Analysis of Brain-Heart Couplings in Epilepsy: Dealing With the Highly Complex Structure of Resulting Interaction Pattern

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***Abstract*— Investigations into brain-heart interactions are gaining increasing importance in various fields of research including epilepsy. Convergent Cross Mapping (CCM) is one method to quantify such interactions and was adapted for the analysis of children with temporal lobe epilepsy (TLE) in the past. Increasing amount of data and data features available produce a high and still rising complexity of results of such interaction analyses. Therefore, aim of this study was the investigation of generalized presentation of those results using our benchmark data set of children with TLE. Tensor decomposition was adapted to take into account spatial, time, frequency, directional and focus side related modes of interactions results achieved by CCM analysis.**

Keywords—brain-heart interaction, epilepsy, convergent cross mapping, empirical mode decomposition, tensor decomposition

I. Introduction

Network physiology implying the quantification of (directed) interactions between and within complex physiological systems and organs has developed into an emerging field of research combining neuroscientific and biomedical research as well as computer sciences [1, 2]. So-called brain-heart interactions quantifying interactions between the cortical activity of the central nervous system, represented e.g. by the electroencephalogram (EEG) and the autonomic nervous system, represented e.g. by specific characteristics of heart rate (HR) depict one sub-area of this emerging field of analyses.

During the last years, brain-heart interactions were analyzed e.g. during sleep [1, 3]. There is a wide range of different approaches to define directed interactions in complex systems (review e.g. in [4]). Furthermore, predictability-based measures like e.g. predictability decomposition taking into account self-, causal- and interaction predictability [5] become more popular. Adaptation of different approaches usually produces complementary information. Convergent Cross Mapping (CCM) – which is adapted in our study - is one of those methods focusing on the nonlinear behavior of interactions and was adapted e.g. for the quantification of brain-heart interactions during epilepsy or other neurological/psychiatric disorders [6, 7]. All of those approaches have to deal with the problem of complex data (in terms of different features of data to be analyzed) and thus, highly complex structure of achieved results.

Therefore, aim of this study is to provide a generalized view on how to deal with highly complex structure of interaction results. Analysis is performed by means of a benchmark data set of children with temporal lobe epilepsy, by which other aspects of analysis of brain-heart interactions like adaptation of advanced CCM taking into account time-frequency features, preserving the nonlinearity of data by means of empirical mode decomposition as well as adaptable statistical measures were already investigated [6, 7]. Additional and new features of data (topography) were included in the new analysis, possibilities and limits of graphical representations were investigated, and the tensor decompositions was introduced to generalize CCM results.

II. Subjects

A benchmark data set also used for former analyses of brain-heart interactions [6, 7] was adapted for our investigation. The set compromised a group of 18 children with TLE (11 female, 7 male, median age 9.4 years, range 6.5 to 18 years, median seizure length 88 s, range 52 to 177 s) obtained during pre-surgical evaluation performed at the Vienna pediatric epilepsy center following a standard protocol. More detailed information with regard to the classification of seizure type, onset and termination can be found in [8]. The standard protocol was approved by the local ethical committee of the Medical University Vienna.

For each child, one-channel ECG was recorded from an electrode placed under the left clavicle. 23 channel EEG were recorded referentially from gold disc electrodes placed according to the extended 10-20 system with additional temporal electrodes. Data were recorded referentially against electrode position CPZ (sampling frequency 256 Hz) and filtered (1 to 70 Hz). Recordings were performed during post-ictal, ictal and pre-ictal period.

III. Methods

A. *Pre-Processing of Data*

One recording per child was selected for analysis. Each recording contained 5 minutes before and 5 min after seizure onset, representing pre-ictal as well as ictal and post-ictal periods. EEG and ECG data were segmented into non-overlapping windows of 30 s length (resulting in 20 windows).

After downsampling of the EEG data from 256 Hz to 64 Hz multivariate empirical mode decomposition (MEMD) was performed for each segment and all 23 EEG channel. MEMD is (besides the preserving of nonlinearity in the data) able to differentiate between defined and individually adapted frequency ranges [9] and results in sets of intrinsic mode functions (IMFs) per channel, per segment and per child. Automated assignment of corresponding IMFs across all children and segments was performed by means of adapted

Kuhn-Munkres algorithms [10]. Only corresponding IMFs across children and segments were inspected according to their frequency content. Four specific IMFs were selected which were of most interest for our analysis: IMF(beta-EEG), IMF(alpha-EEG), IMF(theta-EEG), and IMF(delta-EEG)). After selection of IMFs, their envelopes were computed using the Hilbert transform. Sampling frequency of envelops was 8 Hz. Details of the adapted MEMD approach and calculation of envelops of EEG-IMFs can be found in [11].

