Advantages of Signal-Adaptive Approaches for the Nonlinear, Time-Variant Analysis of Heart Rate Variability of Children with Temporal Lobe Epilepsy

Karin Schiecke, *IEEE Member*, Matthias Wacker, Franz Benninger, Martha Feucht, Lutz Leistritz, and Herbert Witte, *IEEE Member*

***Abstract*— Major aim of our study is to demonstrate that signal-adaptive approaches improve the nonlinear and time-variant analysis of heart rate variability (HRV) of children with temporal lobe epilepsy (TLE). Nonlinear HRV analyses are frequently applied in epileptic patients. As HRV is characterized by components with oscillatory properties frequency-selective methods are in the focus, whereby application of nonlinear analysis to linear filtered signals seems to be doubtful. Signal-adaptive methods that preserve nonlinear properties and utilize only the signal data for an automatic computation of the result could benefit to nonlinear analysis of HRV. Combinations of (1) the signal-adaptive Matched Gabor Transform with time-variant nonlinear bispectral analysis and of (2) signal-adaptive Empirical Mode Decomposition methods with time-variant nonlinear stability analysis are investigated with regard to their application in the analysis of specific HRV components (respiratory sinus arrhythmia and Mayer wave associated low-frequency HRV components) of 18 children with TLE. Changes of timing and coordination of both HRV components during preictal, ictal and postictal periods occur which can be better quantified by advanced signal-adaptive methods. Both approaches contribute with specific importance to the analysis.**

I. Introduction

Heart rate variability (HRV) is frequently used for the analysis of cardiovascular regulatory mechanisms controlled by the autonomic nervous system in human health and disease. Advancements in the analysis of HRV in epilepsy are important to reveal the causes for the sudden unexpected death in epileptic patients (SUDEP) [1]. A first meta-analysis investigating HRV in epilepsy was recently published [2]. HRV courses in the preictal, ictal and postictal period have been investigated by using time- and/or frequency-domain features. Innovative features of time-frequency domain have received much less attention in HRV analysis [3]. In general, HRV is characterized by components with oscillatory (rhythmic) properties. A classification of HRV components into frequency ranges was performed by a Task Force in 1996 [4]. Such a classification gives an excellent orientation for frequency-selective analyses. Two prominent examples of HRV components are the respiratory sinus arrhythmia (RSA) and the low-frequency (LF) HRV component, which is associated to the Mayer waves in systemic blood pressure. In a previous study using concerted time-variant, frequency-selective, linear and nonlinear analyses [5], we could show, that timing and coordination of these components changed 80 to 100 s before seizure onset in children with temporal lobe epilepsy (TLE). In that study, the complex time-frequency Morlet Wavelet Transform (MWT) was adapted as the base of a nonlinear and time-variant bispectral approach that investigates the occurrence of quadratic phase coupling (QPC) between distinct frequency components.

MWT has a time-frequency resolution that is determined by algorithms parameter and therefore needs pre-analysis information to adapt sufficient time-frequency resolution that is required for bispectral analysis [6]. Wacker et al. [7] introduced a time-frequency approach combining the Matching Pursuit algorithm with Gabor Transform (Matched Gabor Transform - MGT). Using this approach, a complete analysis of the complex time-frequency plane can be performed in a signal-adaptive and frequency-selective manner, i.e. signal-adaptive phase analysis is possible. Signal-adaptive methods attempt to avoid any user-specific settings of the algorithm and utilize only the signal data for an automatic computation of the result. Consequently, the combination of the signal-adaptive MGT with time-variant nonlinear QPC analysis by means of bispectral analysis is the *first objective* of this study.

Nonlinear HRV analyses are frequently applied also in epileptic patients. The time-variant estimation of Point Prediction Errors (PPE) is a local estimation of the largest Lyapunov exponent and measures the nonlinear stability/predictability of a signal in its time course. Nonlinear HRV analyses have shown a better reliability across repeated measurements in comparison to linear parameters [8]. These methods are usually not frequency-selective, and the application of nonlinear analysis to linear filtered signals seems to be rather doubtful. An alternative approach is to use a signal-adaptive approach which separates oscillatory signal components in 'natural' frequency ranges. The Empirical Mode Decomposition (EMD) enables a decomposition of a multi-component signal into a set of mono-component signals (so-called Intrinsic Mode Functions IMFs) that are periodic and preserves non-linear properties of the investigated signal [9]. A problem of EMD procedure is the occurrence of 'Mode Mixing' (MM). MM corresponds to the alternative presence of several components of the signal of interest on the same

Research supported by the DFG under Wi 1166/12-1 and Le 2025/6-1.

