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Analysis of Evoked Deep Brain Connectivity

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Abstract— **Establishing dependencies and connectivity among different structures in the human brain is an extremely complex issue. Methods that are often used for connectivity analysis are based on correlation mechanisms. Correlation methods can analyze changes in signal shape or instantaneous power level. Although recent studies imply that observation of results from both groups of methods together can disclose some of the basic functions and behavior of the human brain during mental activity and decision-making, there is no technique covering changes in the shape of signals along with changes in their power levels.**

We present a method using a time evaluation of the correlation along with a comparison of power levels in every available contact pair from intracranial electrodes placed in deep brain structures. Observing shape changes in signals after stimulation together with their power levels provides us with new information about signal character between different structures in the brain during task-related events – visual stimulation with motor response.

The results for a subject with 95 intracerebral contacts used in this paper demonstrate a clear methodology capable of spatially analyzing connectivity among deep brain structures.

I. Introduction

The human brain, and its function in particular, is still an unexplored field in our knowledge. So far we are able to declare that different areas, neuronal populations and individual neurons work together using mild but extremely varied electric signals [1]. These signals spread in various ways. Some use short distance – local links, others participate in global communication usually using central high-capacity connections [2]. All this together creates electric activity that reflect physiologic function.

EEG signals can be captured and further processed by electrodes placed on the scalp – standard scalp EEG, by grip/strip electrodes placed under the scalp – subdural EEG, or by micro/macro electrodes placed in deep brain structures – intracranial EEG. Basically, standard scalp electrodes provide us only with summed signals over all structures. Subdural measurement is able to record signals of better quality, but only intracranial contacts can reach local electric activity in deep brain structures [3]. To observe active and interesting areas such as the Hippocampus or Amygdala without interference from other structures, it is necessary to use intracranial measurement.

The character of measurement itself makes another important difference in the observed signals. Results from long records during relaxation or sleep are different from task-related activity, which is bound to stimulation and is supposed to trigger whole sets of cognitive processes in the brain [4].

The stochastic and non-stationary character of the EEG signal, with its wide frequency range and very low amplitude, makes these signals extremely complex and hard to distinguish from interferences and artefacts. Moreover, in the case of comparing and finding connections between contacts placed in different structures, an intracranial set of electrodes (placed differently in each patient) is not able to provide a proper input data-set for any specialized methods designed for revealing connectivity, which are mostly based on certain types of models [5], [6], [7]. On the other hand, the standard correlation method with its relatively simple mechanism, processing only a couple of contacts at a time, can be extremely effective for this type of data.

We can observe mutual interactions and reactions to stimulation analyzing a couple of signals. A few basic diversions in signals can be found during reaction to stimulation, which can accommodate useful information about brain function and dynamics. Of those that are bound to stimulation (usually taking place 200 – 500 ms after stimulation) the changes in phase and power are most interesting. Phase coupling in a specific frequency range can be detected using a correlation method between two filtered signals. The Hilbert transformation allows us to detect a link between the signal power-envelopes. Coherence computing can be used to detect similarities in frequency domain. Furthermore, each signal from every single contact can also be observed on its own. Significant changes of power after stimulation, which can be compared with another signal from a different contact, are extremely informative. The resulting power activity between these contacts can be further attached with correlation or coherence results for this couple. This comparison can lead to better understanding of the main principles in human brain behavior during task-related events.

This work follows previously published methods, which deal with imaging and representing comprehensive results [8].

II. Methods

A. EEG recordings

Standard semiflexible intracerebral electrodes were used in patients with pharmacoresistant epilepsy. Electrodes were implanted in specific areas, in order to localize seizure origin

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before neurosurgical treatment. The exact position of the electrodes in the brain was verified by post-placement MRI. Recordings were monopolar with earlobe reference. The number of channels in the presented results was 95. The data was down-sampled from 1,024 Hz to 256 Hz. All anatomical structures with any kind of disorder were omitted from analysis.

A visual oddball task was performed to record standard repetitive EEG [1]. Two types of stimulation were used during measurement – target and frequent. Patients were supposed to react to target stimulation by motor response (pressing a button) and to ignore frequent stimuli. The interval between stimuli varied randomly between 4 and 6 seconds and the duration of stimulus exposure was 500 ms. The total length of recording was 25 minutes. Reactions to 50 targets and 50 frequents were used for analysis.

