Spectral analysis of P300 paradigm using High Density EEG in patients with schizophrenia undergoing TMS treatment

Introduction This thesis is the result of my contribution to the ongoing AVH-TMS project at Reykjavik University, Iceland, supported by the National University Hospital of Iceland.
Schizophrenia is a mental illness which has still a lot of unknown. Personalized medicine is a decisive turning point to develop targeted treatments and prevention plans for subjects with this pathology, and it becomes possible through response biomarkers. This exploratory work aims to establish a quantitative methodological tool, based on HD-EEG data analysis, to assess the effect of repetitive transcranial magnetic stimulation (rTMS) on patients with schizophrenia and auditory hallucinations (AH).
1Hz repetitive transcranial magnetic stimulation (rTMS) to the left temporoparietal cortex is considered as a potential treatment of overactive receptive language areas associated with AH. The mechanism of the effect of rTMS on AVH has only been inferred from the hypothesis and the behavioral response is variable. For this reason, physiological measures referable to specific brain areas and biomarkers of target engagement and response are needed to optimize treatment.
Event-related potentials (ERPs) to auditory oddball stimuli have been used in different studies as measures of the physiological response to TMS treatment, being considered related to abnormalities in attentional and memory processes. The P300 is the leading ERP studied as a parameter of voluntary attention.
The innovative aspect of this research was to take into account the spectral analysis of the brain neural oscillations, computing the PSD of the EEG data. The use of HD EEG with 256 electrodes attempted to overcome the spatial limitations of a standard electroencephalogram.
My contribution to the project concerned the EEG pre-processing and analysis.

Participants Ten patients diagnosed with schizophrenia were randomly divided into two groups. Five patients received ten daily sessions of 15 minutes 1Hz frequency rTMS (900 pulses/session) applied at T3-P3 location. This first group is called "treated group" (TG). Five patients received the same treatment with the same intensity but it was applied at the vertex, Cz EEG location. This second group is called "control

group" (CG). A third group of five healthy subjects who did not receive the treatment served as a comparison cohort (HS).
The data were acquired twice in each patient group; before the rTMS treatment (pre-treatment) and within one week after completing the ten sessions of rTMS treatment (post-treatment). Three scales were used to collect clinical information pre- and post-treatment: Psychotic Symptom Rating Scales (PSYRATS), Quality of Life Scale (QoLS), Depression Anxiety Stress Scale (DASS).

P300 recordings P300 experiment was measured with an auditory oddball paradigm attention task. The subjects were sitting in a comfortable chair with their eyes closed. The frequent (F) and the rare (R) auditory stimuli were presented binaurally through headphones. Each trial had 160 frequent stimuli and 40 rare stimuli.
The EEG was recorded using a 256 channel system (ANT Neuro, Netherlands) with an electrooculogram (EOG) electrode placed below the right eye and a ground electrode placed on the left side of the neck. Data pre-processing and analysis were performed with Brainstorm and MATLAB 2018b.

Pre-processing The data were sampled at 1024 Hz and re-referenced to the average of left and right mastoid electrodes (R19R, L19L). A bandpass filter was set between 0.5-70 Hz and notch filter from 49-51 Hz was used to remove undesired monomorphic artefacts from 50 Hz mains electricity. Bad channels were manually removed when EEG voltage was higher than $\pm 80\ \mu$V; if more than 10% of the channels showed too much noise or incorrect signal, the whole trial was rejected. The signals were digitized in epochs of 1200 ms starting 500 ms before the presentation of each auditory stimulus (-500 to +700 ms). Baseline correction was performed using pre-stimulus 500 ms to pre-stimulus 100 ms window and channels marked as bad were removed and interpolated. Individual trials were visually inspected and rejected when indicative of excessive muscle activity, eye movements or other artefacts.

Data analysis The epochs were averaged and the power spectral density (PSD) was computed with Welch's method, using Brainstorm, with the following frequency bands: delta (0.5–4 Hz), theta (4–8 Hz), alpha (8–13 Hz), low beta (13–18 Hz), high beta (18–30 Hz), low gamma (30–70 Hz). The PSD was divided for each frequency band

by the associated bandwidth.
Then, a statistical analysis (paired t-test) was performed between each subject within a cohort, to obtain the significant channels ($p<0.05$). We computed the averaged PSD for each band of each cohort. The different cohorts were compared to understand the behavior pre and post-treatment, the behavior between healthy subjects and the patients with schizophrenia and the different responses to frequent (F) and rare (R) stimuli. Thus, the significant channels between each cohort were intersected and the averaged PSD difference calculated. All these data were plotted according to the brain topology and the significant values were enhanced within those plots.

Results The results showed a higher PSD for the rare stimulus than for the frequent one in the alpha, low and high beta bands and confirmed what is described in the literature, i.e. a higher focus on uncommon events in frequency bands which rely on attention, focus and cognitive process. TG patients presented higher neuronal response for rare stimulus post-treatment, while for CG patients, no remarkable changes were visible to enable interpretation of the TMS effect. Considering this, the higher PSD in alpha, low beta and high beta bands post-treatment can potentially be a decent biomarker of the TMS neural response in patients with schizophrenia and AVH. These observations were consistent with the hypothesis of more effectiveness of T3-P3 rTMS, compared to vertex stimulation. The largest part of our studies was done taking into account averaged data. This choice was made to represent the general behavior of the group, but to understand if this data were representative, the spectral response of individual subjects was studied. One subject of TG and one subject of CG presented opposite behaviors from the other subjects of their groups. Because of the small number of participants, these values gave a heavy contribution to the averaged data, changing the effective result of the group.

This study is not the finish line of our project. The most important limitation is the small number of samples and we are working on new analyses of these data, trying to combine our quantitative results with qualitative clinical outcomes such as symptom severity scales and psychometric tests. This would help to establish a methodological tool to assess quantitatively the cognitive processes of people suffering of AVH.