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Time-variant analysis of phase couplings and amplitude–frequency dependencies of and between frequency components of *EEG* burst patterns in full-term newborns

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ABSTRACT

Objective: Burst activity of the 'trace alternant' (*TA*) *EEG* pattern in the quiet sleep of full-term newborns is investigated to explore the timing and the time-variant coupling characteristics of and between a burst's oscillatory components. The working hypothesis is that signal properties provide information about the neuronal initiation processes of the burst, and about the coupling and interrelation dynamics between cortical low-frequency oscillations and high-frequency spindles in thalamic structures which substantially contribute to the burst pattern.

Methods: For time-variant phase-locking index (*PLI*), phase-synchronization index (*PSI*), quadratic phase coupling (*QPC*) measures, and amplitude–frequency dependency analyses the Gabor and the Hilbert transformation, both implemented as fast Fourier transformation-based approaches, were used. Additionally, models of mutually coupled Duffing oscillators were adapted to the burst data derived from the neonates ('measured bursts'), and the corresponding 'modeled burst' simulations were analyzed in comparison to the measured bursts.

Results: A strong phase-locking of the high-frequency oscillations and synchronization between low- and high-frequency oscillatory activity at burst onset can be observed. The *QPC* courses and the amplitude of all oscillations rise slightly before or at the burst onset and reach their maximum within the following 1–3 s after onset. Additionally, correlative envelope–envelope and envelope–frequency couplings within and between the burst oscillations can be demonstrated. All theses time-variant signal properties can be simulated by the model.

Conclusions: The amplitude-independent phase measures point to a phase stabilization of high-frequency oscillatory activity which occurs before the initiation of the low-frequency oscillation. This finding points to a trigger process in which the thalamus is initially involved. After burst onset the cortical low-frequency oscillation modulates the high-frequency oscillatory activities, where modulation and additional coupling effects can be explained by three mutually coupled oscillators.

Significance: The model-based analysis strategy offers an up-to-date methodological guideline and sets a new standard of analysis for the investigation of *EEG* patterns and event-related potentials.

1. Introduction

As shown in previous studies, the time-variant analysis of burst activity of the 'tracé alternant' (*TA*) *EEG* pattern in healthy full-term neonates presents a unique possibility to study the specific interrelations between neuronal oscillatory networks which are involved in the burst generation in a non-invasive way (e.g., Witte et al., 1997, 2004). The *TA*'s burst activity is composed of major fractions of oscillatory frequency components, fractions of high-frequency components (frequency range 3.0–8.0 Hz), which are highly probably related to a thalamo-cortical network, and fractions of cortical low-frequency components (frequency range 0.5–1.5 Hz).

The specific interrelations between low and high-frequency oscillations can be mathematically modeled as an amplitude modulation (Witte et al., 1997), i.e., a low-frequency oscillation (f_m) modulates the amplitude of a high-frequency oscillation (f_n = carrier frequency) and this results in one spindle or in two successive spindles during the first 2–3 s after burst onset ("initial wave", Witte et al., 1997). A neurophysiological model was given by Steriade (2006), who demonstrated that a depolarization phase of a cortical low-frequency oscillation travels through the corticothalamic pathway and triggers, in the reticular thalamic nucleus, a spindle sequence that is then delivered to the cortex via the dorsal thalamus. This leads to an *EEG* pattern in which the high-frequency

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spindle is superimposed on the low-frequency oscillation with a specific timing. Such a signal constellation, which is composed of a superposition of the modulating signal on the corresponding amplitude-modulated signal, causes a quadratic phase coupling (*QPC*). Bi-spectral analysis, allowing quantification of the *QPC*s between different spectral frequency components of a signal, has already been usefully applied to the study of modulatory interrelations in both normal and pathological *EEG* patterns (e.g., Muthuswamy et al., 1999; Schwab et al., 2004, 2009; Witte et al., 1999). Nevertheless, amplitude modulation describes only a unidirectional coupling, i.e., from the low-frequency to the high-frequency oscillation, and cannot encompass other signal, timing, and coupling characteristics of and between both oscillations.

The major aim of this study is to gain insight into the intrinsic timing and mutual coupling mechanisms of and between the oscillations of the *TA*'s *EEG* burst pattern that will allow inferences on the interrelations of the underlying neuronal generator processes. Additionally, this study provides an up-to-date methodological guideline regarding the time-variant analysis and modeling approaches by which such a detailed *EEG* pattern analysis can be performed.

A narrow-band oscillation can be fully described as an amplitude and frequency modulated cosine $x_n(t) = a_n(t) \cdot \cos[\Phi_n(f_n(t), t)]$, where $a_n(t)$ designates an amplitude modulation and is called an instantaneous envelope (*IE*) and the time-varying argument of the cosine $\Phi_n(f_n(t), t)$ is the instantaneous phase (*IPh*) which can be described as an effect of a modulation of the cosine's frequency $f_n(t)$ (instantaneous frequency *IF*). *IPh* and *IF* are interchangeable, because the *IF* is the first time derivative of the *IPh*. By means of demodulation techniques the oscillation's *IE* and *IF* can be extracted. Additionally, the ability to derive the *IE* and *IF* courses of two oscillatory signal components $x_n(t)$ and $x_m(t)$ (with $\Phi_m(f_m(t), t)$) permits the computation of so-called cross-frequency couplings (Jensen and Colgin, 2007), e.g., envelope-to-envelope and envelope-to-frequency couplings (Eckhorn et al., 2004).