B. Signal Processing

1. Pre-processing

The measured data was processed off-line. Dislocated channels or channels with corrupted information were excluded from selection. The remaining data was segmented before analyzing. Segmentation was performed in accordance with stimuli position. The length of segments was 8 seconds, with the onset of stimulation always placed in the middle of each segment. Segments with arteficial activity were omitted from selection.

Segmented channels were further divided into target and frequent segments and analyzed separately as reactions to different types of stimulation.

Signals were filtered as time signals or signal envelopes in various frequency ranges, coverenig the frequencies: δ (2-4 Hz), θ (4-8 Hz), α (8-12 Hz), β (12-20 Hz), lower γ (20-45 Hz) and upper γ (55-95 Hz).

Segmented, artefact-free and filtered signals were further processed by a correlation method and a method of power comparison. In the last step, all results were depicted in a spatial matrix which can clearly show dependencies among structures. The different frequency bands were analyzed and subsequent processing supposed signals filtered in one frequency band.

2. Correlation

The time evaluation of correlation was applied to determine the coupling between all pairs of channels using moving windows over the complete length of signals. Pearson's correlation coefficient was calculated for every step of the windows and the result (in a range from -1 to 1) was placed in the middle of the current position of the floating window. Windows from both signals were multiplied by Hamming window prior to correlation coefficient calculation to decrease the influence of the border parts.

The width of the floating window is an extremely important parameter for correlation calculation. Using a narrow window can produce false results by correlating pieces of signals that are too short, while the use of a wide window can average results too much. In our case, we used windows 1 second in width (for every frequency range). The step of the window was 10 % of the window width.

The sequence of correlation coefficients was computed by a floating window, through the whole 8-second segment and over all frequent or target segments. The median of correlation functions from all frequent/target segments was calculated to obtain the resulting coupling between certain pair of channels.

Significant parts of its changes, which reflect activity bound to the stimuli, were found in addition to the level of correlation. Significant changes in correlation were analyzed by comparing levels of correlation before (baseline) and after stimulation. The baseline of a length of 500 ms started 0.6 seconds and ended 0.1 seconds before stimulation. A statistically significant difference between the mean value from the baseline region and the mean value from the floating window (one third the width of the baseline) was calculated by the non-parametric Wilcoxon Rank Sum test for paired samples. The difference is marked as significant for $p < 0.01$. The change of correlation after stimulation was then considered as an increase (synchronization) or a decrease (desynchronization). No time delay between channels was considered.

4,465 correlation functions were generated from 95 contacts with marked significant parts. Well-arranged imaging for this amount of results could be achieved by method [8], which put significant changes of one correlation function in one line of the matrix, where significant increases/decreases were represented only by the red/blue color. Every line of the matrix then showed one pair of contacts and every column one step of the floating window. An example of these matrices for reaction to target and frequent stimulation in a specific frequency band can be seen in Figure 1.

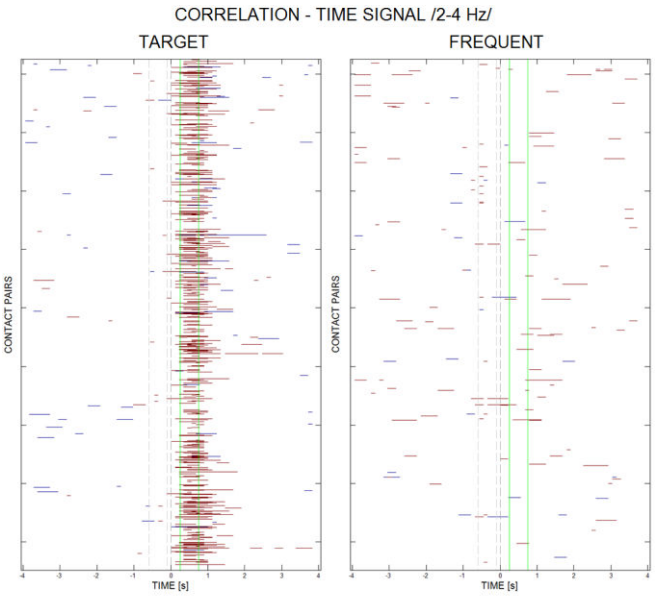

Figure 1: Subject 32, correlation of time signals in the 2 - 4 Hz frequency band. Statistically significant changes (red – increases, blue – decreases) for targets (left) and frequents (right). Stimulation in the middle at 0 seconds, the baseline is marked by light-gray lines, the time cut for spatial matrix (Figure 3) is demarcated by green lines. The vertical axis contains 4,465 pairs of contacts.