QRS detection of segmented ECG data was performed after digital band pass filtering (10 – 50 Hz) of the ECG and an interpolation by cubic splines (interpolated sampling frequency 1024 Hz) to detect the time of the maximum amplitude of each R-wave. The resulting series of events was used for the HR computation. Series of events were low-pass filtered by means of a FFT-filter (cutoff frequency ≤ half of the mean HR, French-Holden algorithm). Multiplication of the low-pass filtered series of events with the sampling rate and with 60 beats per minute (bpm) and a downsampling to 8 Hz resulted in the final HR representation.

B. Analysis by Convergent Cross Mapping (CCM)

General idea of CCM is to include nonlinearity into the causation between time series X and Y by looking at the correspondence between so-called shadow manifolds constructed from lagged coordinates of time series values of X and Y. The basic CCM approach was introduced by Sugihara et al. [12]. Practically, interaction between both time series are quantified by means of CCM correlation defined by the absolute value of the Pearson correlation coefficient between the original time series X (or Y, respectively) and an estimation of X using the convergent cross mapping with Y (or estimation of Y using the convergent cross mapping with X, respectively).

Thus, bivariate, directed CCM values can be achieved for any pair of time series X and Y. If X drives Y stronger than vice versa CCM values from X to Y will converge faster and/or reach a higher plateau than CCM values from Y to X. Interval-based estimation of CCM can be performed by using a sliding window of an appropriate length. Further details of adapted CCM estimation routine and performed simulations as well as practical details of the basic algorithm can be found in [12, 13].

Concerning the monitoring of epileptic patients the focus of CCM analyses have to be directed also to a segmented CCM approach using non-overlapping windows of data for analysis. Adaptation of segmented approach is accompanied by a loss of time information but provides the possibility of analyzing long-term recordings (usually of at least 24 h).

An inherent problem of all of those CCM approaches is the statistical analysis and graphical representation of highly complex results. First attempts to generalize the analysis of brain-heart interaction by means of CCM can be found in [7].

General processing scheme of adapted CCM approach for our present investigation of benchmark data analysis of children with TLE can be found in Figure 1. Bivariate (between HR and each EEG-IMFs), directed (both direction of interaction) and segmented (20 windows) CCM was estimated for each child (N=18), each EEG channel (K=23) and all four frequency ranges (EEG-IMFs). According to this specific and highly complex structure of data calculation of median CCM over children according to their focus side (n=9 for left or right focus group, respectively) resulted in five relevant dimensions of CCM: space, time, frequency, direction and focus side.

C. Representation by Tensor Decomposition

Tensor decomposition techniques are adapted for the re-organization and reduction of the dimension of our high-dimensional CCM results. In general, a tensor is a multi-dimensional matrix or a multi-way array. The order of a tensor indicates the number of geometrical dimensions or the number of independent modes [14]. Tensors of order three and higher are called higher-order tensors. Tensor decomposition techniques do not provide additional information but can clearly improve the interpretation and visualization of large-scale data like results of brain-heart interaction analyses. An overview of existing approaches can be found in [15]. A very common technique for decomposing of higher-order tensors is the so-called PARAFAC (parallel factor decomposition) which was introduced by Harshman [16].

From the practical point of view, PARAFAC decomposes the tensor into a sum of multi-linear factors without imposing orthogonality constraints, giving a unique solution of the PARAFAC model under very mild conditions [17]. The contribution of particular factors at each level of a specfic mode of the analyzed data set is given by the weights of the factors [16]. Application of tensor decomposition for the interpretation of results of interaction analyses can be found e.g. in [18] (results of time-variant partial directed coherence) and [11] (results of time-variant coherence). For our CCM results, we adapted PARAFAC for a tensor decomposition using a number of five factors taking into account five different modes: space, time, frequency, direction of interaction and focus side (see Figure 1). Tensor decomposition is uniquely identifiable up to scaling and permutation. Thus, ordinate of each of our factors is in [a.u.].