K. Schiecke is with the Institute of Medical Statistics, Computer Sciences and Documentation, Jena University Hospital, Friedrich Schiller University Jena, Germany (corresponding author to provide phone: +49-3641-934131; fax: +49-3641-933200; e-mail: Karin.Schiecke@med.uni-jena.de).

M. Wacker, L. Leistritz and H. Witte are with the Institute of Medical Statistics, Computer Sciences and Documentation, Jena University Hospital, Friedrich Schiller University Jena, Germany (e-mail: Matthias.Wacker@gmail.com, Lutz.Leistritz@med.uni-jena.de and Herbert.Witte@med.uni-jena.de).

F. Benninger is with the Department of Child and Adolescent Neuropsychiatry, and M. Feucht is with the Department of Child and Adolescent Medicine, University Hospital Vienna, Austria (e-mail: franz.benninger@meduniwien.ac.at and martha.feucht@meduniwien.ac.at).

978-1-4244-7929-0/14/$26.00 ©2014 IEEE

IMF. Advanced approaches like Complete Ensemble Empirical Mode Decomposition with adaptive noise (CEMD) [10] reduce the degree of MM. Consequently, the *second objective* of this study is to show the advantages and disadvantages of different EMD approaches for the separation of distinct oscillatory components from HRV, its influence on the estimation of PPE for these HRV components and to compare these results to standard PPE analysis.

General focus of our work is not to predict or detect a seizure but to provide more information on the mechanisms leading to changes of the autonomic nervous system before, during and after seizure.

I. Data Material

Pre-surgical evaluation was performed at the Vienna pediatric epilepsy center following a standard protocol. EEG was recorded referentially from gold disc electrodes placed according to the extended 10-20 system with additional temporal electrodes. One-channel ECG was recorded from an electrode placed under the left clavicle. EEG and ECG data were recorded referentially against CP_Z and filtered (1 to 70 Hz, sampling frequency 256 Hz). Seizure onset and termination in the EEG were determined independently by two neurologists experienced in the field of epilepsy. EEG and ECG recordings including 10 minute epochs (5 minutes before (preictal state) and 5 min after the seizure onset (seizure and postictal state)) were stored for each seizure. QRS detection was performed after band pass filtering (10 – 50 Hz) and interpolation by cubic splines (1024 Hz). The resulting series of events was used for the HR computation. The low-pass filtered event series was computed by applying the French-Holden algorithm and down sampled to 8 Hz. A group of 18 children who had one seizure recording of at least 10 min (K = 18 seizures; median age 9 years 4 months, range 6 years 6 months to 18 years 0 months; median seizure length 88 s, range 52 to 177 s) were analyzed. All results were achieved by grand mean analysis over 18 seizures.

II. Methods

The entire processing scheme of our investigation is represented in Fig. 1. In a first strand, investigation of nonlinear QPC is performed by comparing MWT-based and signal-adaptive MGT-based approach (methods/results section A). A second strand contrasts the results of the PPE estimation of the original HRV with the signal-adaptive EMD-based investigation of the PPE of distinct IMFs (methods/results section B).

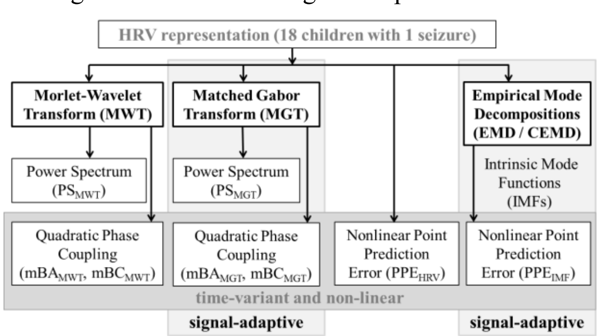

Figure 1. Processing scheme of the performed HRV analysis.

