Synopse

Study Title: E**v**a**l**uation of **tA**CS Effect by ad**v**anced Neurocomputational Methods in Schizophreni**a** (VLTAVA)

Summary:

The aims of the project are to evaluate, whether transcranial alternating current stimulation (tACS) intervention enhances cognitive functions in schizophrenia (SCH) patients, examine how this change is reflected in various neurophysiological research methods, and develop methods for advanced brain dynamics modeling and tACS-induced perturbations prediction by functional magnetic resonance imaging (fMRI) and electroencephalogram (EEG) co-registration. The study is a two-center, two-parallel-group, randomized-controlled trial with a four-week follow-up. The subjects will be enrolled and assigned into one of the two experimental study arms. The subjects will be required to complete one screening visit, two study visits (baseline and end-of-treatment), 10 treatment visits and one follow-up visit.

At the screening visit, health status will be assessed, inclusion and exclusion criteria will be verified and informed consent will be signed.

The treatment administration phase consists of 10 treatment visits, delivered five times a week.

For a detailed description of the treatment, please refer to the figure at the end of the document.

Safety measures will include documentation of adverse events (AE) during and after the procedures and if needed medical assistance.

Study Objectives:

The aim of this study is to test the efficacy of the theta-gamma tACS intervention on alleviating cognitive deficits in patients with SCH, to observe the neurophysiological correlates of these results, and to develop a model of the effect of tACS. The results could help to introduce tACS into clinical practice, and represent a suitable alternative for patients with SCH suffering from cognitive deficits. A predictive model of the effect of tACS, could serve to identify potential responders, i.e. patients who will benefit from the intervention.

In connection with the objectives, we are planning to test the following hypotheses:

We hypothesize that active tACS protocol will enhance cognitive functions, which will be reflected in improved performance in cognitive tests, namely in: higher number of correct responses, less errors, shorter reaction times. We predict that these changes in cognitive functions will be related to electrophysiological changes in measured in electroencephalogram – EEG (such as event-related potentials (ERPs), functional connectivity, power spectral density, etc.), transcranial magnetic stimulation – TMS, and combined functional magnetic resonance imaging and EEG – fMRI-EEG.

Primary Endpoint:

The primary outcome will be Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) score change in the domain Delayed memory Index, from baseline (V0) to week two (V1) between the active and sham group. Basic statistical comparison will be carried out using a Student t-test.

Secondary Endpoint

The secondary endpoints will be change in N-back test performance over the course of the intervention (Day 1 – Day 14) between the active and sham group, changes in RBANS overall score, RBANS score in domains Immediate memory, Visuospatial abilities, Language and Attention, score change in other cognitive tests (Trail Making Test – TMT, Sternberg Memory Test, Wisconsin Card Sorting Test – WCST), Positive and Negative Syndrome Scale (PANSS) scale, Speech abilities testing, EEG, fMRI-EEG and TMS signal change from baseline (V0) to week two (V1) and week six (V2), RBANS score change in Delayed memory domain from baseline (V0) to week six (V2) between the active and sham group. Post-hoc analyses will include the stratification of patients into groups according to baseline RBANS and PANSS, and development of predictive models of tACS effect.

fMR-EEG: Resting state and task related fMRI-EEG will be acquired. Seed-based and region-of-interest-based functional connectivity will be analyzed. Task related fMRI-EEG will be analyzed to assess the activity of brain networks.

EEG: Resting state and task related EEG data will be analyzed using power spectral analysis and functional connectivity analysis. Distributed source localization of selected frequency components among regions of interest will be carried out. Event-related potentials (ERPs) and mismatch negativity (MMN) will be computed from task related EEG data, with the use of Sternberg Memory Test and Auditory Oddball Task.

TMS: Measurement of motor threshold through single pulse TMS and paired pulse TMS will be conducted.

Study Population:

60 subjects. Subjects that fall within inclusion criteria, and do not meet any of the exclusion criteria will be considered for participation in the study.

Subject Inclusion Criteria

1] Male and female outpatients at age 18-70 years; 2] Meet DSM-V criteria for SCH as determined by Structured Clinical Interview for DSM-V (SCID-5); 3] The mental ability to understand and sign Informed Consent Form; 4] Being on a stable and adequate dose of antipsychotics and/or antidepressants (monotherapy or combination) for at least four weeks prior to enrollment

Subject Exclusion Criteria

Any subject who is meeting any of the following criteria will be excluded from participation in the study:

1] Psychiatric comorbidity on axis I and II according to DSM-V six months before enrollment to the study except SCH related disorders;
2] Personality disorder that makes participation in the trial difficult;
3] Substance dependence except for nicotine;
4] Substantial suicidal risk as judged by the treating psychiatrist
5] Sensory and motor disabilities precluding participation in computer-based tests
6] Electronic or metal implants in the head.

Study Duration: The estimated time required to complete the study and analyze data is sixty (60) months.

Subject Participation Duration: Subjects will be required to complete one screening visit, two study visits (baseline and end-of-treatment), 10 treatment visits and one follow-up visit. The approximate subject participation duration is approximately two (2) months from the enrollment.

Group I: active tACS Group 2: sham tACS	V -1 (inclusion)	V 0 (baseline)	Treatment 1 - 10 tACS sessions	V 1 (end of intervention)	V 2 (follow up)
Day	**-20 - -2**	**-2 - 0**	**0 - 14±2**	**14±2**	**42±2**
Informed consent	+				
Inclusion/exclusion criteria	+				
Demographic data	+				
Anamnesis (including environmental factors)	+				
Medical History	+				
Documentation of medication	+	+		+	+
PANSS		+		+	+
RBANS		+		+	+
TMT		+		+	+
WCST		+		+	+
EEG (resting state)		+		+	+
EEG (task related)		**+ only WP2**		**+ only WP2**	**+ only WP2**
Speech abilities testing		**+ only WP1**		**+ only WP1**	**+ only WP1**
TMS		**+ only WP2**		**+ only WP2**	**+ only WP2**
fMRI-EEG		**+ only WP2**		**+ only WP2**	**+ only WP2**
N-back			+		

Table 1. Assessment and other study procedures