Quadratic Phase Couplings in the EEG of Premature and Full-term Newborn during Quiet Sleep

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1. Introduction
The maturation of the neonatal brain manifests itself in a number of changes in the EEG characteristics which was shown by longitudinal studies starting in the premature period [1] and by studies comparing EEG characteristics of premature and full-term newborns at different conceptual ages and from neonatal through infancy period [2]. Analytical criteria depicting the different maturational stages and a comprehensive description of normal and pathological EEG patterns in the different maturational and behavioral stages are given in a glossary by Andre et al. [3]. TD in premature newborns and TA in full-term newborns is a specific characteristic of brain electogenesis in early human development. Both are characterized by the occurrence of alternating periods of high-voltage electroencephalogram (EEG) activity (burst) and decreased activity (interburst). The age-related change from a strongly discontinuous to more continuous EEG patterns is an indicator for brain maturation [4]. We have shown that a 10-s-rhythmicy of quadratic phase coupling (QPC) between low-frequency (0.5–1.5 Hz) and high-frequency oscillation (3–8 Hz) during TA in full-term newborns exists [5]. A high QPC indicates a strong amplitude modulation of the transient high-frequency oscillation (thalamocortical oscillation) through the low-frequency oscillation (cortical oscillation) which is superimposed by the high-frequency oscillation. Our hypothesis is that the rhythmic QPC modulation is caused by an interaction between cortical, thalamocortical and neurovegetative brain structures. Investigations of the QPC of the EEG and the heart rate variability of premature newborns during TD showed that at least a “cross talk” between brain structures of the autonomic nervous system and those which generate the burst pattern exists [6]. Subject of the present study was the comparison of the rhythmic modulation of the QPC during TD and TA. The QPC courses for both groups of newborns were computed and differences in their rhythmicity were statistically evaluated.

2. Methods
2.1 Subjects and Recordings
Two groups of newborns were analysed (Table 1): five premature newborns (mean conceptual age 29.8 weeks, range 27–31 weeks, mean birth weight 1416 g,
range 1170–1750 g, mean 5 min APGAR-score 8.6) and five full-term newborns (mean conceptual age 39.8 weeks, range 38 – 41 weeks, mean birth weight 3112 g, range 2670–3420 g, mean 5 min APGAR-score 9). All newborns were clinically and neurologically normal, none showed any EEG abnormality. Electrode locations correspond to the 10–20 systems (Fp1, Fp2, C3, C4, T3, T4, O1, O2). EEG, ECG, impedance respirogram and EOG were recorded. The bipolar EEG recordings Fp1–T3, Fp2–T4, C1–O1 and C2–O2 were chosen for analysis because the recordings of the premature newborns were performed in a clinical setting and the bipolar montage was directly applied. A 50 Hz low pass filter, 0.3 s time constant and sensitivity of 50 V per 6 mm was used for the EEG recordings. Due to different sampling equipment the sampling rate was 281 Hz for the premature newborns and 128 Hz for the full-term newborns. Only the EEG recorded during the first quiet sleep was selected. Data were filtered and sampled down to 70.25 Hz or 64 Hz, respectively.

### 2.2 Time-variant Parametric Bispectral Approach and Statistical Analysis

The time-variant parametric bispectral analysis is based on an estimation of time-variant autoregressive (AR) parameters taking into account moments of higher order. The transfer function of the estimated AR-filter can be applied to calculate the parametric bispectrum. We used the time-variant biamplitude as an instantaneous QPC measure for the continue EEG recordings of both groups of newborns (time-resolution: 0.114 s or 0.125 s, frequency resolution: 0.137 Hz or 0.125 Hz). The time-variant mean biamplitude (mBA) was computed for the region of interest (ROI) [0.5 – 1.5 Hz] × [3.0 – 6.0 Hz] [5, 6]. A radial basis function network (RBFN) was adapted to smooth the mBA time courses of EEG (RBFN_mBA) for a better automated identification of peaks of the mBA. After identification of peaks in the RBFN_mBA time differences of peaks (TDP) were computed between subsequent maxima of the RBFN_mBA course for all newborns and all EEG registrations. Median and quartiles of TDP were extracted to quantify the rhythmicity of QPC. The computational procedures of the time-variant parametric mBA estimation, the adaptation of the RBFB_mBA as well as the calculation of TDP are described in detail by Schwab et al. [7].

