Assessment of Changes in Functional Brain Connectivity During Depression Treatment with TMS Using Granger Causality Based Methods

Gajane Mikalkeniene[1, 2], Kastytis Dapsys[1,3]

[1] Republican Vilnius Psychiatric Hospital, Vilnius, Lithuania;
[2] Faculty of Medicine, Vilnius University, Vilnius, Lithuania;
[3] Life Sciences Center, Vilnius University, Vilnius, Lithuania
gajane.marga@gmail.com

Abstract. Directed transfer function (DTF) method was used to assess brain connectivity disturbances in depression. The results were depicted as a brain model with the electroencephalographic (EEG) registration points, through which the directions of bioelectric activity transfer are defined. Transcranial magnetic stimulation (TMS) is used as an alternative treatment for drug-resistant depression and is considered to restore impaired connections. The combination of TMS and EEG allows to study changes of functional brain connectivity (FBC) in a non-invasive way. It was found that the FBC of resistant patients differed more from that of healthy subjects than in non-resistant patients. The largest changes in connectivity were identified in theta frequency.

Keywords: functional brain connectivity, electroencephalography, depression, direct transfer function, transcranial magnetic stimulation

1 Background

Granger causality based functional brain connectivity (FBC) methods allow to research connectivity disorders, such as depression. Granger causality is a statistical concept of causality based on prediction, testing whether one timeline forecasts another. In neuroscience, testing multiple timelines allows to extract directionality of brain bioelectric activity [1].

One of methods to evaluate FBC is a directed transfer function (DTF) [2]. The results of this function can be depicted by a model of the brain with the presented electroencephalographic (EEG) registration points, through which the areas of bioelectric activity and directions of activity transfer are defined. A model made with implemented directed transfer function includes all EEG channels, their connections, connection power and causal

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interactions (directionality) in specific frequency ranges [3]. The method was chosen based on the fact that different brain states in disorders are frequency-dependent, and each frequency band must be considered separately [4].

Transcranial magnetic stimulation (TMS) is used as an alternative treatment for drug-resistant depression and is considered to restore impaired connections. The combination of TMS and EEG allows to study changes in brain connectivity in a non-invasive way.

The calculation and assessment of brain connectivity can be performed with artificial neural networks, their programming and training (by machine learning), for possible prediction of changes in the connectivity of depressed patients after applying various treatment methods. This would predict which treatment would affect the brain the most and how it would be possible to achieve remission more quickly.

The aim of the study was to research functional brain connectivity during depression treatment.

2 Methods

The study was performed with 2 groups of subjects. One was a control group of 15 healthy subjects, 7 males and 8 females, who were 23–70 years old (average 46,5 ± 17,1 years). Another one was a group of drug-resistant TMS patients, 15 subjects, 7 males and 8 females, 19–70 years old (average 46,6 ± 18,6 years). All patients had recurrent depressive disorder (F33.2 according to ICD-10). From this group, 10 patients were treated with iTBS protocol stimulation at the prefrontal dorsolateral cortex (PFDLC) of the left cerebral hemisphere, 3 – high-frequency kTMS (10 Hz) at the PFDLC of the left cerebral hemisphere, the other 2 patients were treated with low-frequency kTMS (1 Hz) at the PFDLC of the right hemisphere. The used stimulation protocols were selected for each patient by a psychiatrist according to the prevailing symptoms. The procedures of the assigned protocol ranged from a total of 20 to 44 procedures over the course of the course (average 32 ± 6.6 procedures). The medication treatment of all patients was continued according to the doctor’s instructions.

Data was collected using digital EEG system Galileo Sirius Mizar with Galileo NT software (by EBNeuro, Italy) [5]. 20 electrodes (Fp1, Fp2, F7, F3, Fz, F4, F8, T3, C3, Cz, C4, T4, T5, P3, Pz, P4, T6, O1, Oz, O2) were applied.

The open-source Matlab add-on Brainstorm [6] was used for data processing and analysis [7]. This method allows the assessment of functional connectivity from the recorded EEG signal [8]. Brainstorm-based functional connectivity is known to be efficiently detected, with an average accuracy of 89% [9]. An artifact-free segment of 30 s was selected from the total EEG recording. A notch filter and a band-pass (1–40 Hz) filter were applied to the recording section. EEG data was calculated as matrices which were processed by Granger causality method to summarize it as graph and direction image.