A. Morlet Wavelet Transform, Matched Gabor Transform and Bispectral Analysis

The frequency-dependent complex analytic signal $y^k(t,f_n)$ of $x^k(t)$ (HRV) is computed using MWT [6], where k (k=1,..,K) designates the seizure recordings (one for each child, K=18). The time-variant power spectrum and phase can be calculated on the basis of $y^k(t,f_n)$ for each recording k. By ensemble averaging the representative time-variant power spectrum PS_{MWT} can be estimated.

The MGT generates in a first step (Matching Pursuit) for each k a linear combination of atoms $d_j^k(t)$ from a redundant dictionary D that approximates $x^k(t)$. Secondly, each atom is analyzed with its own analysis time-window to generate a set of time-frequency planes $y_j^k(t,f_n)$. *F*inally theses planes are combined to obtain $y^k(t,f_n)$. The time-variant power spectrum and phase can be calculated on the basis of this complex frequency plane for each recording k, and again, the representative time-variant power spectrum PS_{MGT} by ensemble averaging.

Additionally, the time-variant QPC between the frequency bands given below is computed using time-variant biamplitude and bicoherence. QPC is a phase effect, that occurs e.g. in the presence of amplitude modulations. In the case of amplitude modulation, f_1 is the frequency of the modulating component (LF), f_2 is the frequency (carrier frequency) of the modulated component (RSA). For each seizure ($k=1,\dots,K$), the trias of $y^k(t,f_1)$, $y^k(t,f_2)$ and the complex conjugate $y^{*k}(t,f_1+f_2)$ can be calculated for every frequency pair (f_1, f_2) and at each time-point t. The trias is base of the estimation of the time-variant biamplitude or bicoherence (amplitude-independent). To reduce the three dimensions of this time-variant bispectral measures the mean biamplitude (mBA_{MWT}, mBA_{MGT}) and the mean bicoherence (mBC_{MWT}, mBC_{MGT}) in the ROI were computed by calculating a mean value over F_1 x F_2 for each time point (for details see [11]). We investigated QPC between the LF-related and the RSA-related HRV component for MWT and MGT, i.e. ROI was set to F_1=[0.075 Hz, 0.15 Hz] and F_2=[0.25 Hz, 0.35 Hz].

B. Empirical Mode Decompositions and PPE

The standard EMD separates the HRV into IMFs. The computation of an IMF by the iterative EMD algorithm [9] can be summarized as follows:

1. Identify of all local extrema.
2. Interpolate (cubic splines) between the maxima and between the minima which provides two envelope courses.
3. Calculate the mean envelope and the difference between the mean envelope and the signal.
4. Iterate on the residuals until the criteria for the IMF is fulfilled.
5. Use the residuum instead of the signal to compute the next IMF.
6. Repeat steps 1. – 5. for each following IMF until the stopping criteria.

The CEMD provides a better spectral separation of the IMFs (modes) than the EMD. This is achieved by averaging the modes obtained by EMD applied to several realizations of Gaussian white noise (particular noise at each stage of decomposition [10]) added to the original signals. Therefore, we performed EMD and CEMD to separate the HRV into IMFs and to compare the influence of MM. Inter-individual correspondence of IMFs between different patients in one method (N=18) was achieved by using an extension of the Kuhn-Munkres algorithm. The correspondence of IMFs of both methods to specific HRV components was determined by using mean FFT spectra over all children per.

The IMFs of the HRV preserve nonlinear properties thereby allowing the introduction of the combination of EMD/CEMD of the HRV with the estimation of the PPE. Detailed information on the estimation of the PPE can be found in [12]. A positive PPE is equivalent to a low stability (predictability), a negative or vanishing PPE indicates a high stability (predictability) of a signal. In order to estimate confidence tubes of the mean time-courses of PPEs time-courses without any particular distribution assumption, a Bootstrap approach was used. 1000 Bootstrap replications of each extracted parameters were computed. The 2.5% quantile defined the lower bound, and the 97.5% quantile defined the upper bound of the confidence tube.