For statistical evaluation a linear mixed effects model was performed to assess group differences with the TDP as dependent variable [8]. Besides group membership electrode positions were included as a covariate. Linear mixed-effects models offer the advantage of allowing the investigation of variability between patients (heterogeneity) and simultaneously adjusting for the within-subject correlation due to several measurements per subject. Therefore, this approach explicitly provides the possibility to investigate the different total times of recordings and resulting different numbers of TDP which were available for both groups of newborns (Table 1). Model regression coefficients are reported together with a 95% confidence interval (CI). Confidence intervals were obtained using the percentiles of the bootstrap distribution.

### 3. Results

Exemplary for the frontal-temporal positions, the EEG recordings Fp1–T3 and calculated time-variant QPC courses (mBA and RBFN_mBA) are shown in Figure 1A. In the premature newborns the discontinuity of the EEG is pronounced (Figure 1, upper panel). In the recordings of the full-term newborns (Figure 1, lower panel) the absolute amplitude of the interburst pattern (background activity) is higher than in the premature newborns. In the central-occipital EEG recordings (C3–O1, C4–O2, not shown) the burst amplitude is reduced in comparison to the frontal-temporal recordings. The time courses of the mBA/RBFN_mBA are clearly dominated by the sequential alteration of burst and interburst patterns for both groups of newborns. The mBA/RBFN_mBA course rises during the occurrence of the EEG burst pattern quantifying the occurrence of QPC in the respective ROI (Figure 1B). The intensity and rhythmicity of such QPC is most stable for the full-term newborns (Figure 1C, lower panel) and for the frontal-temporal registration. The QPC courses of the premature newborns were less intense but showed a similar rhythmicity. In contrast to the full-term newborns the rhythmicity of the premature newborns was interrupted by some periods with out any rises in the mBA/RBFN_mBA (Figure 1B/Figure 1C, upper panel).

Figure 2 summarises the results of the TDP analysis for both groups of newborns. Boxplots are given exemplary for one frontal-temporal (Fp1–T3) and central-occipital (C3–O1) recording and for all newborns. The median of the TDP is be-

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**Table 1** Description of newborns and analysed recordings. Conceptual age (CA) in weeks, developmental status, total time of EEG recordings in s and identified time differences of peaks (TDP) per bipolar registration are given for each newborn.

<table>
<thead>
<tr>
<th>Initial of newborn</th>
<th>CA (weeks)</th>
<th>Status</th>
<th>Length of recordings</th>
<th>Number of TDP</th>
<th>Fp1–T3</th>
<th>Fp2–T4</th>
<th>C1–O1</th>
<th>C2–O2</th>
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<tbody>
<tr>
<td>#1</td>
<td>31</td>
<td>premature</td>
<td>560 s</td>
<td>36</td>
<td>34</td>
<td>35</td>
<td>33</td>
<td></td>
</tr>
<tr>
<td>#2</td>
<td>27</td>
<td>premature</td>
<td>760 s</td>
<td>42</td>
<td>44</td>
<td>44</td>
<td>43</td>
<td></td>
</tr>
<tr>
<td>#3</td>
<td>31</td>
<td>premature</td>
<td>750 s</td>
<td>52</td>
<td>50</td>
<td>40</td>
<td>50</td>
<td></td>
</tr>
<tr>
<td>#4</td>
<td>29</td>
<td>premature</td>
<td>750 s</td>
<td>43</td>
<td>40</td>
<td>40</td>
<td>45</td>
<td></td>
</tr>
<tr>
<td>#5</td>
<td>31</td>
<td>premature</td>
<td>540 s</td>
<td>43</td>
<td>30</td>
<td>43</td>
<td>38</td>
<td></td>
</tr>
<tr>
<td>#6</td>
<td>40</td>
<td>full-term</td>
<td>832 s</td>
<td>71</td>
<td>67</td>
<td>70</td>
<td>69</td>
<td></td>
</tr>
<tr>
<td>#7</td>
<td>38</td>
<td>full-term</td>
<td>459 s</td>
<td>38</td>
<td>33</td>
<td>33</td>
<td>30</td>
<td></td>
</tr>
<tr>
<td>#8</td>
<td>41</td>
<td>full-term</td>
<td>814 s</td>
<td>57</td>
<td>55</td>
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<td></td>
</tr>
<tr>
<td>#9</td>
<td>40</td>
<td>full-term</td>
<td>564 s</td>
<td>41</td>
<td>42</td>
<td>40</td>
<td>40</td>
<td></td>
</tr>
<tr>
<td>#10</td>
<td>40</td>
<td>full-term</td>
<td>326 s</td>
<td>26</td>
<td>25</td>
<td>22</td>
<td>24</td>
<td></td>
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</table>
between 8 s and 11 s (0.09–0.125 Hz) for the full-term newborns and between 11 s and 17 s (0.06–0.09 Hz) for the premature newborns at different EEG registrations. The higher median of the TDP for the premature newborns is accompanied by a higher inter quartile range in comparison to the full-term newborns for all EEG recordings. The results of the premature newborns show a much higher inter-individual variation than the full-term newborns. The results of the linear mixed model reveal that TDP in full-term newborns is on average 4.94 s lower than in premature newborns with 95% CI (−6.00, −3.78). A model including electrode position did not lead to better fit (LRS = 2.132805, df = 3, p = 0.55).

