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Structural damage in early preterm brain changes the electric resting state networks☆

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ABSTRACT

A robust functional bimodality is found in the long-range spatial correlations of newborn cortical activity, and it likely provides the developmentally crucial functional coordination during the initial growth of brain networks. This study searched for possible acute effects on this large scale cortical coordination after acute structural brain lesion in early preterm infants.

EEG recordings were obtained from preterm infants without (n = 11) and with (n = 6) haemorrhagic brain lesion detected in their routine ultrasound exam. The spatial cortical correlations in band-specific amplitudes were examined within two amplitude regimes, high and low amplitude periods, respectively. Technical validation of our analytical approach showed that bimodality of this kind is a genuine physiological characteristic of each brain network. It was not observed in datasets created from uniform noise, neither is it found between randomly paired signals. Hence, the observed bimodality arises from specific interactions between cortical regions. We found that significant long-range amplitude correlations are found in most signal pairs in both groups at high amplitudes, but the correlations are generally weaker in newborns with brain lesions. The group difference is larger during high mode, however the difference did not have any statistically apparent topology. Graph theoretical analysis confirmed a significantly larger weight dispersion in the newborns with brain lesion. Comparison of graph measures to a child's performance at two years showed that lower clustering coefficient and weight dispersion were both correlated to better neurodevelopmental outcomes. Our findings suggest that the common preterm brain haemorrhage causes diffuse changes in the functional long-range cortical correlations. It has been recently recognized that the high mode network activity is crucial for early brain development. The present observations may hence offer a mechanistic link between early lesion and the later emergence of complex neurocognitive sequelae.

Introduction

Spontaneous brain activity is known to exhibit large-scale correlations that have recently gained wide interest in the neuroscience community (Hipp et al., 2012; Kolchinsky et al., 2014; Menon, 2013). These resting state networks (RSNs) are often studied by observing slow, spatially correlated fluctuations in the blood oxygenation level dependent (BOLD) signals in the functional magnetic resonance imaging (fMRI; Biswal et al., 1995; Fox and Raichle, 2007; Zhang and Raichle, 2010; Biswal et al., 2010). They are even observed in sleeping human newborns as interhemispherically spanning RSNs that are in many ways comparable to those seen in older subjects (Doria et al., 2010; Fransson et al., 2007; Smyser et al., 2010). Recent works in adults have also reported spatial correlations in band-specific power of electroencephalograph (EEG) or magnetoencephalograph (MEG) with resemblance to the RSNs described from resting state fMRI signals (rs-fMRI; Hipp et al., 2012; Brookes et al., 2011; Mantini et al., 2007; Pasquale et al., 2010), however these EEG/MEG-based network constellations exhibit spatial and temporal dynamics that cannot be paralleled in their rs-fMRI counterparts (Betzel et al., 2012; Brookes et al., 2014; Omidvarnia et al., 2014). In this work, we will use the term eRSN (electric RSN) to refer to the EEG-based measures of spatial amplitude correlations (see also Omidvarnia et al., 2014).

Our recent study on preterm and term human infants found robust spatial correlations in the cortical activity of the preterm and term

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infants (Omidvarnia et al., 2014). We disclosed two temporally distinct modes that alternate at subsecond scale: epochs with high amplitudes (i.e., high mode) are characterized by widespread spatial correlations, while epochs with low amplitudes (i.e. low mode) show hardly any spatial correlations. This 'functional bimodality' is fully compatible with emerging views in basic neurobiology where early brain networks are known to operate in two modes: The high mode is associated with self-organizing, locally generated spontaneous activity transients (SATs, also known as bursts in the neonatal EEG literature; Palmu et al., 2010) and the low mode representing low-amplitude intervals between SATs (Vanhatalo et al., 2005). Bimodality in spatial correlations decreases from the preterm period to term age (Omidvarnia et al., 2014). It is now generally accepted that cortical mechanisms related to high mode connectivity, the SAT type events, are crucial for the activity-dependent development of brain networks before experience-driven network organization starts at late gestation or infancy (Blankenship and Feller, 2010; Colonnese and Khazipov, 2012; Hanganu-Opatz, 2010).

Early human preterm infants are at high risk for intraventricular haemorrhage (IVH) during the first days of life, which leads to a high likelihood of severe neurocognitive sequelae (Kidokoro et al., 2014; Panigrahy et al., 2012; Tsai et al., 2014). Cranial ultrasound is currently the gold standard in routine identification of IVH, however little is known about the acute effects of IVH on brain function, which however is likely at causal pathway mediating the IVH-related neuro-developmental risks. Early assessment of brain function after IVH could, for instance, offer a significantly improved identification of infants for early interventions (Spittle et al., 2012).