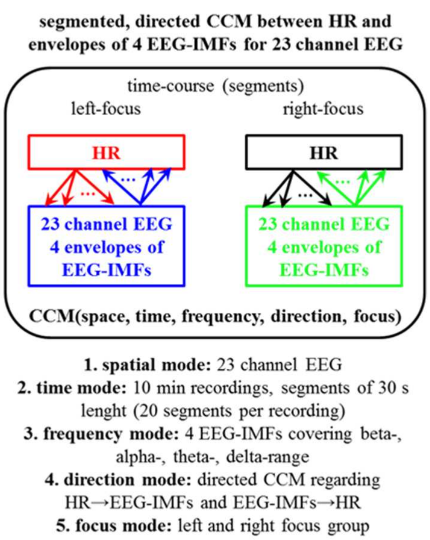

Fig. 1. General processing scheme of adapted CCM approach. Complex structure of analyzed data and resulting dimensions of CCM results are given. Introduced color code will be adapted to following figures.

IV. Results

A. Time-Courses of CCM

Looking at recordings of pre-ictal, ictal and post-ictal periods of epileptic seizures, presentation of time-courses of brain-heart interactions and thus, their development over time in dependence to the specific period of seizure is one main goal of interaction analyses. Taking also into account the relevant frequency information (4 different EEG-IMFs of interest) and spatial distribution of findings (topography of 23 EEG channel) presentation of CCM results is rather complex.

In Figure 2 time courses of median CCM (group results over n=9 children, respectively) are shown for left and right focus group (left and right column in Figure 2) and for all investigated EEG-IMFs (lines in Figure 2). Each subplot contains both direction of interaction (see color code in Figure 2) and all 23 EEG channel available. Time-courses of CCM are able to replicate main characteristics of brain-heart interactions found in already in former study. There, one electrode at ipsi-lateral position (T3 for left and T4 for right focus group) and one electrode at contra-lateral position (T4 and T3, respectively) was analyzed. In general, interactions are higher from EEG to HR than vice versa, highest interactions can be found in the delta-range, and interactions from HR to EEG sharply increases with onset of seizure in all frequency ranges with sharpest increase in the alpha-range. Information regarding spatial distribution of interaction is not really differentiable in this kind of graphical representation. We can only note, that most of the EEG channel show similar behavior with regard to the time-course of CCM, and there are differences in the variance over channels (e.g. less variance for delta, most variance for beta-range).

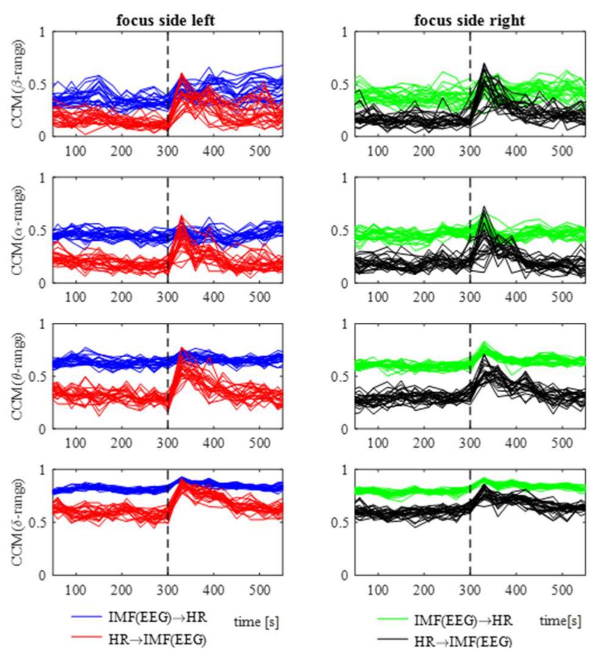

Fig. 2. Time-courses of median CCM (group results). CCM results are given for left and right focus side (n=9 in each group, left and right column of subplots), for all investigated EEG-IMFs (lines of subplots) and for all investigated EEG-channels (within each subplot). Direction of interaction is assigned by color code (see Figure 1), onset of seizure by black, dashed line.

B. *Topographic Views of CCM*

Lack of visibility of spatial information in Figure 2 leads to the need to provide also topographic views of CCM results. Topographic representation of median CCM group results is given separately for the left focus group (n=9) in Figure 3 and for the right focus group (n=9) in Figure 4. Only results of interaction between HR and EEG-IMFs in the alpha-range are shown. Strength of CCM is assigned by color code, time-course is implemented by one topographic view per segment of 30 s, and direction of interaction is given by separate lines of topographic views (first and second line: time evolution of CCM from EEG-IMF to HR, third and fourth line: time evolution of CCM from HR to EEG-IMF).

