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EARLY DEVELOPMENT OF SYNCHRONY IN CORTICAL ACTIVATIONS IN THE HUMAN

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Abstract—Early intermittent cortical activity is thought to play a crucial role in the growth of neuronal network development, and large scale brain networks are known to provide the basis for higher brain functions. Yet, the early development of the large scale synchrony in cortical activations is unknown. Here, we tested the hypothesis that the early intermittent cortical activations seen in the human scalp EEG show a clear developmental course during the last trimester of pregnancy, the period of intensive growth of cortico-cortical connections. We recorded scalp EEG from altogether 22 premature infants at post-menstrual age between 30 and 44 weeks, and the early cortical synchrony was quantified using recently introduced activation synchrony index (ASI). The developmental correlations of ASI were computed for individual EEG signals as well as anatomically and mathematically defined spatial subgroups. We report two main findings. First, we observed a robust and statistically significant increase in ASI in all cortical areas. Second, there were significant spatial gradients in the synchrony in fronto-occipital and left-to-right directions. These findings provide evidence that early cortical activity is increasingly synchronized across the neocortex. The ASI-based metrics introduced in our work allow direct translational comparison to *in vivo* animal models, as well as hold promise for implementation as a functional developmental biomarker in future research on human neonates.

Key words: neonatal EEG, brain connectivity, biomarker, early development, brain monitoring.

INTRODUCTION

Large-scale spatio-temporal correlations in neuronal activity are considered to provide the functional basis for a range of brain functions in distributed networks (Bressler and Menon, 2010; Uhlhaas et al., 2010; Palva and Palva, 2011). These correlations are readily observed in the neuronal activity, as well as in the fluctuation of cerebral blood flow (Biswal et al., 1995; Jerbi et al., 2010), and they also correlate with behavioral states (Raichle, 2010; Palva and Palva, 2011; Hutchison et al., 2013).

Little is known about the early ontogenesis of functional communication in the human neuronal networks. Recent anatomical studies have disclosed an account of the microscopic development of structural networks in the human fetus (Kostovic and Jovanov-Milosevic, 2006; Kostovic and Judas, 2010), which sets the physical frame to how the early neuronal dynamics may emerge during latter half of gestation. Some features of large-scale spatial coordination in the electrical activity of the brain have been reported in sleeping human newborns (Tokariev et al., 2012; Omidvarnia et al., 2014). It is known that two modes of brain activity (Vanhatalo and Kaila, 2006) alternate in sub-second time scales between a relative quiescence and its interruptions by spontaneous activity transients (SAT, a.k.a. burst; Vanhatalo et al., 2005). These SATs are thought to provide the endogenous driver needed for activity-dependent wiring of the early brain networks, prior to onset of genuine sensory experience (Hanganu-Opatz, 2010; Kilb et al., 2011; Colonnese and Khazipov, 2012).

Early clinical studies on neonatal EEG established that the temporal co-incidence of these activity bursts between the hemispheres, commonly called "interhemispheric synchrony" (IHS), is a good marker of normally developing EEG activity at term age. A developmental increase in IHS was found during the last trimester of pregnancy (Lombroso, 1979), however, the existing literature is based on subjective and largely qualitative EEG assessment that compromises the validity of

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Abbreviations: AC, Algebraic connectivity; ASI, activation synchrony index; cx-cx, cortico-cortical; EDTF, energy weighted temporal dependency function; GS, Global Synchrony; IHS, interhemispheric synchrony; iqr, interquartile range; IVH, intraventricular hemorrhage; MST, Minimum spanning tree; PMA, postmenstrual age; SAT, spontaneous activity transients.

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detailed findings. Moreover, there are no reports on spatial differences in the development of synchrony between cortical areas, yet histological studies have clearly established distinct developmental trajectories in the growth of long-range cortico-cortical (cx-cx) pathways (Judas et al., 2005; Kostovic and Jovanov-Milosevic, 2006).

We have recently developed and validated a measure for IHS, called activation synchrony index (ASI), which statistically quantifies the temporal coincidence of SAT in the cortical activity (Räsänen et al., 2013; Koolen et al., 2014b). Since late 1970s, the clinical EEG review has involved visual assessment of IHS as one of the key parameters of EEG maturation and normality (Lombroso, 1979). Our benchmarking study with visual reading and other synchrony measures showed that ASI is most accurately emulating the clinically recognized phenomenon of cx-cx EEG synchrony. This has opened the possibility to study how the synchrony between cortical activations evolves during prematurity. In the present study, we aimed to characterize the developmental correlations of cx-cx synchrony during the last ten weeks of pregnancy, which is characterized by the rapid development of long-range cx-cx connections. In particular, we wanted to disclose potential spatial gradients, as well as assess whether the developmental changes are robust enough to even allow using the ASI-based cx-cx synchrony as a maturational measure.

