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Analysis of infant cortical synchrony is constrained by the number of recording electrodes and the recording montage

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HIGHLIGHTS

- Analysis of brain connectivity from the neonatal EEG is strongly enhanced by adding the number of electrodes.
- Sensitivity and specificity of cortical synchrony estimates depend on the analysis montage; average and Laplacian montage have the best performance.
- The number of electrodes defines the optimal montage and it also sets the limits for the level of analytic details.

ABSTRACT

Objective: To assess how the recording montage in the neonatal EEG influences the detection of cortical source signals and their phase interactions.
Methods: Scalp EEG was simulated by forward modeling 20–200 simultaneously active sources covering the cortical surface of a realistic neonatal head model. We assessed systematically how the number of scalp electrodes (11–85), analysis montage, or the size of cortical sources affect the detection of cortical phase synchrony. Statistical metrics were developed for quantifying the resolution and reliability of the montages.
Results: The findings converge to show that an increase in the number of recording electrodes leads to a systematic improvement in the detection of true cortical phase synchrony. While there is always a ceiling effect with respect to discernible cortical details, we show that the average and Laplacian montages exhibit superior specificity and sensitivity as compared to other conventional montages.
Conclusions: Reliability in assessing true neonatal cortical synchrony is directly related to the choice of EEG recording and analysis configurations. Because of the high conductivity of the neonatal skull, the conventional neonatal EEG recordings are spatially far too sparse for pertinent studies, and this loss of information cannot be recovered by re-montaging during analysis.
Significance: Future neonatal EEG studies will need prospective planning of recording configuration to allow analysis of spatial details required by each study question. Our findings also advice about the level of details in brain synchrony that can be studied with existing datasets or by using conventional EEG recordings.

1. Introduction

Interactions between brain areas are fundamental for most brain functions. These interactions may be observed with both invasive and non-invasive electrophysiological methods and appear to support neuronal communication, integration, and functional binding via spatiotemporal constellations of phase-correlated cortical oscillations (Stam and van Straaten, 2012). Several levels of evidence, ranging from simulations to

Abbreviations: 3D, three-dimensional; BEM, boundary element method; CDH, cumulative density histograms; (c)DS, (cumulative) degree of smearing; (c)FNP, (cumulative) false negative probability; CSD, current source density; EEG, electroencephalography; hdEEG, high density EEG; IED, inter-electrode distance; M, number of discernible parcels; MEG, magnetoencephalography; MFC, montage fidelity coefficient; MRI, magnetic resonance imaging; PD, parcel diameter; PDH, probability density histogram; PLV, phase locking value; (r/i)PLV, real/imaginary part of PLV.

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experimental models and studies on human infants, support the idea that early neuronal network activities are crucial for the maturation of lifetime brain functions (Colonnese and Khazipov, 2012; Kilb et al., 2011). This has increased the interest in understanding how brain areas interact during early development (Grieve et al., 2008; Omidvarnia et al., 2014) and how the neurocognitive abnormalities arise from early adversities via altering early neuronal network activity (Krüger et al., 2012).

The introduction of novel dense array EEG recording methods (30–130 electrodes) into neonatal work has opened the possibility to study spatial details in neonatal brain activity in both hospital and laboratory settings (Grieve et al., 2008; Odabaee et al., 2013; Omidvarnia et al., 2014; Tokariev et al., 2012; Wallois et al., 2009). The recent theoretical work has shown that the information content, or spatial richness, of EEG signal that can be recorded from the neonatal scalp is dramatically higher than what is conventionally thought (Grieve et al., 2003, 2004; Odabaee et al., 2013). Pragmatically, this implies that conventional EEG recordings with eight to twenty electrodes (André et al., 2010) provide a significantly deficient representation of brain activity, because much if not most EEG activity available at scalp is ignored.

While the need for an increased number of recording electrodes has been established, there is no information about how the number of electrodes translates to the ability to study details of individual cortical activities, or how the neuronal interactions between brain areas are seen in the EEG when using different numbers of recording electrodes or analysis montages. Such information would be instrumental for several aspects of an appropriate study design on early brain network activity. First, it would be important to understand the level of neuroanatomical detail in brain function that can be plausibly studied using a limited number of scalp electrodes as is the case in most clinical recordings of sick infants. Second, it would be important to know how the recording montage affects the brain activity and interaction estimates, and how this depends on the number of recording electrodes. Third, defining the optimal recording and analysis settings, as well as estimating the trade-offs related to compromises, will be necessary in the scientific search of understanding early brain network function. While some of these issues have been studied in adults, the substantially different head geometry, much smaller dimensions and higher skull conductivity in infants lead to significant differences in the information yielded by EEG between infants and adults, and preclude the extrapolation of adult literature into the neonatal context. Notably, adult literature has focused on the effects of reference choice on amplitude-dependent measures of EEG (Essl and Rappelsberger, 1998; Nunez et al., 1997, 1999; Pascual-Marqui and Lehmann, 1993; Wolpaw and Wood, 1982; Yao et al., 2005, 2007), while the effects on phase synchrony have not been studied before.