Topographic representations of results are able to reveal additional information, especially with regard to the focus side. In general, there is again more interaction from EEG-IMFs to HR than vice versa at all investigated segments and for both focus groups. The sharp increase of interaction from HR to EEG-IMFs in the alpha-range at the onset of seizure can be clearly identified now for specific electrode positions with regard of focus side (T3, C3 for left focus, T4 for right focus) and is more pronounced for the right focus group. Interactions from EEG-IMFs in the alpha range to HR shows higher and more generalized increase for the right focus group than for the left one. Similar topographic representations of results can be also achieved for all other frequency ranges of interest (beta-range, theta-range, delta-range), but introduced possibility to show also time-course and directional aspects those interactions clearly produces a high amount of rather complex presentations. In particular, this applies with regard of increasing number of segments (e.g. 24 h recordings) and of frequency-ranges of interest (e.g. analysis of sEEG of adult epileptic patients).

C. *Tensor Decomposition*

Graphical representations of time-courses and/or topographic views of brain-heart interactions were able to give complementary information but reduce available information in at least one dimension of results (time-courses: lack of spatial mode; topographic views: lack or high complexity of frequency mode). Therefore, tensor decomposition was adapted for a better generalization of achieved results.

In Figure 5, results of tensor decomposition are given by using five factors (columns from left to right) and all relevant five modes (lines of subplots; first: spatial mode, second: time-mode, third: frequency mode, fourth: direction mode, fifth: focus mode) implying the highest generalization of CCM results possible. Factors 1 to 5 presents specific spatial loadings being connected with different other modes. Concerning the time mode, factor 1 represents behavior during seizure, factor 2 and 3 during pre- and post-ictal period, and factor 4 and 5 during post-ictal period. Looking at the frequency mode, factor 1 and 3 represent all frequencies, factor 2 only delta, factor 4 and 5 are more pronounced for higher frequencies. Taking into account the direction mode, factor 1 (and factor 2) is slightly more pronounced for EEG-IMFs to HR (and vice versa, respectively), factor 3 is only visible for one direction (EEF-IMFs to HR), and factors 4 and 5 represent both directions equally. Last but not least, regarding the focus mode, factors 1 to 3 represent both focus groups equally, and factor 4 (and factor 5) is more pronounced for right (and left focus group, respectively).

Thus, tensor decomposition is able to generalize results of brain-heart interaction analyses thereby providing additional information not visible by separate time-, frequency- and/or topography-related representation of interaction results. Also, less generalized application of tensor decomposition are imaginable: e.g. better readable tensor decompositions using only 3 modes (spatial, time and frequency mode) could be adapted by generating four separate tensor decompositions taking into account direction of interaction (two possibilities) and focus side (two possibilities).

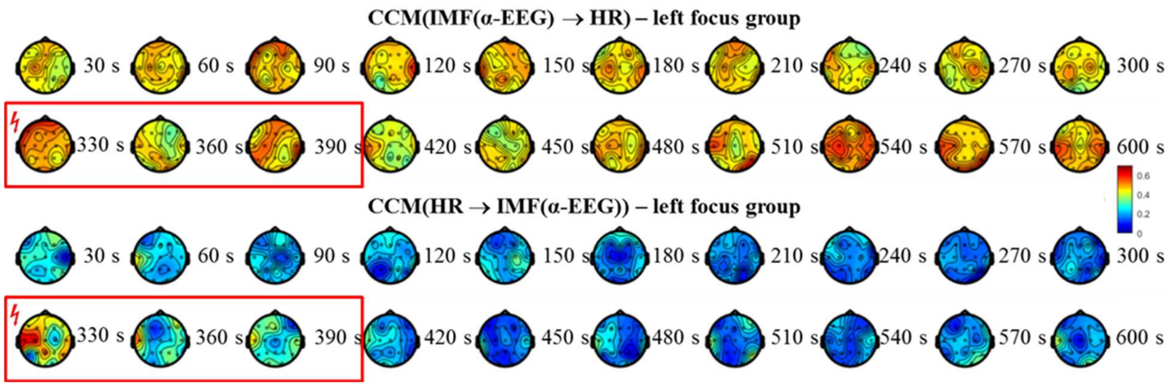

Fig. 3. Topographic views of median CCM (group results). CCM results are shown for left focus group (n=9) and only between HR and EEG-IMFs in the alpha-range. Color code assigns strength of interaction (red: high interaction, blue: low interaction). One view per analyzed segment of 30 s is given. Above two lines represent CCM interactions from EEG-IMF to HR, lower two lines CCM interactions from HR to EEG-IMF. Red rectangles designate median duration of seizure (90 s), red flash onset of seizure.