Our present study was set out to examine the IVH effects on early eRSN at different frequencies by comparing a group of preterm infants without IVH to those with major IVH, including parenchymal involvement. In addition, the specificity of these long-range correlations to the given pairs of EEG channels was studied by assessing the presence of comparable signal correlations in simulated data or in EEG signal pairs from different individuals. These experiments were designed to answer two questions: First, are cortical long-range correlations affected by IVH in preterm infants whose EEG appears normal in the clinical, visual assessment? Second, what is the spatial topology of this effect, and are the graph theoretical metrics of normal and lesioned brain networks different?

Methods

The present eRSN analysis paradigm was originally developed for neonatal EEG signals (Omidvarnia et al., 2014), and its outline is schematically shown in Fig. 1. Background physiological rationale is based on identifying developmentally important EEG events, the SATs (also known as bursts), in the newborn EEG signal (Vanhatalo et al., 2005). They have a duration of up to several seconds consisting of high frequency oscillations (>3 Hz) nested on the low frequency fluctuations (<1 Hz) (Vanhatalo et al., 2005). Extraction of higher frequency components from newborn EEG signals by band-pass filtering followed by obtaining their instantaneous amplitude (i.e., band amplitude fluctuations or BAFs) will indirectly focus on these events (Tokariev et al., 2012; Hartley et al., 2012). Below, details of this workflow are explained, including the modifications performed for this study, as well as technical validation of our eRSN findings.

Pre-processing

Each continuous EEG segment underwent a sequence of pre-processing steps: i) initial temporal band-pass filtering at 1–30 Hz, ii) re-montaging into the Laplacian current source density (CSD) montage with 21 channels ($\gamma = 5 \times 10^{-6}$ and $m = 4$, see also Perrin et al., 1989), including interpolation of bad or missing EEG channels (see below), and iii) signal orthogonalization to alleviate volume conduction effects.

Re-montaging and channel interpolations

Due to the absence of reliable head models for neonatal EEG source reconstruction (Odabaee et al., 2013), we conducted our analysis using the Laplacian (CSD) montage (Perrin et al., 1989) based on the spherical spline interpolation as implemented in the open source MATLAB-based CSD toolbox (Kayser and Tenke, 2006). We chose minimal spatial smoothing controlled by the parameter γ in the CSD re-montaging step (cf. Odabaee et al., 2013). Interpolation of visually identified missing or bad channels was done in four datasets using spherical interpolation (function '*eeg_interp*' of EEGLAB toolbox; Delorme and Makeig, 2004). We acknowledge that this commonly used approach might lead to slight underestimation of spatial correlations due to the very high spatial density of newborn scalp EEG (Odabaee et al., 2013, 2014). However, the number of interpolated channels (~1% of all channels in our study) was so low that we don't expect it to significantly confound our findings.

Orthogonalization

The common instantaneous amplitude components characteristic of spatial smearing in the surface EEG signals were further suppressed by taking the orthogonal projection of each EEG signal power onto the others as described in Hipp et al., 2012. Our earlier study showed that the typical volume conduction effect, the amplitude correlations between nearby EEG signals, is strongly reduced by orthogonalization (Omidvarnia et al., 2014). The detailed procedure is explained below.

Extraction of the event-level EEG fluctuations

Frequency-specific BAF extraction was performed using the Hilbert transform within three frequency bands: 3–8 Hz, 8–15 Hz and 3–15 Hz using a set of 3rd order Butterworth filters through a zero-phase digital filtering in both the forward and backward directions (MATLAB command *filtfilt*). The first two frequency bands correspond

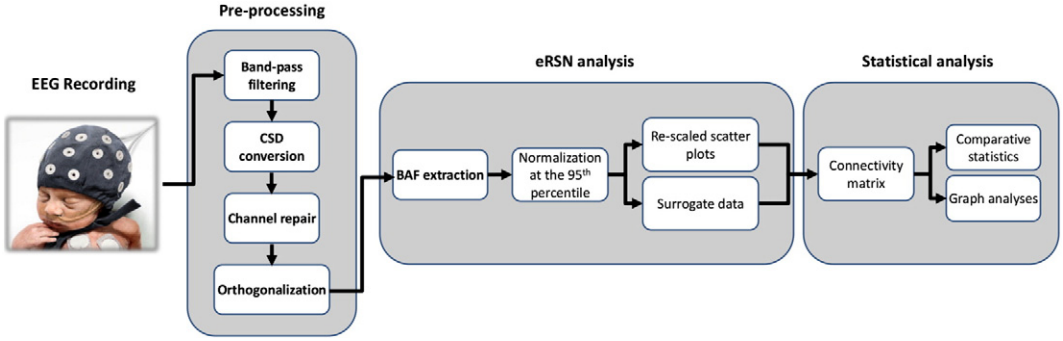

Fig. 1. Overall workflow of the eRSN analysis. See Omidvarnia et al. (2014) for more details.