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Use of time-variant coherence as a general tool for analysis of interrelations between brain electrical processes

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1 Introduction

Functional or effective connectivity are operational measures which describe different aspects of interrelations of neuronal assemblies. The electrophysiological phenomena related to both kinds of connectivity reflect a 'temporal correlation between spatially remote neurophyiological events' [1]. Consequently, a method is needed which measures the temporal correlation between separate brain electrical processes. The coherence spectrum can be interpreted as the squared linear correlation coefficient between two signals for each frequency component. The time-variant coherence approach between two signals leads to a sequence of coherence spectra for each sampling point (coherence spectrogram). Therefore, by means of a defined location of EEG electrodes on the scalp, the spatial (topographic) information can be considered and the time variant coherence spectrum designates the temporal frequency-selective correlation.

The results of the first applications of such an analysis tool shed light on the cortical processing of ultra short-term cognitive processes [2, 3].

This study deals with aim to summarise results of three of our present applications [4, 5, 6] which can be seen as an extension of the concept of time-variant coherence analysing phenomena of connectivity between brain electrical processes:

1. The first application (<u>AP 1- conditioning</u>) supported observations that the development of correlation among cell assemblies of the brain is a basic element of associative learning or conditioning [4]. The 'subjects' task was to learn that a visual stimulus (red colour) was always terminated by a painful electrical stimulus (10-ms duration) applied to the left midfinger (condition A) whereas no such painful stimulus (condition B) was given at the end of another visual stimulus (green colour).
2. The second application (<u>AP 2- correction quality</u>) shows the utility of time-variant coherence for the evaluation of the correction quality after elimination of ocular artefacts in MEG data [5].
3. The third application (<u>AP 3- sedation depth</u>) demonstrates that the transient coupling of two brain electrical processes can be used as an indicator for the depth of sedation in intensive care patients [6].

All applications were based on adaptive autoregressive modelling of nonstationary time series by means of Kalman filtering [7]. This paper is focused on the different methodical concepts of signal processing on the basis of this fundamental algorithm.

2 Methods and Material

2.1 Definition of time-variant coherence (TVC)

The time-variant coherence analysis used in all applications of this study is based on the estimation of autoregressive (AR) coefficients updated at each sampling point by Kalman algorithm. The algorithm was described in detail by Arnold et al. [7]. Accordingly, the coherence

$$\gamma_n^2(f) = \frac{|S_{xy,n}(f)|^2}{S_{xx,n}(f) \cdot S_{yy,n}(f)}$$

can be computed from momentary estimations of autospectra ($S_{xx,n}$ and $S_{yy,n}$) of two time series $\{x_n\}$ and $\{y_n\}$ as well as from the momentary cross-spectrum ($S_{xy,n}$) as a function of frequency (f) and time (n). This procedure results in time sequence of coherence spectra. For example, the mean coherence within a frequency band can be extracted from this sequence and plotted as a time-variant parameter. Investigations regarding the AR model order were performed by means of Akaike's information criterion [8].

2.2 General concepts of signal processing

There are two different concepts in studying interrelations between electrical and/or magnetical sources by means of TVC:

1. The TVC between two EEG(MEG) channels can be computed. However, a pre-processing has been applied before. As a rule, the use of a reference-free EEG recording has been recommended [9]. Therefore, a high pass filtering of the genuine cortical signals of AP1 by a Laplacian was used. Furthermore, a rejection of ocular artefacts is necessary. AP2 deals with the aim to show, how the TVC can be used to control the rejection quality. The TVC between one EEG/MEG and one EOG channel was computed after artefact rejection.
2. The TVC between two time-variant parameters of one EEG/MEG channel can be used for the identification of interrelations of two unknown generator structures. This concept based on the assumption that different frequency ranges have been generated by different brain electrical processes. In general, the coupling or interrelations of frequency ranges can be described by bispectral analysis [10]. We used the envelope curves of EEG frequency components as one input signal of the TVC, the second input signal was a low-frequency component computed by means of filtering. This concept was used in AP 3.