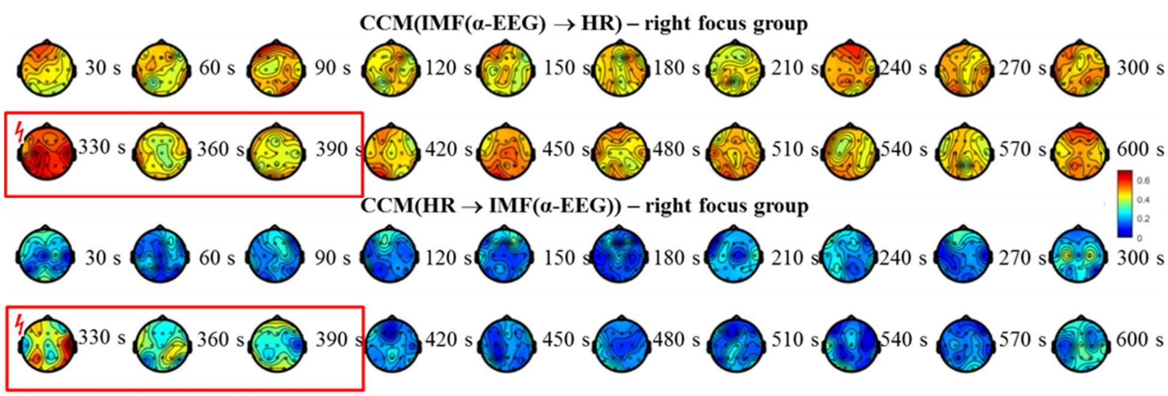

Fig. 4. Topographic views of median CCM (group results). CCM results are shown for right focus group (n=9) and only between HR and EEG-IMFs in the alpha-range. Color code assigns strength of interaction (red: high interaction, blue: low interaction). One view per analyzed segment of 30 s is given. Above two lines represent CCM interactions from EEG-IMF to HR, lower two lines CCM interactions from HR to EEG-IMF. Red rectangles designate median duration of seizure (90 s), red flash onset of seizure.

