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Statistical significance of task related deep brain EEG dynamic changes in the time-frequency domain

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Abstract — **We present an off-line analysis procedure for exploring brain activity recorded from intra-cerebral electroencephalographic data (SEEG). The objective is to determine the statistical differences between different types of stimulations in the time-frequency domain. The procedure is based on computing relative signal power change and subsequent statistical analysis. An example of characteristic statistically significant event-related de/synchronization (ERD/ERS) detected across different frequency bands following different oddball stimuli is presented. The method is used for off-line functional classification of different brain areas.**

I. Introduction

An oddball task is one of the most commonly used experimental paradigms in cognitive neuroscience. During this task a human subject discriminates between two simple stimuli [1]. In the case of our study, we used a visual oddball task, during which subjects continuously focused their eyes on a monitor screen with visual stimulation. The stimulation is based on two types of pictures presented in random order: first one is "X" usually called target and second one is "O" usually called non-target stimuli. Numbers of stimuli were 50 for target ("X") and 250 for non-target "O". Each subject was asked to respond to the target stimulus as quickly as possible by pressing a switch and to ignore a more frequent non-target stimulus. The duration of visual stimuli was constant at 500 ms. The inter-stimuli interval was between 4 and 6 seconds. SEEG was collected simultaneously during the performance of this task.

SEEG can be recorded using macro or microelectrodes which are placed in deep brain structures. These depth electrodes are implanted to localize epileptic seizure origin before surgical treatment. The character of the analyzed SEEG signals is strongly determined by the size and placement of the electrodes and, of course, the selected brain structure.

Although a visual oddball task can be considered a relatively easy task, a lot of functional brain areas and brain functions are activated (cognition, attention, short-term memory, assessment of stimulus relevance, decision-making, movement planning, and movement execution) [1,2,3,4,5]. It is known that not all these brain processes are triggered by frequent stimuli. Therefore, the signal will be analyzed as phase-locked or non-phase-locked. The external environment also has a great influence on human attention and affects the resulting SEEG signal. The length and difficulty of the task causes subject fatigue, which causes later reactions and an increased error rate. Therefore, statistical analysis must be performed in order to ensure the validity of any conclusions reached during the study.

We will demonstrate the procedure of SEEG data analysis and a statistical validation technique used for analysis of two stimuli data sets recorded from deep human brain structures. As an example we will use only one contact, although many structures included in the temporal and/or frontal, parietal and occipital lobes were analyzed.

II. Methods

A. EEG Recordings

We analyzed 10 drug-resistant epileptic patients undergoing SEEG recordings in order to localize their seizure onset zone. Each patient received 6-15 standard semiflexible electrodes (ALCIS) with a diameter of 0.8 mm, a length of each contact of 2 mm, with an inter-contact interval of 1.5 mm used for invasive EEG monitoring. The exact position of the electrodes was checked by postplacement MRI with electrodes in situ. The recordings were performed using the EEG system TruScan (Deymed diagnostic, Alien Technic). The recordings were mono-polar, with a linked earlobe reference. The sampling rate was 1 kHz and up to 128 contacts were recorded per subject. Standard anti-aliasing filters were used. ECG, EMG and EOG were also recorded along with SEEG data. Simultaneous SEEG and scalp measurement is extremely problematic, but a limited number of scalp electrodes were recorded (Fz,Pz,Cz). For further analysis we used only structures located outside the seizure onset zone. In total, 898 intracerebral sites were investigated in all the subjects.

III. Data analysis

A. Data segmentation

Data was visually inspected and segmented into 8-second segments according to the stimuli trigger onset. Segments containing artificial signals or mistaken responses were excluded from further processing. The same number of trials was used for each type of stimuli in each subject. The number of analyzed trials varied from 25 to 50 depending on the subject and the data quality.

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B. *Phase-locked signal analysis*

After trend elimination in each segment, the data was filtered with 0.2–40 Hz bandwidths and averaged to obtain evoked responses. The baseline interval was determined 600–100 ms before stimuli. The mean values computed from the baseline intervals were subtracted within each trial. Event-related potentials (ERPs) were then analyzed. An example of the ERPs can be seen in Figure 1.

Two types of statistical significance tests were used. The significance of ERP components was computed using a nonparametric Wilcoxon (signed rank) test for paired samples. In each period, two vectors were compared — one consisting of mean amplitudes calculated within a floating window (the length of which was a third of the baseline) and a second vector consisting of mean amplitudes computed from the baseline region of each trial. Statistically significant areas were visualized by thick lines as shown in Figure 1. The differences between modalities (target, non-target amplitude) were analyzed by a non-paired t-test. The statistical difference was indicated by a line inserted below the plot (Scheffé's procedure can be used in the case of more than two stimuli types).