III. Results

A. *Morlet Wavelet Transform, Matched Gabor Transform and Bispectral Analysis*

In Fig. 2A the centered HRV courses of all 18 seizures and the averaged HRV course (bold black line) are shown. Important time points (black line: burst onset, dotted black line: end of burst, red line: start of preonset acceleration, blue line: maximum of acceleration and start of deceleration, green line: end of deceleration of HRV) are depicted in a colored 'bar code' that is transferred to other figures.

Fig. 2B depicts time-frequency related PS_{MWT} (left) and PS_{MGT} (right). The according mBA and mBC courses in the ROI are shown in Fig. 2C/D. For bispectral analysis a frequency resolution was chosen that is high enough to depict relevant frequencies and side bands (white lines in both time-variant PS in Fig. 2B). As MWT has a frequency-related time-frequency resolution, the time-resolution of the LF-related component has to be set rather low to achieve the required frequency resolution of the RSA-related component. The signal-adaptive MGT automatically provides an adequate time-frequency resolution. The mBA/mBC_{MWT} and mBA/mBC_{MGT} courses (Fig. 2C/D) show similar time pattern (rise at 100 s before seizure onset, nearly complete vanish with seizure and rise after end of seizure, high accordance with colored 'bar code') but higher time-resolution for MGT. Differences between MWT- and MGT-related approach are more distinct by considering not only the resulting mBA/mBC courses but the underlying biamplitude (BA) at the single time-points. In Fig. 3 the BA at the time points 240 s and 300 s and the ROI for the calculation of mBA/mBC (white rectangle) are depicted for both approaches. Results of MWT-related BA illustrate the side-effects of the frequency-related time-frequency resolution of MWT: a rather high frequency-resolution in the ROI at the cost of low time-resolution causing 'smearing' over time.

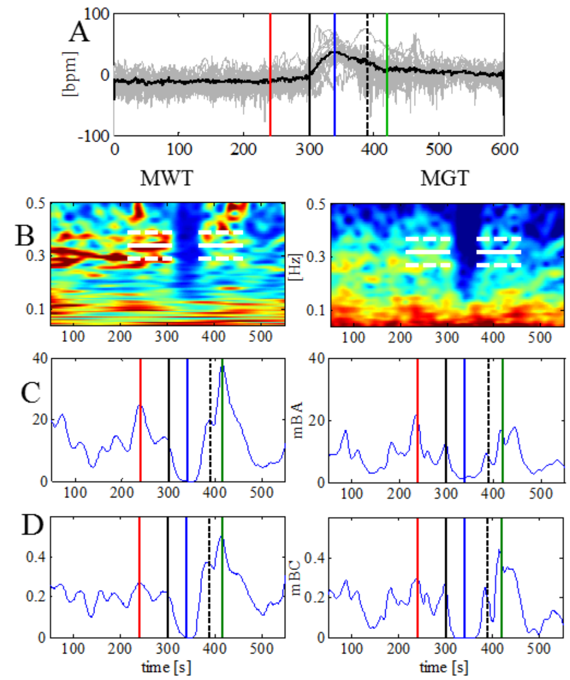

Figure 2. Original HRV courses (A) and MWT- (left) as well as MGT-based (right) results of power spectral and bispectral analysis (B-D). Time-variant PS (B) and mBA (C) as well as mBC (D) are shown.

