. Second, we took the range of empirical regression slope values (around 0.23) from our analysis of neonatal EEG (cf. Fig. 1) to limit the focus in z axis (the color). After limiting the focus in depth and slope (x and y, respectively), the graph will return the range of y values, the skull conductivity, that is within the range of 0.06–0.2 S/m.

Discussion

Our findings support the notion that the EEG recorded from the newborn scalp is very focal by nature, and that such focality is the result of high conductivity of the skull tissue. The EEG activity generated by a focal source was found to decay within few centimeters at the scalp, which is, on the average, three times steeper decay than in the adult EEG. Simulations using realistic neonatal head model indicate that neonatal skull conductivity is close to that of soft tissues, and hence orders of magnitude higher than conventionally assumed for the adult skull. Our results are fully consistent with recent empiric (Odabaee et al., 2012) and simulation findings (Grieve et al., 2003), and our findings of spatial correlation in the adult EEG data compares well with prior similar analyses on adults (Nunez et al., 1999). This work also validates the recent suggestions (Despotovic et al., 2012; Odabaee et al., 2013) on the need to use higher skull conductivity for the neonatal skull.

The observed steep spatial decay of amplitudes is consistent with the recently reported high spatial complexity in the neonatal EEG (Odabaee et al., 2013). Moreover, it implicitly explains why we saw no significant difference between electrodes in the midline and other scalp areas. This is in an apparent conflict with the common assumption of EEG distortion by fontanels in neonates, however such thinking results from the ignorance of the particular developmental histology of the neonatal skull tissue. It has been clearly established (Ernst et al., 2011) that neonatal skull bone is not ossified at birth, that the skull tissue undergoes a membranous type ossification during early life, and that the histological structure of skull remains trabecular (Christie, 1949; Epstein, 1974) for a longer time, hence providing tissue pathways with high electric conductivity until the skull becomes fully ossified later in life. Our conclusion of very high neonatal skull conductivity, indeed comparable to other soft tissues, is fully compatible with these well known anatomical considerations.

There are three factors that cannot be directly controlled, but they may potentially confound our empirical analysis. Their bias is, however, likely to lead to a conservative estimate of skull conductivity, because they tend to make the slopes of spatial decay flatter. First, our hdEEG only includes 64 channels which results in inter-electrode distance of about 20–30 mm. Such spatial sampling implies that the amplitudes and linear correlations decayed within the nearest few electrodes already. The linear regression slopes were computed from the nearest few electrodes in each case. This obvious limitation in the accuracy of results could be overcome by replicating the findings with substantially higher number of recording electrodes (see, for instance, Welch et al., 2013). Second, an unrelated brain activity across cortical areas may unavoidably bias estimates of spatial decays (of both transient amplitudes and interelectrode correlations) towards flatter slopes. Third, it is obvious that the cortical generators are not point sources, but that they have an unknown spatial extent. The true spatial decay related to signal smearing in the conductive tissues should be analyzed from the edge of the putative cortical generator area, if such is known. It is also possible that distant cortical sites have high signal correlations due to their genuine synchrony (Bressler and Menon, 2010; González et al., 2011; Omidvarnia et al., 2013; Palva et al., 2010; Tokariev et al., 2012), which would lead to a flatter spatial decay of correlations due to physiological rather than volume conduction effects.

Source localization in neonatal EEG has recently gained considerable interest due to the rapid progress in developmental neuroscience and computational methods (Despotovic et al., 2013; Roche-Labarbe et al., 2008). The recent introduction of hdEEG recording methods (Tifer et al., 2006; Grieve et al., 2008; Roche-Labarbe et al., 2008; Stjerna et al., 2012; Welch et al., 2013); has been the crucial technical advance opening the way for improvements in source localization approaches. It is intriguing in this context, that our findings are indirectly challenging the view based on adult EEG, that source localization or source space signal analysis (Palva et al., 2010; Schoffelen and Gross, 2009) would be superior to signal space (i.e. raw scalp EEG data) analyses. The high spatial specificity of neonatal EEG shown here (Grieve et al., 2003; Odabaee et al., 2013) implies relatively little cross talk between scalp EEG channels. Hence, the typically used low numbers of scalp electrodes, ranging from the conventional eight (André et al., 2010) to about 20–30 electrodes (Omidvarnia et al., 2013), can be considered to yield relatively non-redundant signals. In such a situation, projecting signals onto cortical source space may have limited additional value in separating them from each other (e.g. for analysis of overall network connectivity). However, substantial increase in the electrode number (e.g. 128 or 256 channels; see Welch et al., 2013) will lead to situations where disambiguation with source level analysis will be helpful for identifying sources with different cortical orientations, as well as for eliminating the spatial mixing that unavoidably comes between very closely spaced scalp electrodes. In addition, anatomical localization of EEG signal sources will still be very useful for combining EEG and functional MRI studies that became accessible after recent safety studies in neonates (Vanhatalo et al., 2013).
While the conventional neonatal EEG recordings are spatially too under sampled to genuinely gain from source localization, it is still possible to add further spatial localizing information with the following advances: First, the number of electrodes from the presently used 64 channel should be increased, and the anatomical positioning of electrodes in each recording session should be considerably improved from the presently used anatomical landmarks (cf. (Hellström et al., 1963)). These challenges are already solved and the methods exist for their clinical implementation (Welch et al., 2013). Second, the head model used for source localization needs to be computed for each individual recording session because of the substantial variability in head geometries between neonates, as well as within the same infant (due to development) between different recording sessions. Third, the EEG activity in neonates arises from different underlying mechanisms where much of the early activity is, indeed, orchestrated by immature thalamo-cortical or subplate-cortex networks. Details of the networks involved in early EEG generation are only known from experimental animal models, which have shown spatially coordinated spontaneous activity transients that are distinct from those giving rise to traditional EEG oscillations of older subjects (e.g. Brockmann et al., 2011; Colonnesi and Khazipov, 2012; Khazipov and Luhmann, 2006; Kilb et al., 2011; Tolner et al., 2012; Vanhatalo and Kaila, 2006), which are not compatible with the a priori assumptions that underlie the adult source reconstruction paradigms. All these issues pose significant technical, physiological, ethical, and logistical challenges in attempts to push the limits of spatial source localization of neonatal brain activity.

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