3. Power Comparison

The instantaneous power levels with significant changes in every single contact were examined along with correlation. Prior to calculation of significant changes, the power levels of signals in a certain frequency band were determined by Hilbert transform. Subsequently, the calculation of significant changes was again performed by setting the baseline before stimulation and comparing the mean value of power from this area with the mean value of power from the floating window, which was again one-third the width of the baseline and went through the whole segment. The same probability value ($p < 0.01$) for a non-parametric test for paired samples was used.

In the next step, the significant power changes from all pairs of channels were analyzed. Five states were evaluated: a significant increase or decrease in both channels, a significant increase or decrease in one channel with no change in the other channel, and opposite activity in the channels (a significant increase in one accompanied by a significant decrease in the second). The results placed in a similar matrix as in Figure 1 can be seen in Figure 2. Every line accommodated information about one pair of contacts, while the columns created evolution in time.

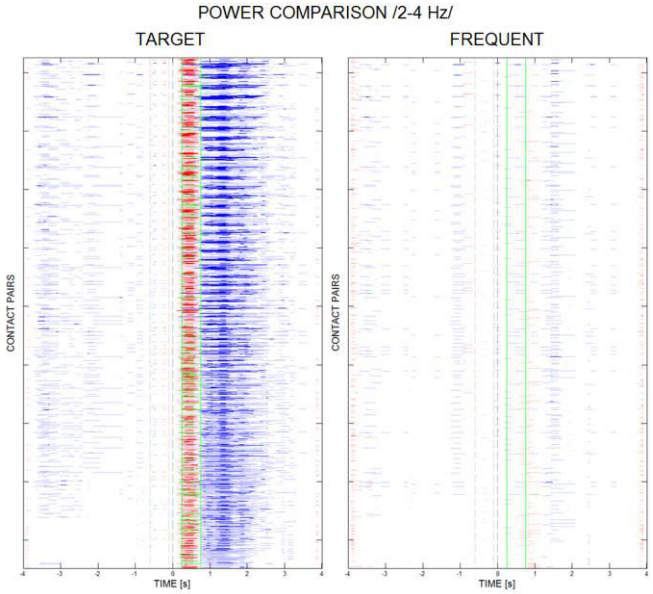

Figure 2: Subject 32, power comparison in the 2 - 4 Hz frequency band. Statistically significant changes between two signals (red – increase in both, blue – decrease in both, light-red/blue – increase/decrease in only one of the signals, green – increase in one with decrease in the other). Stimulation in the middle at 0 seconds, the baseline is marked by light-gray lines, the time cut for spatial matrix (Figure 3) is demarcated by green lines.

4. Spatial Matrix

The spatial matrix was created for the purpose of better understanding as to how the synchronization or desynchronization is bound to power increases or decreases. Time areas (green vertical lines in Figures 1 and 2) were selected from the results in the previous figures. Every line in this selected time area was then represented as one point in the spatial matrix – Figure 3. The final color of points representing the correlation, which are placed in the upper half of the matrix, was given by dividing the area that represents a significant increase/decrease (in the selected time cut) by the entire selected time cut. The color of the power points placed in the lower part of matrix was simply determined by the dominant activity of power in the same time area.

Furthermore, contacts for this imaging were arranged in accordance with their spatial localization in the brain, meaning that the matrix provided us with well-arranged information about activities in particular structures in the brain (separated in Figure 3 by black lines).

III. Results

Having an overview of results from all contact pairs for correlation and power together with summarized outcomes in a spatial matrix may provide us with information about reactions to various types of stimulation and any connection between changes in correlations and power levels in contacts.

The results of the correlation of the time signal, filtered in the frequency range 2 – 4 Hz in Figure 1, clearly showed significant increases in correlation after target stimulation in most of the couples. This activity occurred mostly in the time interval 250 – 1,000 ms after stimulation. A significant increase in power levels followed by a significant decrease after target stimulation appeared in the same time interval - Figure 2. In most of the couples the decrease in power levels lasted until 2 seconds after stimulation. The opposite activity was detected in the minimum of couples.