EXPERIMENTAL PROCEDURES

Data acquisition

The main dataset consisted of 22 recordings in 20 infants, recorded at a postmenstrual age (PMA) of 30–44 weeks at the Neonatal Intensive Care Unit of the University Hospitals of Leuven, Belgium (Koolen, 2014a,b). In this pilot-study, we used broad inclusion criteria and have included 2 infants with intraventricular hemorrhage (IVH) grade III, however no infants had parenchymal lesions such as parenchymal infarction or periventricular leukomalacia. Most importantly, the infants were clinically stable by the time of EEG recording. More clinical details of the infant group are given in Table 1. Two infants had consecutive recordings performed for clinical reasons to assess their brain development. Their two EEG recordings were entered as independent samples, however we also computed the group results with only one recording from each infant, and we saw no meaningful differences in the results. The lower age limit was set to 30 weeks PMA, to assess the developmental window at an age when the majority of thalamocortical connections is already established, whereas an intensive growth of cortical–cortical connections exists (Kostovic and Jovanov-Milosevic, 2006; Jovanov-Milošević et al., 2009; Kostovic and Judas, 2010). One term infant was excluded because of missing tracé discontinue EEG patterns, the foundation of ASI analysis. The recording time was at minimum 4 h, and a clinical expert (A.D.) selected the most discontinuous EEG, resembling quiet sleep in older patients, for 2 × 10 min in each recording. All EEG measurements were recorded at 250 Hz, with 8 electrodes (Fp1, Fp2, C3, C4, T3, T4, O1, O2) placed according to the 10–20 standard locations and reference electrode Cz (BRAIN RT, OSG equipment, Mechelen, Belgium). The protocol was approved by the Ethics Committee of the University Hospitals of Leuven, Belgium. Preprocessing the data involved applying a 50 and 100 Hz Notch filter and a 1–20-Hz band pass filter to capture the interesting burst information present in this frequency range.

Analysis of synchrony

We analyzed the synchrony between cortical areas by using the recently developed measure ASI, which estimates the temporal relationships between newborn cortical events (for further details, see Räsänen et al., 2013). Our primary aim was to study the development of ASI from prematurity to term age. In addition, we also studied spatial differences in ASI development, as well as the temporal fluctuations of ASI within each recording session in order to assess its methodological stability and potential use as a maturational measure of functional connectivity.

Technically, ASI (and mutual information in general) captures all non-linear correlations between the signals and is invariant to any coordinate transforms of the input data, which is not true for normal correlational analysis (see, e.g., Herzel and Große, 1995). We have directly compared ASI to the cross-correlation of the raw signal or the signal energy function, neither of which is suitable for capturing the temporal relations of interest in our context (Räsänen et al., 2013). Other somewhat comparable measures would include the correlation coefficient between amplitude envelopes (see e.g. Hipp et al., 2012; Tokariev et al., 2015b) and the computation of the slope between quantized amplitude envelopes (e.g. Omidvarnia et al., 2014, 2015), neither of which is designed to statistically test the presence of temporal delays, a key feature of interest in assessing cx-cx activation synchrony in the preterm EEG signal. Due to the computational robustness and the ability to emulate clinical EEG review, ASI is also a putative, practical biomarker to describe preterm maturation in the context of a real-world hospital environment.

Computation of ASI

Temporal relationships between pairs of EEG signals were computed using a previously described measure ASI (Räsänen et al., 2013), which was recently shown to perform well in distinguishing normality in EEG traces from term patients (Koolen et al., 2014b). ASI provides a statistical measure for the temporal coupling of two quantized EEG amplitudes with higher ASI values reflecting larger synchrony between the signals, whereas an ASI of zero means that the two signals are statistically independent. The algorithm consists of the following steps (Räsänen et al., 2013):

1. The signal is first down sampled to 50 Hz. Higher frequencies (which are related to the burst events) are pre-emphasized with a first order FIR high-pass filter ($H(z) = 1–0.95\,z^{-1}$).