2.3 Study design, subjects, data recording

<u>AP 1 - Conditioning</u>: The 'subjects' task was to learn that a visual stimulus (red colour) was always terminated by a painful electrical stimulus (10-ms duration) applied to the left midfinger (condition A) whereas no such painful stimulus (condition B) was given at the end of another visual stimulus (green colour). Duration of visual stimuli was 3000ms. Both visual stimuli were applied in random order for a total number of 120 trials with 60 stimuli representing each condition. The intertrial interval was 4 s. Sixteen healthy, right handed student volunteers (nine female) participated in the experiment. EEG data were recorded from 31 electrodes mounted on the subject's scalp according to the international 10-20-

system (with additional electrodes interspaced between standard electrodes. The electrode Cz was used as common reference, the sampling rate was 200 Hz.

AP 2 - Correction quality: For the magnetoencephalographic (MEG) investigations of the auditory evoked field (AEF) schizophrenic patients and controls were stimulated monaurally, using computer-generated tone-tips, delivered to the probands via a plastic tube. Auditory stimuli consisted of 1000Hz, 90dB tone pips with 50ms duration and 10ms rise- and fall-times, and a randomised interstimulus interval between 800 and 1800ms. Each session consisted of 270 trials and each trial had a length of 512 ms. The study group consisted of 17 medicated male schizophrenics and 17 age- and sex-matched healthy controls. Recordings were performed using a 31 channel first-order biomagnometer (Philips GmbH), positioned contralaterally to the stimulated ear over the temporal lobe. The EOG was recorded with a pair of electrodes, one positioned below the eye and the other one laterally above the eye ipsilateral to the MEG recording side. The sampling frequency of MEG and EOG was 1000 Hz. A down-sampling to lower rates was performed after digital low pass filtering.

AP 3 - sedation depth: The burst-suppression pattern of the EEG during sedation was used for investigations. A rising intracranial pressure, refractory to conventional therapy (ventricular drainage - if available, hyperventilation to a $PaCO_2$ below 4.6 kPa and infusion of Mannitol®), was the indication for increasing the basic sedation by adding i.v.-hypnotics. The investigations were carried out on a group of 12 patients with various neurosurgical diseases. All of them were given individual basic sedation to ensure controlled mechanical ventilation and safe nursing. The EEG was recorded from an eight channel analogous EEG (Neurofax 5610G, Nihon Kohden, Japan); the electrodes were placed in superior lengthwise positions according to the international 10-20 system with Cz as reference being the favoured recording modus in important clinical studies. The sampling frequency was 256 Hz. A down-sampling to a rate of 128 Hz was performed after digital low pass filtering with a upper cut-off frequency of 64 Hz.

3 Results

AP 1- Conditioning: Our methodical investigations led to an optimal computation scheme which can be summarised as follows. In a first step of pre-processing the correction of eye movement and blink interferences was performed by means of standard methods [11]. In a second step a current source density analysis was carried out in order to maximise the topographical distribution of sources and sinks to obtain reference-free measures for each electrode [12]. Pairs of electrodes (Fig. 1) between the two regions of interests I and II (electrodes covered the occipital lobe, the primary and secondary somatosensory projection areas of fingers on the homunculus of both hemispheres, and the midline of the brain) were considered for coherence analysis (electrode of region I versus electrode of region II) using all possible combinations. The mean coherence within the frequency range of 37-43 Hz (due to the theory of Singer [13]) was extracted as time-variant coherence parameter. The time-window for the detailed analysis covered the last 250 ms prior to the application of the painful stimulus (arrow in Fig. 1). In spite of using this time window the time-variant coherence was computed for each entire trial. The coherence measures extracted from the analysis window were transformed using Fisher's z-transformation and collapsed to averaged coherence measures for each subject, each pair of electrodes, and each condition of visual stimulation. The trial sequences were subdivided into five blocks of 12 trials (to trace the process of development of the coherence between different electrode sites throughout the course of acquisition. After testing the normal distribution, these mean coherences were submitted to an ANOVA analysis (repeated measurements) with the within factor blocks (five levels) and experimental condition.