The averages of the FBC strength were calculated for each direction in each group using the frequency-dependent spectral connectivity assessment. Between-group and within-group differences in FBC were assessed using a permutation t-test based with an adapted Monte Carlo randomization method [10]. Patient groups were evaluated before and after treatment, compared with a control group. Bonferroni correction was applied.

Further, results are presented as absolute values, in order to evaluate only the number of differences and the density of directions, in order to develop the method of FBC representation analysis proposed in this paper.

3 Results

DTF was assessed in such EEG frequency bands as delta (2–4 Hz), theta (4–8 Hz), alpha (8–12 Hz), beta (12–32 Hz), gamma (32–40 Hz). The biggest changes were noticed in theta frequency band.

28 directions of patients brain electrical activity have changed after treatment with TMS (fig, 1). Results are plotted as the connectivity graph by a chord diagram showing connectivity of the bioelectric activity areas defined by electrodes. The color of the edges shows the value of the connectivity metric. The directionality is shown with an arrowhead at the center for the arc connecting two nodes [11].

Comparing DTF between patients before (fig. 2a) and after (fig. 2b) treatment in relation to healthy subjects, 11 directions changed after treatment (fig. 2).

The results show that transcranial magnetic stimulation changes the functional brain connectivity but it still differs significantly from the healthy subjects.

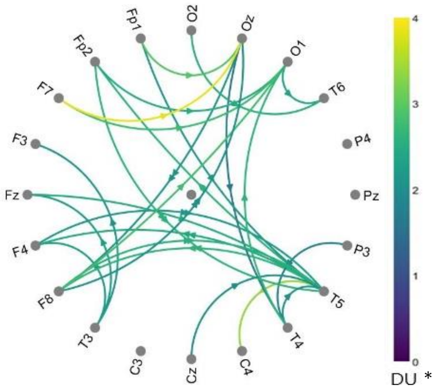

Fig. 1. Changes in brain theta band functional connectivity of depressed patients after treatment with TMS.
**DU – dimensionless units*

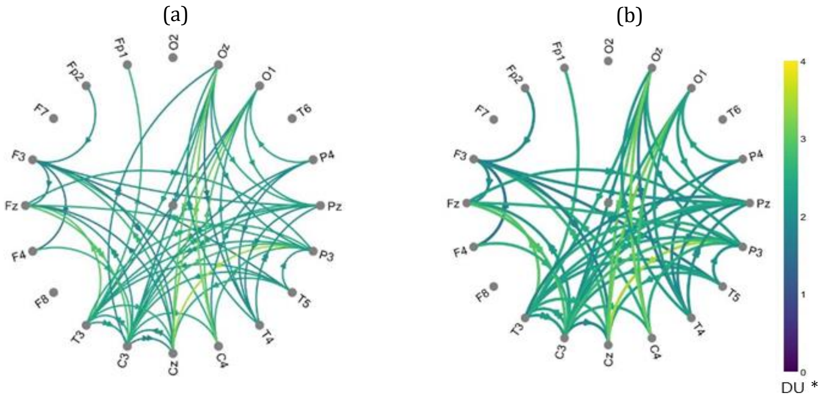

Fig. 2. Functional connectivity differences in brain theta band between patients and healthy subjects before (a) and after (b) treatment.
**DU – dimensionless units*

4 Conclusions

Directed transfer function assessment using Matlab add-on Brainstorm is an effective way of functional brain connectivity graphic evaluation. Using Brainstorm to assess patients' data it was noticed that most of changes (before-after patients' treatment and comparing with healthy subjects) were in EEG theta frequency. Using this method for assessment of bigger subject groups could show more specific tendencies of depression treatment efficacy based on EEG frequencies. Authors hypothesize that artificial neural networks based on Brainstorm calculations could be created and used as part of DTF assessment research. It could be implemented for prediction of possible medicament or TMS treatment impact on each subject's bioelectric brain activity.

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