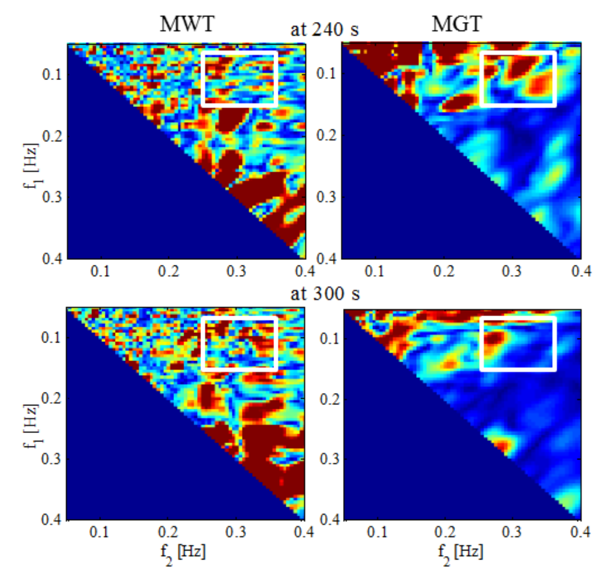

Figure 3. Representation of BA_{MWT} (left) and BA_{MGT}/(right) at distinct time point t_1=240 s (upper) and t_2=300 s (lower panel).

B. *Empirical Mode Decompositions and PPE*

The mean PPE-course of the original HRV (Fig. 4A) starts to decrease (higher stability/predictability of the signal) around 100 s before seizure onset, further decreases during seizure and increases after seizure (no complete recuperation). FFT-based power spectral analysis (Fig. 4B) of the HRV (black) and defined IMFs (other colors; IMF_1 to IMF_4 for EMD, IMF_1 and IMF_5 to IMF_8 for CEMD) was able to determine the correspondence of IMFs to different HRV components. IMF_1 (=blue) is mainly related to noise in both approaches, IMF_2 (=red) for EMD and IMF_5 (=red) for CEMD to the RSA (≈0.3 Hz), IMF_3 (=green) for EMD and IMF_7 (=yellow) for CEMD to the LF (≈0.1 Hz). The occurrence of MM is visible for EMD (broader and overlapping peaks of IMF_2 to IMF_4 in Fig. 4B left), whereas CEMD is able to clearly separate those components (Fig. 4B right). PPE-courses of IMFs (Fig. 4C/D) are able to better depict time-pattern as PPE of original HRV and show that CEMD results in a lower degree of MM and with it in more distinct differences between preictal, ictal and postictal periods.

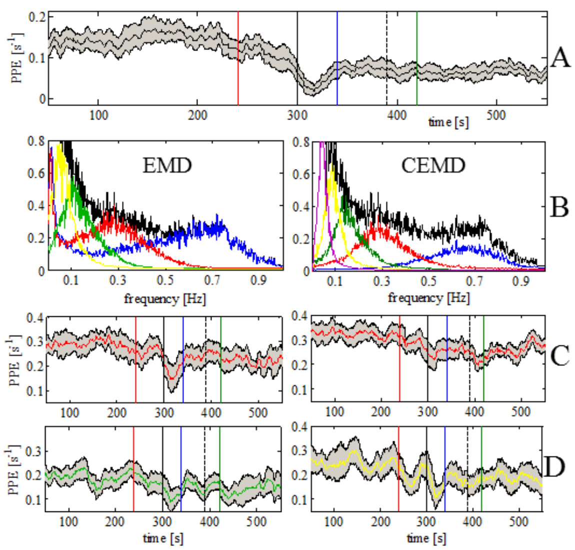

Figure 4. Results of time-variant PPE analysis of original HRV (A) as well as of EMD- (left) and CEMD-based (right) approach (B-D). FFT-based mean spectra of IMFs over all children and the whole analysis interval are shown (B). Mean PPE courses with confidence tubes are depicted for RSA-related (C) and LF- related (D) IMFs.

IV. Discussion And Conclusion

Our methodological study demonstrates the possibilities and advantages of the combination of signal-adaptive approaches with different nonlinear measures in the analysis of HRV in children with TLE. By means of our advanced time-processing scheme characteristics of the HRV before, during and after TLE seizure in children were investigated and quantified. The epileptic seizure is a time-dependent process and HRV analysis of the preictal state may provide information with regard to coupling mechanisms between the involved cortical structures and the autonomic nervous system. A result which has been confirmed by many studies is that an increase of the HR precedes the EEG seizure onset by up to about 50 s in 75 - 80 % of TLE patients [13].