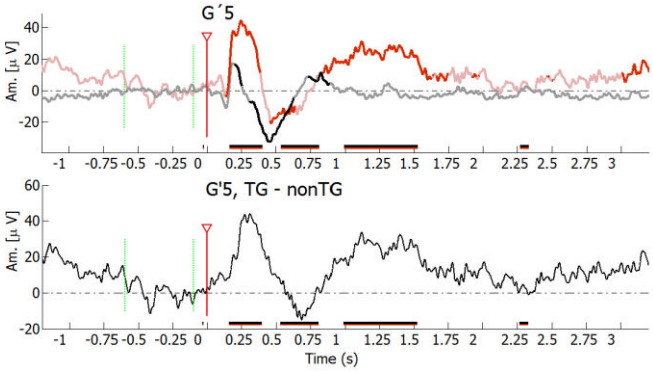

Figure 1: The analysis of evoked potentials (ERP). Filtered and averaged signals in the 0.2-40 Hz frequency band. Targets are marked in red and non-targets in black (upper). Statistically significant amplitude changes related to the baseline are marked by a dark color. The difference between modalities is shown below. The stimulation position is marked by the red line, the baseline position is marked by the green line.

A time-frequency analysis (TFA) was computed for every averaged signal in the frequency range 2–40 Hz. Here each row of the TFA matrix represents signal power envelopes computed by Hilbert transform in a 4 Hz frequency bandwidth. The frequency step between two lines is 1 Hz. The X-axis represents time, the Y- axis represents frequency. In this way, the power of the phase coherent signal is decomposed to the time-frequency domain. Each row of the matrix is normalized by the mean value of the row. For the same contact we show the TFA analysis for target and non-target stimuli in Figure 2.

C. *Non -Phase-Locked signal analysis*

On another signal example we will demonstrate a typical results obtained using a Time frequency analysis [6,7] with elimination of phase-locked signals. This method was used to determine the event-related desynchronization or synchronization (ERD/ERS) [8].

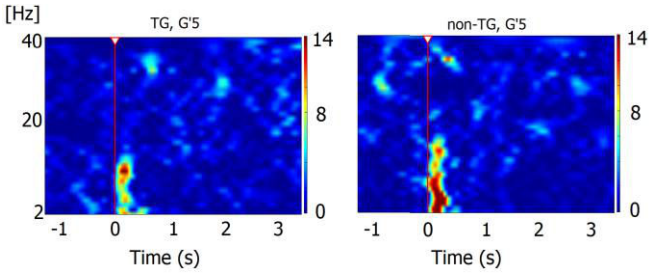

Figure 2: The time-frequency analysis (TFA) of evoked potentials (ERP). The TFA is computed from averaged signals. The target (left) and non-target (right) responses for the same analyzed contact. The location of stimulation (time zero) is indicated by the red line.

In this procedure a time signal was averaged and this average was subtracted from each trial. After the signal subtraction the TFA matrix was calculated in a similar way as in the previous case for phase-locked signals (B): each row of the TFA matrix represents signal power envelopes computed by Hilbert transform in a 4 Hz frequency bandwidth. The frequency step between two lines was 1 Hz. The computed frequency range was 2–200 Hz. Moreover, each row of the TFA matrix was averaged over trials and the averaged TFA matrix was recomputed according to the following equations:

$$ERS = \left(\frac{PW(t)}{PW_{BL}} - 1 \right) \times 100, when \frac{PW(t)}{PW_{BL}} \geq 1 \qquad (1)$$

$$ERD = \left(\frac{1}{\frac{PW(t)}{PW_{BL}}} - 1 \right) \times 100, when \frac{PW(t)}{PW_{BL}} < 1 \qquad (2)$$

where:

PW(t) is instantaneous power and PW_{BL} is mean power from the baseline computed 0.1 to 0.6 seconds before the stimuli trigger onset. A relative decrease in power (blue color) indicates an induced ERD, an increase (red color) indicates ERS. The color representation is limited to the values +/- 100 to preserve a normalized resulting scale as seen in Figure 3.

D. *Statistical analysis in the time-frequency domain*

A statistical analysis in the time-frequency domain is very similar to the statistical analysis of ERPs. In this case, a power of each row of the TFA matrix was analyzed instead of amplitudes.

- *Instantaneous power vs. baseline*

The significance of power ERS/ERD components in the range from 2 to 200 Hz was computed using a nonparametric Wilcoxon (signed rank) test for paired samples. A subsequently described procedure was performed for all power envelopes calculated in a 4 Hz frequency band width with the frequency step of 1 Hz.