Additionally, the specific pattern characteristics of the *TA* must be considered, which is characterized by alternating periods of burst (augmented) and interburst (depressed) activity. The burst activity arises abruptly and merges continuously into the interburst about 3–4 s after burst onset. As mentioned above, experimental findings have shown that corticothalamic systems interact and induce the generation of the burst pattern (Steriade, 2001). Accordingly, the occurrence and timing of the onset-related (triggered) phase-locking phenomena of burst oscillations may indicate generation characteristics of the neuronal oscillators. This phase characteristic can be quantified by the phase-locking index (*PLI*). Additionally, if two oscillations with different frequencies are synchronized, then an interaction between both generator processes (cortical and thalamic) can be assumed. Phase-locking characteristics of two oscillatory frequency components can result in *n:m* synchronization phenomena (phase-to-phase coupling), i.e., the variability of the generalized phase difference $\Delta\Phi = n \cdot \Phi_m - m \cdot \Phi_n$ between both oscillations is low (Lachaux et al., 1999). Synchronization can be quantified by the phase-synchronization index (*PSI*). If the timing of the phase-locking, and with that the synchronization of the low and high-frequency oscillations, are combined with an amplitude modulation of the high-frequency oscillation caused by the same low-frequency oscillation, then *QPC* characteristics result. However, *QPC* measures signify only a basic relationship between frequencies and phases and cannot provide inferences about a modulation process. Yet *QPC* based on amplitude modulations can be detected and quantified by means of an appropriate *IE* analysis (Arnold et al., 2002). The quantification of the time-variant interplay of such a specific configuration of signal characteristics in the *TA*'s burst may reveal time-variant properties of its generating process. However, the connection between phase-locking, synchronization and *QPC* is valid only when the frequency phase variability (modulation) of both oscillations is low. The *IF* course provides information on the variability, meaning stability or instability, of the oscillation frequency.

Considering all these interacting time-variant signal characteristics and all mutual dependencies between these properties, the connecting of analysis results to a convincing and plausible neuronal generation hypothesis is only possible by using an appropriate modeling strategy (Witte et al., 2008), i.e., for interpretation of analysis results the modeling is essential.

2. Materials and methods

2.1. Subjects

In this study data from our earlier studies are used (Helbig et al., 2006; Witte et al., 2004), thus a detailed description of subjects and data selection procedures is not provided here. An 8-channel *EEG* of six normotrophic full-term neonates during quiet and active sleep was recorded (10–20-system, linked-ear reference, Fp_1, Fp_2, C_3, C_4, T_3, T_4, O_1, O_2) and digitized after 30 Hz low-pass filtering with 128 Hz sampling rate. In contrast to the studies mentioned above, the original *EEG* recordings with linked-ear reference are used in this investigation. Heart rate, respiratory movements and EOG were recorded simultaneously for sleep state detection. The burst-interburst *EEG* patterns (tracé alternant), which are closely related to quiet sleep, were segmented by two trained physicians independently. As described by Eiselt et al. (2001) the time limits of burst and interburst periods were visually detected by two trained physicians independently and marked by using an interactive data display program. Detected limits varied between both observers; these however were less than 0.2 s and an overall agreement of about 95% was determined. The burst pattern was defined with bilaterally synchronous 2–5 s bursts of slow waves (≈1–3 Hz, 50–100 μV). Therefore, bursts were only chosen if their duration was >2 and <4.5 s and their asynchronous occurrence over both hemispheres was less than 0.5 s.

Four seconds before (interburst) and 6 s after the burst onset were considered (Fig. 1). For each neonate $K = 17$ intervals were analyzed (minimal number of patterns in one neonate), where the first 17 subsequent bursts of the trace alternant were used for interval selection. Primarily the *EEG* at the Fp_1 electrode was analyzed because here the *QPC* couplings showed strong magnitudes (Helbig et al., 2006; Witte et al., 2004). For the computation of the *PLI* and *PSI* a down-sampling (Matlab) was used to reduce the dimension of the data. After down-sampling the new Nyquist frequency was 16 Hz (1:4 down-sampling).

2.2. Analysis methods

2.2.1. Processing scheme

For this study we used a processing scheme which combines advanced time-variant (tv) analysis approaches which are suitable for studying dynamic brain oscillations (e.g., Le Van Quyen and Bragin, 2007; Witte et al., 2008), where each method provides additional or complementary information about couplings and interactions between the oscillatory signal components. Analysis of the phase-locked oscillations of the burst activity is the first step to identify the individual frequency bands in which the phase-locking occurs. tv phase-locking analysis encompasses amplitude-dependent and amplitude-independent phase-locking measures (Section 2.2.3) and quantifies the phase stability of one frequency component with reference to a certain point in time. Subsequently, for quantifying the stability of the phase difference between two frequency components the tv phase-synchronization index (*PSI*) is applied. The phase-locking of two oscillations can result in *n*:*m*