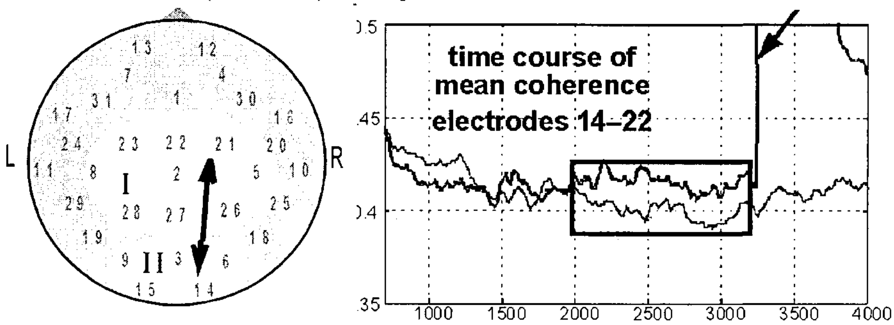

Fig. 1: Left: Electrode locations and regions of interests (I: occipital cortex; II fields of postcentral projection and of somatosensory association of left hand). Right: Result (grand mean) of time-variant coherence analysis between electrodes 14 and 22 (thick line: condition A; thin line: condition B).

The neurophysiological results gave evidence for the existence of a transient neural connectivity between occipital brain regions processing the visual stimulus and primary somatosensory brain regions processing the painful stimulus. Both regions seemed to communicate toward the end of the visual stimulus as a result of conditioning (learning). In detail, there is a clear evidence that condition A (visual stimulus followed by a painful stimulus) was associated with larger coherences then were seen for condition B (other visual stimulus which was not followed by a painful stimulus) between occipital electrode sites and electrode sites on the contralateral somatosensory projection area. One significant result (grand mean data about all subjects and trials) is represented in Fig. 1. The time-course of the mean coherence (37-43 Hz) is significantly different between condition A and B before the painful stimulus occurs. The difference are small but systematic across subjects and statistically significant ($p<0.05$ [4]).

AP 2- Correction quality : The computation scheme was given by Witte et al. [14] and modified for the use of time-variant coherence instead of FFT (fast Fourier transformation) based coherence estimation. Following methodical procedure can be suggested. After the correction [method, see [5]), the time-variant coherence was used to evaluate the correction quality. The corrected MEG interval and the corresponding EOG interval were used as input signals of TVC. It can be demonstrated that the time-course of TVC decreases significantly after correction for times when amplitudes of the EOG are large. In the extended (original) algorithm the ocular artefact can also be detected in evaluating the coherence spectrum. Accordingly, an extended version would be able to detect the artefact in a first run of the program and the correction quality could be determined in a second run.

AP 3 - Sedation depth : The processing scheme for this application is given in Fig 2 A. The EEG during burst-suppression patterns (BSP) was subdivided into a sequence of burst and suppression patterns using a modified version of our method for burst onset detection in neonatal EEG [15].

The following processing methods were started automatically by the segmentation algorithm (burst onset) and the results were averaged: (1) Estimation of the biamplitude; (2) Low-pass filtering 0-2.5Hz; (3) Calculation of the envelope curve of the frequency components within the frequency bands 3-7.5Hz and 8-12Hz. On the basis of visual inspection, burst-like EEG patterns were selected manually from the EEG during basic sedation. Such EEG patterns start with a high-amplitude (negative) wave (≈1Hz). The EEG intervals separated were analysed given above. The envelope curve of EEG activity within the frequency bands 3-7.5Hz and 8-12Hz was computed by means of filtering [16]. The resulting continuous envelope curves (additionally filtered between 0.5-2.5Hz) and a low-frequency component of the EEG (0-2.5Hz) were used as input signals for an instantaneous coherence analysis.