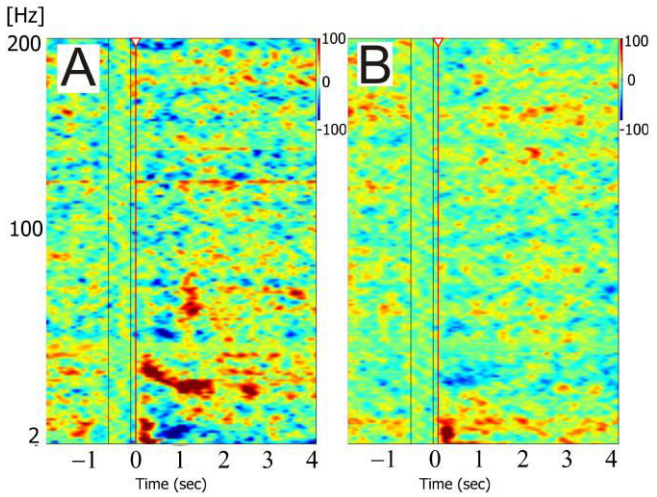

Figure 3: TFA computed for target (A) and non-target (B) stimuli. A relative decrease in band power (blue color) indicates induced ERD, an increase (red) indicates ERS. The location of stimulation is indicated by the red line, the baseline position is marked by the green line.

In each time, two vectors were compared — one consisting of mean power calculated within a floating window (the length of which was a third of the baseline) and a second vector consisting of mean power computed from the baseline region of each trial. A results are displayed in the statistical significance map as is shown in Figure 4. Obtained statistical maps in the time-frequency domain summarize two types of information: the position of significant p values and the sign of the power change relative to the baseline. In the case of a relative decrease in power, the area is marked by a blue color and in the case of a relative increase in power the area is marked by a red color. Darkness of colors correspond to the obtained level of significance: light color corresponds to the p<=0.05 and dark color corresponds to the p<=0.01. Target and non-target trials has very different number of trials. To be able compare the p-values from both, only the same number of uniformly selected trials were analyzed.

- *Target vs. non-target stimuli*

We used a t-test in the time-frequency domain for each row of the TFA matrix to determine statistically significant differences of power computed for target and non-target stimuli.

Relative power changes and differences between target and non-target power were considered as significant for $p < 0.01$ (dark gray) or $0.01 < p < 0.05$ (light gray), which can be seen in Figure 5.

IV. Bipolar Montages

Far field potentials are usually caused by the volume conduction from surface neocortical discharges or by transsynaptic propagation. Bipolar montages were used to confirm the local generators of potentials and to identify common far field potentials. Bipolar montages were computed by a signal subtraction with the nearest located contact. Signal processing was the same as described above.

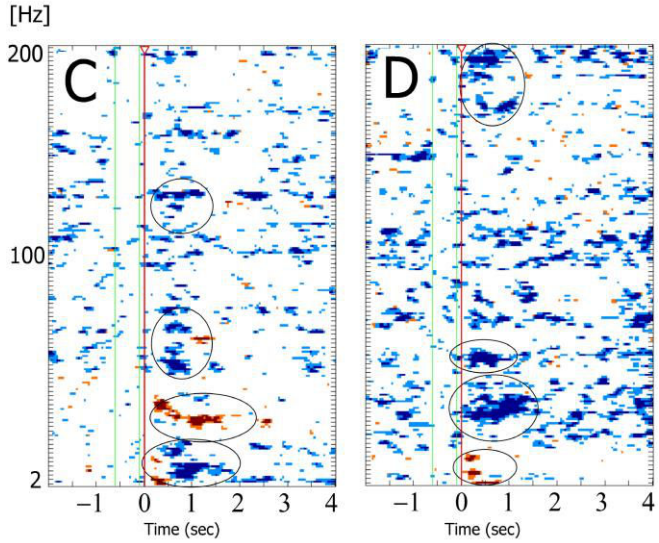

Figure 4: TFA – statistical significance computed for target (C) and non-target (D) stimuli trials. The marked areas correspond to two levels of statistical significance (p<=0.05 – light, p<=0.01 – dark color), while a red/blue color shows how the relative power increases/decreases as well. Interesting areas are marked by circles.