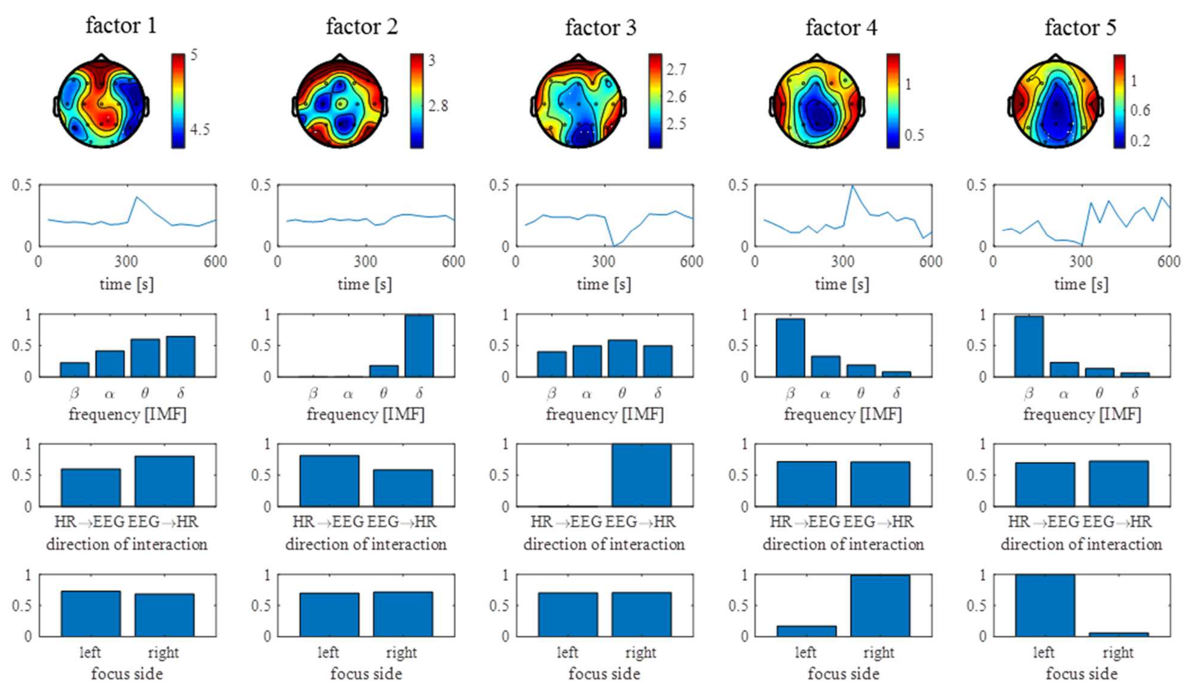

Fig. 5. Results of tensor decomposition of median CCM (group results). Five factors (columns from left to right) and five specific modes (lines from above to below: spatial mode, time mode, frequency mode, direction mode and focus mode) are shown.

V. DISCUSSION AND COMCLUSION

Our study was able to provide a generalized view on the highly complex results of brain-heart interaction analysis by means of CCM for a benchmark data set of children with TLE. Additional data features were included into the analysis to cover the full range of modes of interest like topography, time, frequency, directionality and focus side relation. Tensor decomposition was able to extract in particular new aspects of brain heart interactions during TLE with regard to the focus side and the generalization of seizure. Here, complementary investigations looking e.g. at the inter-ictal cardiorespiratory variability of children with TLE [19] or the shift of the 'epileptic network' rather than 'epileptic focus' concept [20] may be helpful.

Further generalization of CCM approach would imply the use of this approach for epilepsy monitoring in adult patients. Therefore, segmented use of CCM was implemented in this study to be able to expand our approach to much longer recordings possibly also implying more frequency ranges of interest and/or more electrode positions to be analyzed.

Tensor decomposition proofed to be successful in presenting condensed views on results of brain-heart interaction analyses. PARAFAC provides a reorganization and dimension reduction of the results of performed analysis. Thus, a better interpretation of the results of time-frequency analyses [21] but also including other features is possible Tensor decomposition was already adapted for other kinds of coupling analyses like monitoring of brain hemodynamics couplings in neonates [22] or the investigation of EEG couplings by means of partial directed coherence in a human balance control experiment [23]. Further applications of tensor decomposition for interaction analyses should investigate in particular the influence of number of factors used and the relation of this number of factors and number of modes investigated.

In conclusion, results of our generalization are transferable to many other methods to quantify brain-heart interactions and should undergo deeper analysis for specific features of concrete applications. Future work should employ also the inclusion of statistical measure into the generalized presentation of interaction results.

REFERENCES

[1] R. P. Bartsch, K. K. Liu, A. Bashan, and P. Ivanov, "Network Physiology: How Organ Systems Dynamically Interact," *PLoS One,* vol. 10, no. 11, p. e0142143, 2015.

[2] P. C. Ivanov, K. Liu, and R. P. Bartsch, "Focus on the emerging new fields of network physiology and network medicine," (in English), *New Journal of Physics,* vol. 18, p. 100201, Oct 13 2016.

[3] L. Faes, D. Marinazzo, F. Jurysta, and G. Nollo, "Linear and non-linear brain-heart and brain-brain interactions during sleep," *Physiol Meas,* vol. 36, no. 4, pp. 683-698, Mar 23 2015.

[4] K. J. Blinowska, "Review of the methods of determination of directed connectivity from multichannel data," (in English), *Medical & Biological Engineering & Computing,* vol. 49, no. 5, pp. 521-529, May 2011.

[5] L. Faes, D. Marinazzo, S. Stramaglia, F. Jurysta, A. Porta, and N. Giandomenico, "Predictability decomposition detects the impairment of brain-heart dynamical networks during sleep disorders and their recovery with treatment," *Philos Trans A Math Phys Eng Sci,* vol. 374, no. 2067, May 13 2016.

[6] K. Schiecke *et al.*, "Nonlinear Directed Interactions Between HRV and EEG Activity in Children With TLE," (in eng), *IEEE Trans Biomed Eng,* vol. 63, no. 12, pp. 2497-2504, Dec 2016.