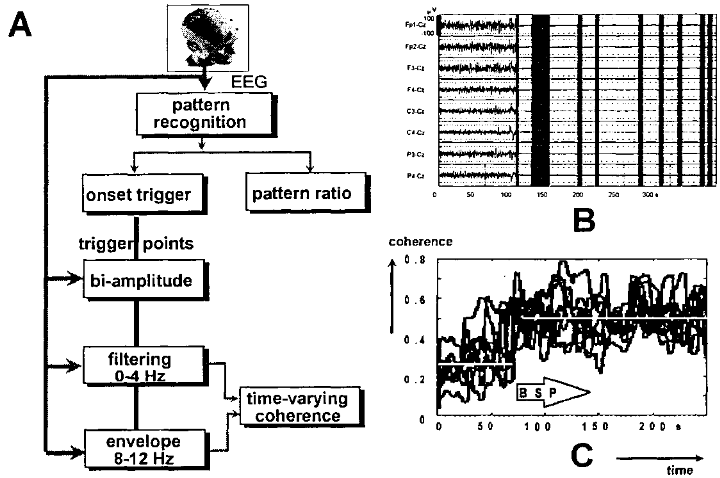

Fig. 2: (A) Processing scheme for EEG pattern analysis in sedated patients. (B) EEG recording entering BSP with segmentation in burst (grey background) and suppression patterns. (C) Superposition of all courses of the mean TVC within the frequency band 0.8 - 2.5Hz during EEG recording entering BSP (all patients N=12; Fp1-Cz).

In the biamplitude representations, two separable peaks with the co-ordinate range ≈4,5-5/2Hz and ≈9/0,5Hz can be recognised with the best expression at Fp1/2-Cz. These results can be derived from the grand mean data of the biamplitude (Fig. 2 C) as well as from the averaged biamplitude representations in each patient. These findings designate interrelations between the frequency ranges 0-2.5Hz⇔3-7.5Hz as well as 0-2.5Hz⇔8-12Hz.

An amplitude modulation seems to be the most probable reason for the appearance of the biamplitude peaks, i.e. a low-frequency component modulates the amplitude of faster EEG components. The degree of amplitude modulation can be quantified continuously by means of instantaneous coherence analysis between an envelope curve of the modulated component and the low-frequency component 0-2.5Hz (modulation component). The analysis was focused on the coherence between the low-pass filtered (0-2.5Hz) signal component and envelope (3-7.5Hz) as well as between the low-pass filtered (0-2.5Hz) signal component and envelope (8-12Hz), because corresponding peaks appeared in the biamplitude representation. The mean coherence values within the band 0.8-2.5Hz were derived from the resulting coherence spectrogram and plotted as time course. Fig. 2 C shows the superposition of all courses of the mean coherence within the frequency band 0.8-2.5Hz during EEG recording entering BSP (all patients N=12; Fp1-Cz). According to the design of our study, the different influences of the injuries, treatment regimes, drugs etc. on the interrelation effects cannot be separated, but a relation between the degree of interrelations and the depth of sedation can be postulated.

4 Discussion

It can be demonstrated that the time-variant coherence can be used as an efficient method in analysing interrelations between signals. Due to EEG/MEG analysis, this new approach leads to novel knowledge of transient interrelations between brain electrical processes. For the first time such ultra short-term effects could be demonstrated. The studies were performed on the basis of representative groups and the results have been evaluated statistically. The use of the Kalman filter algorithm for the estimation procedures has some advantage compared with other approaches. First, Kalman filters can be constructed for multivariate systems (i.e. partial and multiple coherences can be estimated in a time-variant manner) with stochastic variations of the parameters. The properties of the resulting estimates can be described theoretically. Furthermore, it is not necessary to search for a suitable set of base functions to model the temporal evolution of coefficients or to implement procedures for the detection of change points. Secondly, the Kalman filter is suitable for implementation on microcomputers. Because of its recursive structure, it allows on-line processing.

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