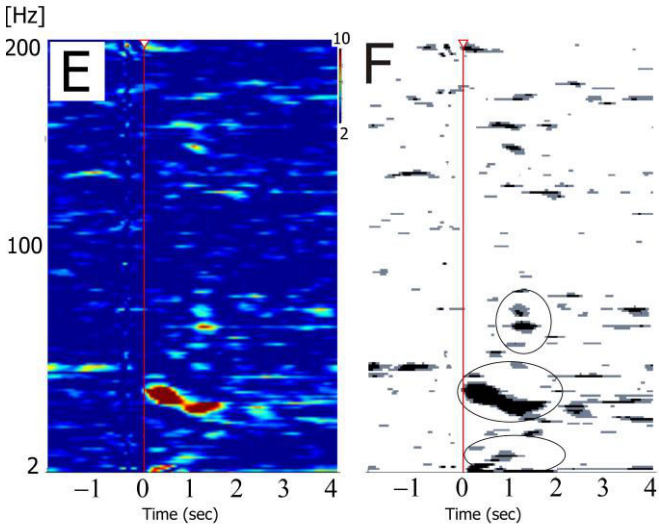

Figure 5: TFA – negative logarithm of probability value -log(p) (E) indicates the statistical significance of the difference between target and non-target stimulus from Figure 3,4). More clear visualization is shown in (F), where marked areas correspond to two levels of statistical significance (light color: p<=0.05, dark color: p<=0.01). The most prominent areas are marked by circles.

V. Results

We used a standard approach for ERD/ERS quantification that we supplemented by a validation procedure in the time-frequency domain. Our method described marks out statistically significant areas, where

(1) the signal power increases/decreases relative to the baseline region, and where

(2) the brain activity significantly differs for the different stimulation types.

Identifying these areas may serve to determine individual frequencies that are typical for each subject. We used

different baseline lengths and compared the statistically significant areas achieved. The results depend sensitively on the baseline length. Therefore, a sufficiently long baseline is preferred. Nevertheless, it is necessary to carefully examine the data by visual inspection. The calculation of significance maps validates the results achieved and greatly facilitates artifact validation. A majority of artifacts can be relatively easy located by comparison of the time-frequency power map and the corresponding significance map as can be seen from the example in Figure 6. In this case major artifacts are concentrated in the area of frequency range from 2 to 40 Hz.

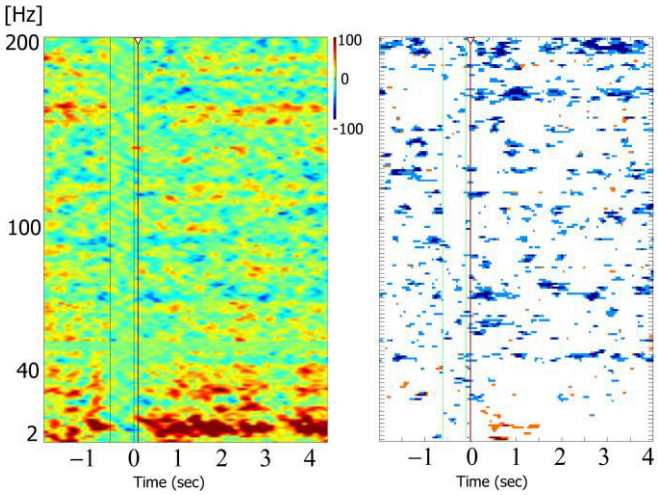

Figure 6: The TFA computed for target stimuli and the contact located in the left side hippocampus. A relative increase in band power in the frequency band up to 40 Hz indicates very strong activity (left). In comparison with the statistics map (right), we can conclude that this activity was not stimuli dependent and may be caused by artifacts or by latent epileptic activity.

VI. CONCLUSION

Large-scale neural network dynamics are investigated using various methods such as non-invasive electroencephalography, functional MRI or magnetoencephalography, etc. These methods are useful for macroscopic description, but they are not able to capture the mesoscopic scale among neural assemblies. This is the reason why intracerebral electroencephalographic recordings (SEEG) play an irreplaceable role in brain research. SEEG measurements are limited by the number of scanned contacts, but allow analysis of neuronal activity in deep brain structures, which is not achievable in any other way. SEEG measured by macro or microelectrodes placed in deep brain structures differs considerably from measurements on the scalp. The analysis of SEEG data requires an appropriate statistical analysis and a sufficiently large number of trials.

Here we present clear method for phase non-locked evoked signal analysis based on TFA. TFA is in generally a signal representation in the time and frequency domain. Different forms of TFA including wavelets etc. can be found in the literature [7,10]. The TFA described above is method based on Fast Fourier Transform [12] and instantaneous power envelope computation (Hilbert transform) without need of overlapping and without the lost of time information, which is need for the analysis of short time events after the stimuli.

One of the main goals of the neurological research is the functional mapping of the brain. Our time-frequency statistical significance maps between target and non-target stimulus help us locate a typical brain areas involved during visual oddball task.

Described procedures were implemented in ScopeMAT and Physioplore software running under the MATLAB.

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