2. Methods and materials

2.1. Overview of the methodological approach

We assessed here the accuracy with which local cortical dynamics and inter-areal interactions can be detected in human babies with variable numbers of scalp EEG electrodes and different re-referencing, i.e. montage options. This assessment was split into two parts: First, we used two complementary 'montage performance metrics' to index the performance of different montages and electrode numbers in detecting the cortical activity with variable parcellation resolutions. Second, we used two other 'coupling detection metrics' to see how well each montage and electrode number can detect coupling between signals from different cortical parcels, i.e. areas with coherent activity.

To quantify rigorously the relationship between scalp EEG signals and the underlying cortical (i.e. 'true' neuronal) signals, we obtained virtual EEG recordings by forward modeling simulated time series in cortical parcellations of variable resolutions (20–200 parcels fully covering the cortical surface). As the basis for the forward model we used boundary element method (BEM; Geselowitz, 1967; Kybic et al., 2005) applied to 3D model based on an anatomical MRI of a healthy neonate.

An overview of the protocol is presented in Fig. 1, the generation of the head model is shown in Fig. 2, and the methods used to assess performance metrics for the different electrode numbers and montages are illustrated in Figs. 3 and 4.

2.2. Head model generation

Anatomical model: We used a magnetic resonance image (MRI, Philips 3T scanner, Helsinki University Central Hospital) of a healthy fullterm baby. Raw MRI slices (pixel size 0.9 mm) were segmented manually (Fig. 1A, Fig. 2B) by a clinician using the FSL software (Jenkinson et al., 2012; Smith et al., 2004). 3D surfaces of the brain, inner skull, outer skull and scalp were reconstructed with Brainstorm software (Tadel et al., 2011). To improve computational performance, the scalp, inner skull, and outer skull surfaces were downsampled to 2562 vertices (5120 faces) and the brain surface to 4322 vertices (8640 faces). Fixed orientation dipoles normal to the vertices of the brain surface then comprised the source space with ~3 mm separation between sources. Forward operator (Fig. 1B) for the resulting three-shell head model (Fig. 2C) was computed using symmetric boundary element method (BEM) in the OpenMEEG software (Gramfort et al., 2010; Kybic et al., 2005). To validate the results obtained with this source model as well as to examine the impact that a fully gyrated cortical surface would have on the output results, a 'gyrated model' was also used. In this model the original baby brain source model was replaced with a cortical surface source model with fixed surface-normal dipoles obtained from an adult subject, rescaled to the size of the baby brain and downsampled to have the same number of source vertices. The adult cortical surface (cortex-CSF border) was taken from 'Colin27' adult head model (Holmes et al., 1998) that is available in Brainstorm software.

Tissue conductivities: Following the recent study of Despotovic et al. (2013), we used the conductivity values 0.43 S/m and 1.79 S/m for the scalp and intracranial layer, respectively. Due to variability in the estimates of neonatal skull conductivities, we ran our simulations using two values, one that is near the traditional estimates (0.033 S/m) and another that is closer to recent suggestions that neonatal skull layer is highly conductive (0.2 S/m) (Despotovic et al., 2013; Grieve et al., 2004; Odabaee et al., 2013; Roche-Labarbe et al., 2008). In the gyrated model only skull conductivity of 0.2 S/m was tested.

2.3. Signal simulations

2.3.1. Simulation of cortical parcel signals

To simulate cortical neuronal activity that is locally coherent, source dipoles oriented normally to the cortical surface were clustered (Figs. 1C and 2C) with closest neighbors using K-means approach (Baumgartner et al., 2000; Hanson et al., 2007) to give 20 to 200 cortical parcels (N_p = 20, 40, 60, 80, 100, 120, 140, 160, 180 and 200). Increase in N_p results in a decrease in the parcel size (see Fig. 2D for the parcel diameters) and the corresponding scalp potentials. We created a new cortical parcellation for each iteration of the simulations in order to eliminate the possibility of any given realization of the source parcellation introducing systematic distortions into the results. For each parcel, a unique parcel signal $S_p(t)$ was generated (white noise; nominal sampling frequency

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