The clear benefit of our signal-adaptive approaches is that user-optimized settings of the algorithms are not required. Furthermore, PPE and bispectral analyses are able to describe nonlinear, in terms of information processing different properties of a signal [12]. PPE analysis quantifies the theoretical predictability/causality of a signal, whereas bispectral analysis examines nonlinear couplings between distinct frequency components. Based on signal-adaptive MGT bispectral analysis describes the QPC between RSA- and LF-HRV components with higher time-resolution than obtained by means of a user-optimized MWT. A combination of EMD/CEMD and PPE yields a frequency-selective, time-variant view of the nonlinear properties of the HRV. The use of CEMD results in a lower degree of MM. Combination of all investigated methods yields complementary descriptions and thus an improved analysis of timing and coordination of HRV components during preictal, ictal and postictal periods

References

[1] B. Moseley, L. Bateman, J. J. Millichap, E. Wirrell, and C. P. Panayiotopoulos, "Autonomic epileptic seizures, autonomic effects of seizures, and SUDEP," *Epilepsy & Behavior,* vol. 26, pp. 375-85, Mar 2013.

[2] P. A. Lotufo, L. Valiengo, I. M. Bensenor, and A. R. Brunoni, "A systematic review and meta-analysis of heart rate variability in epilepsy and antiepileptic drugs," *Epilepsia,* vol. 53, pp. 272-82, 2012.

[3] U. Rajendra Acharya, K. Paul Joseph, N. Kannathal, C. M. Lim, and J. S. Suri, "Heart rate variability: a review," *Medical & Biological Engineering & Computing,* vol. 44, pp. 1031-51, Dec 2006.

[4] Task-Force, "Heart rate variability. Standards of measurement, physiological interpretation, and clinical use. ," *European Heart Journal,* vol. 17, pp. 354-81, Mar 1996.

[5] K. Schiecke, M. Wacker, D. Piper, F. Benninger, M. Feucht, and H. Witte, "Time-variant, frequency-selective, linear and non-linear analysis of the heart rate variability in children with temporal lobe epilepsy," *IEEE Transactions on Biomedical Engineering* vol. DOI 10.1109/TBME.2014.2307481, 2014.

[6] M. Wacker and H. Witte, "Time-frequency techniques in biomedical signal analysis. a tutorial review of similarities and differences," *Methods of Information in Medicine,* vol. 52, pp. 279-96, 2013.

[7] M. Wacker and H. Witte, "Adaptive phase extraction: incorporating the Gabor transform in the matching pursuit algorithm," *IEEE Transactions on Biomedical Engineering* vol. 58, pp. 2844-51, 2011.

[8] R. Maestri, G. D. Pinna, A. Porta, R. Balocchi, R. Sassi, M. G. Signorini, *et al.*, "Assessing nonlinear properties of heart rate variability from short-term recordings: are these measurements reliable?," *Physiological Measurement,* vol. 28, pp. 1067-77, 2007.

[9] N. E. Huang, Z. Shen, S. R. Long, M. L. C. Wu, H. H. Shih, Q. N. Zheng, *et al.*, "The empirical mode decomposition and the Hilbert spectrum for nonlinear and non-stationary time series analysis," *Proceedings of the Royal Society of London Series A,* vol. 454, pp. 903-995, 1998.

[10] M. E. Torres, M. A. Colominas, G. Schlotthauer, and P. Flandrin, "A complete ensemble empirical mode decomposition with adaptive noise," in *IEEE Int. Conf. on Acoust., Speech and Signal Proc. ICASSP-11*, Prague (CZ), 2011, pp. 4144-4147.

[11] K. Schwab, M. Eiselt, C. Schelenz, and H. Witte, "Time-variant parametric estimation of transient quadratic phase couplings during electroencephalographic burst activity," *Methods of Information in Medicine,* vol. 44, pp. 374-383, 2005.

[12] K. Schwab, T. Groh, M. Schwab, and H. Witte, "Nonlinear analysis and modeling of cortical activation and deactivation patterns in the immature fetal electrocorticogram," *Chaos,* vol. 19, p. 015111, Mar 2009.

[13] F. Leutmezer, C. Schernthaner, S. Lurger, K. Potzelberger, and C. Baumgartner, "Electrocardiographic changes at the onset of epileptic seizures," *Epilepsia,* vol. 44, pp. 348-54, Mar 2003.