An evident difference between reactions to target and frequent stimulation was found. Reactions to targets were unquestionably bound to stimulation and more significant than reactions to frequents.

The spatial matrix arranged results in a different manner. Contacts arranged in order with their real placement in the brain allowed us to see which structures are more active and which contact pair with significant correlation made a contribution towards the power increase or decrease. Increases in correlation in all structures accompanied by both – increases and decreases in power levels were mostly detected in the 2 – 4 Hz frequency band and the time area 250 – 750 ms after stimulation. The most correlation increases appeared in the inferior frontal gyrus (GFI) and postcentralis gyrus (GPOST). A noticeable number of power increases were also detected in the GFI. Remarkable power decreases appeared in the praecentralis gyrus (GPREC). The opposite activity of power changes was detected in a few contact pairs.

IV. Discussion

The data from the measurement of a patient with 95 channels in his deep brain structures was used for the study presented in this paper. The vast amount of results produced by analysis was processed by methods that are able to depict a well-arranged overview together with spatial information about individual activities in different areas in the human brain.

The results provided clear information about all contacts placed in the brain, although interpretation must be performed with respect to the character of the data and the

parameters of the calculations. The position and the width of the baseline covering only relaxation after/prior stimulation may have a crucial influence on the results, in addition to the width of the floating window and its step. Another important fact is that no time delay between channels was considered. This means that this method assumes reaction to stimulation in two places at the same time [8].