[7] K. Schiecke, A. Schumann, F. Benninger, M. Feucht, K. J. Baer, and P. Schlattmann, "Brain-heart interactions considering complex physiological data: processing schemes for time-variant, frequency-dependent, topographical and statistical examination of directed interactions by convergent cross mapping," *Physiol Meas,* vol. 40, no. 11, p. 114001, Dec 2 2019.

[8] H. Mayer, F. Benninger, L. Urak, B. Plattner, J. Geldner, and M. Feucht, "EKG abnormalities in children and adolescents with symptomatic temporal lobe epilepsy," *Neurology,* vol. 63, no. 2, pp. 324-8, Jul 27 2004.

[9] N. Rehman and D. P. Mandic, "Multivariate empirical mode decomposition," (in English), *Proc Roy Soc A-Math Phys,* vol. 466, no. 2117, pp. 1291-1302, May 8 2010.

[10] K. Schiecke *et al.*, "Assignment of Empirical Mode Decomposition Components and Its Application to Biomedical Signals," (in English), *Methods of Information in Medicine,* vol. 54, no. 5, pp. 461-473, 2015.

[11] D. Piper, K. Schiecke, B. Pester, F. Benninger, M. Feucht, and H. Witte, "Time-variant coherence between heart rate variability and EEG activity in epileptic patients: an advanced coupling analysis between physiological networks " *New J. Phys. ,* vol. 16 115012, 2014.

[12] G. Sugihara *et al.*, "Detecting causality in complex ecosystems," *Science,* vol. 338, no. 6106, pp. 496-500, Oct 26 2012.

[13] K. Schiecke, B. Pester, M. Feucht, L. Leistritz, and H. Witte, "Convergent Cross Mapping: Basic concept, influence of estimation parameters and practical application," *Conf Proc IEEE Eng Med Biol Soc,* vol. 2015, pp. 7418-21, 2015.

[14] R. Bro, "PARAFAC. Tutorial and applications," *Chemometrics and Intelligent Laboratory Systems,* vol. 38, no. 2, pp. 149-171, 1997.

[15] A. Cichocki, R. Zdunek, A. H. Phan, and S. Amari, *Nonnegative matrix and tensor factorizations: applications to exploratory multi-way data analysis and blind source separation*. Chichester: Wiley Publishing, 2009.

[16] R. A. Harshman, "Foundations of the PARAFAC procedure: models and conditions for an" explanatory" multimodal factor analysis," *UCLA Working Papers in Phonetics,* vol. 16, pp. 1-84, 1970.

[17] M. Morup, L. K. Hansen, C. S. Herrmann, J. Parnas, and S. M. Arnfred, "Parallel Factor Analysis as an exploratory tool for wavelet transformed event-related EEG," (in English), *Neuroimage,* vol. 29, no. 3, pp. 938-947, Feb 1 2006.

[18] B. Pester, C. Ligges, L. Leistritz, H. Witte, and K. Schiecke, "Advanced Insights into Functional Brain Connectivity by Combining Tensor Decomposition and Partial Directed Coherence," (in English), *Plos One,* vol. 10, no. 6, p. e0129293, Jun 5 2015.

[19] C. Varon *et al.*, "Interictal cardiorespiratory variability in temporal lobe and absence epilepsy in childhood," *Physiol Meas,* vol. 36, no. 4, pp. 845-56, Apr 2015.

[20] K. Lehnertz and H. Dickten, "Assessing directionality and strength of coupling through symbolic analysis: an application to epilepsy patients," *Philos Trans A Math Phys Eng Sci,* vol. 373, no. 2034, p. 20140094, Feb 13 2015.

[21] C. Baumgartner *et al.*, "Discussion of "time-frequency techniques in biomedical signal analysis: a tutorial review of similarities and differences"," *Methods Inf Med,* vol. 52, no. 4, pp. 297-307, 2013.

[22] A. Caicedo *et al.*, "Monitoring of Brain Hemodynamics Coupling in Neonates using Updated Tensor Decompositions," *Conf Proc IEEE Eng Med Biol Soc,* vol. 2019, pp. 660-663, Jul 2019.

[23] A. Mierau, B. Pester, T. Hulsdunker, K. Schiecke, H. K. Struder, and H. Witte, "Cortical Correlates of Human Balance Control," *Brain Topogr,* vol. 30, no. 4, pp. 434-446, Jul 2017.