4. Discussion and Conclusions

The results of our study were derived from premature and full-term newborns whose EEG was previously investigated by means of other time-variant analysis approaches like time-variant power, coherence, synchronization and phase-locking and directed interaction measures. The main result of this study is that the properties of the QPC rhythmicity change between 30th week of conceptual age (premature, mean value) and 39th week of conceptual age (full-term, mean-value). For the full-term newborns, a stable rhythmicity of QPC in the TA EEG pattern was found to be around 0.1 Hz (10 s), for the premature newborns, the rhythmicity was less stable and significantly lower than 0.1 Hz (>10 s). The lower stability in premature newborns results rather from “interruptions” of the stable rhythmicity of 0.1 Hz than from longer TDPs and these “interruptions” were more pronounced the earlier premature newborns suggesting a continuous development of the thalamo-cortico cortical interactions between 30th and 39th week conceptual age.

How can these rhythms and their characteristics be explained? We hypothesized that this QPC rhythm might correlate to the timing of the Mayer-Traube-Hering wave of the blood pressure. We have demonstrated that in our group of premature newborns the QPC of the heart rate variability (ROI [0.02–0.15 Hz] × [0.4–1.5 Hz]) rises 1 s before EEG burst onset and concluded that a “cross talk” between brain structures of the autonomic nervous system and those which generate the burst pattern exists [6]. The frequency difference of the resulting QPC rhythm can be explained by this “cross-talk” hypothesis. We have found that the so-called 10s wave (0.1 Hz) is a dominant low-frequency component of the heart rate during TA in our group of full-term newborns [9]. Andriessen et al. [10] showed a clear low-frequency spectral peak in the cardiovascular fluctuations in premature newborns at 0.08 Hz (12.5 s). Furthermore, a maturational increase of the amplitude and the spectral power [11] of the mid-frequency (0.05–0.2 Hz) in the heart rate variability of premature and full-term newborns was found. An investigation of the occurrence of QPC in the heart rate of our full-term newborns revealed a QPC rhythmicity of 0.09–0.12 Hz [9]. Furthermore, a correlation between EEG burst-to-burst intervals and HR acceleration in premature infants has been shown by Pfurtscheller et al. [12].

The results of our study were derived from premature and full-term newborns whose EEG was previously investigated by means of other time-variant analysis approaches like time-variant power, coherence, synchronization and phase-locking and directed interaction measures (e.g. [4, 13]). The results of this study must be validated by other clinical studies which are based on larger groups. However, by means of this study the impetus should be given to
use our methodology and findings as a basic concept for further studies.

Acknowledgements
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References

![Figure 2](image-url)

Figure 2
Boxplots of the TDP between subsequent maxima of the course of RBFN_{mBA} for two EEG registrations and all newborns. For number of TDP per analysed newborn see Table 1.