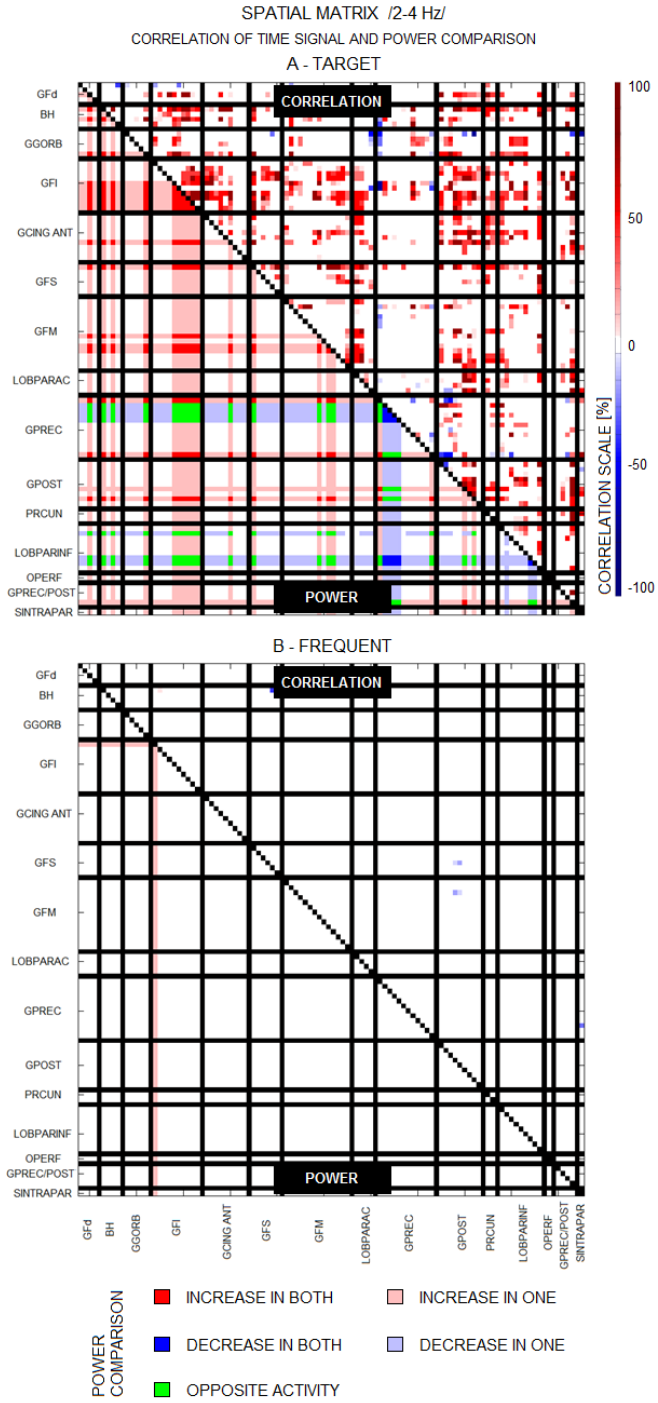

Figure 3: Subject 32, spatial matrix - correlation of time signal and power comparison in 2 - 4 Hz frequency band, A – target, B – frequent, for time cut 250 – 750 ms (green lines in Figure 1 and 2). Upper half of each matrix: Correlation – the percentage of significant changes in time area (red – increase, blue – decrease). Lower half: Power – increases/decreases in both or in one channel or opposite activity.

The common far fields in channels caused by parasitic signals that disseminate along the electrode must be taken into account when observing the final number of correlations and power changes, particularly in the case of contacts with seemingly similar activity placed very close to each other or on the same electrode.

The outcomes of our analysis supported our supposition that phase coupling (synchronization) is accompanied by significant changes in power levels. This phenomenon can be seen in all three figures. Significant changes in correlation and power levels took place at the same time after target stimulation. The evolution of results in time caused the final image in the spatial matrix to have a different appearance for every position in the time area, particularly for power changes that changed from increases to decreases around 750 ms after stimulation. The position of the time interval for the spatial matrix is, however, also an important parameter. In the frequency band 2 – 4 Hz, the synchronizations accompanied by increases in power levels appeared as the first activity after target stimulation as a result of evoked activity, followed 500 ms later by a decrease in power level, probably caused by cognitive processes. The reactions in different frequency bands were diverse or, for some frequencies, even opposite to the signal manners in the 2 – 4 Hz frequency band.

Significant changes in correlation and power levels appeared very seldom during reactions to frequent stimulation. Differences between reactions to target and frequent stimulation showed that an increase of activity was clearly bound to target stimulation. These processes in the human brain can, therefore, be assigned to mental activity. The sudden changes in signal phase, which is coupled with phase changes of signals from another parts of the brain, accompanied by changes in power levels indicated an increase of attention followed by reaction and the processing of some relevant information (stimulation) noticed by the patient.

REFERENCES

[1] M. Brazdil, *et al.,* "On the Time Course of Synchronization Patterns of Neuronal Discharges in the Human Brain during Cognitive Tasks", in *Frontiers in Human Neuroscience*, submitted for publication.

[2] M.P. van den Heuvel, *et al*., "High-cost, high-capacity backbone for global brain communication", in *Neuroscience, PNAS Early Edition*. Available: http://www.pnas.org/content/109/28/11372

[3] G. Gomez-Herrero, M. Atienza, K. Egiazarian, J. L. Cantero, "Measuring Directional Coupling between EEG Sources", in *NeuroImage*, vol. 43, 2008, pp. 497-508.

[4] M. Brazdil, *et al.,* "Directional Functional Coupling of Cerebral Rhythms Between Anterior Cingulate and Dorsolateral Prefrontal Areas During Rare Stimuli: A Directed Transfer Function Analysis of Human Depth EEG Signal", in *Human Brain Mapping*, vol. 18(4), 2009, pp. 138-146.

[5] P. Jiruska, J. Proks, O. Drbal, P. Sovka, P. Marusic, P. Mares, "Comparison of Different Methods of Time Shift Measurement in EEG", in *Physiological Research*, vol. 54(4), 2005, pp. 459-465.

[6] A. Schoegl, G. Supp, "Analysing Event-related EEG Data With Multivariate Autoregressive Parameters", in *Progress in Brain Research*, vol. 159, 2006, pp. 135-145.

[7] L. Baccala, K. Sameshima, "Overcoming the Limitations of Correlation Analysis for Many Simultaneously Processed Neural Structures", in *Progress in Brain Research*, vol. 130, 2000, pp. 33-47.

[8] P. Klimeš, *et al*., "Intracranial EEG Connectivity Analysis and Result Imaging", in *International Journal of Bioscience, Biochemstry and Bioinformatics*, Vol. 2, No. 4, 2012, pp. 275-279.