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Transcranial alternating current stimulation for cognitive deficit in schizophrenia: effects and electrophysiological changes

Submission date
24/01/2024

Recruitment status
Recruiting

Registration date
23/02/2024

Overall study status
Ongoing

Last Edited
07/05/2025

Condition category
Mental and Behavioural Disorders

[X] Prospectively registered
[_] Protocol
[_] Statistical analysis plan
[_] Results
[_] Individual participant data
[X] Record updated in last year

Plain English summary of protocol

Background and study aims
Cognitive impairment is one of the major symptom groups in patients with schizophrenia (SCH), along with positive and negative symptoms. Reviews suggest that 80% of SCH patients suffer from some kind of cognitive impairment. Impairment in particular cognitive domains is associated with changes in brain network dynamics and endogenous oscillations. Whereas the positive and negative symptoms can be treated with a range of pharmacological agents, pharmacological treatment of cognitive symptoms does not produce sufficient results. Therefore, there is a demand for other methods and therapeutic approaches, as well as for a more detailed understanding of the underlying pathology and mechanisms of action of the proposed intervention methods. One of the possible interventions is transcranial alternating current stimulation (tACS).

TACS is one of the non-invasive brain stimulation (NIBS) methods. Using electrodes, placed on the scalp, alternating current is applied to predefined areas of the brain, and interferes with endogenous oscillations in brain networks. Dysfunctions in endogenous network oscillations have been found in SCH and linked to several SCH symptoms. As for the cognitive domain, studies suggest hyperactivation of resting-state theta phase-gamma amplitude coupling as one of the mechanisms of cognitive dysfunction, or theta band and gamma band oscillations reduction and gamma band shift in working memory (WM) task. Gamma-band oscillations over the prefrontal cortex are a correlate of performing a WM task, with a gamma power increase in higher load WM task. For SCH, tACS has a greater effect when administered in multiple sessions.

Cognitive impairment is one of the major symptom groups in patients with SCH, with a significant lack of effective treatment strategies. The underlying pathology seems to be related to disturbances in endogenous oscillations, but the exact mechanisms are not yet known. TACS might be able through manipulation of endogenous oscillations improve this cognitive impairment. The purpose of the proposed study is to evaluate the effect of 10 sessions of tACS on cognition in SCH patients. If successful, the results could help introduce tACS into clinical practice and represent a safe intervention method. Electrophysiological changes, measured on EEG, TMS and fMRI-EEG, when correlated with the results of cognitive tests, could give insights

into the pathology of cognitive impairment in SCH, with possible translation into other disorders. FMRI-EEG can distinguish the effect of tACS, which helps in gaining a deeper knowledge of brain network organization and can be used for the creation of tACS predictive models. These could potentially help stratify responders from non-responders.

Who can participate?
Adults aged 18-70 years old with SCH

What does the study involve?
The study includes a 2-week tACS treatment with ongoing assessment of clinical status and fMRI-EEG and EEG examinations before and after tACS treatment.

What are the possible benefits and risks of participating?
Benefits:
Improvement of cognition and/or overall status after tACS treatment.
Risks:
Adverse effects (AE) during tACS treatment are usually very low, with discomfort, burning feeling and phosphenes being the most common AE. This AE should not lead to withdrawal.

Where is the study run from?
National Institute of Mental Health (Czechia), Psychiatrická nemocnice Bohnice Hospital (Czechia)

When is the study starting, and how long is it expected to run for?
November 2023 to February 2029

Who is funding the study?
National Institute of Mental Health (Czechia)

Who is the main contact?
Assoc. Prof. Monika Klírová M.D., Ph.D., monika.klirova@nudz.cz

Contact information

Type(s)
Public, Scientific, Principal Investigator

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Additional identifiers

EudraCT/CTIS number
Nil known

IRAS number

ClinicalTrials.gov number
Nil known

Secondary identifying numbers
SUKL: VLTAVA_01; File No. sukls301462/2023

Study information

Scientific Title
EVaLuation of TAcs effect by adVanced neurocomputational methods in schizophreniA

Acronym
VLTAVA

Study objectives
Current study hypothesis as of 07/05/2025:
We hypothesize that an active transcranial alternating current stimulation (tACS) protocol will enhance cognitive functions, which will be reflected in improved performance in cognitive tests, namely in: a higher number of correct responses, fewer errors, and shorter reaction times. We predict that these changes in cognitive functions will be related to electrophysiological changes measured in electroencephalogram – EEG (such as event-related potentials (ERPs), functional connectivity, power spectral density, etc.), and transcranial magnetic stimulation – TMS.

Previous study hypothesis:
We hypothesize that an active transcranial alternating current stimulation (tACS) protocol will enhance cognitive functions, which will be reflected in improved performance in cognitive tests, namely in: a higher number of correct responses, fewer errors, and shorter reaction times. We predict that these changes in cognitive functions will be related to electrophysiological changes 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.

Ethics approval required
Ethics approval required

Ethics approval(s)
Approved 18/01/2024, National Institute of Mental Health Ethics Committee (Topolova 748, Klecany, 25067, Czech Republic; +420 (0)283 088 312; ek@nudz.cz), ref: 11/24

Study design
Randomized parallel-group interventional double-blind placebo-controlled trial

Primary study design

Interventional

Secondary study design
Randomised controlled trial

Study setting(s)
Hospital

Study type(s)
Treatment, Efficacy

Participant information sheet
See study outputs table

Health condition(s) or problem(s) studied
Schizophrenia

Interventions
Patients diagnosed with schizophrenia will be included in the study. Patients will be randomly allocated according to permuted block design to one of two intervention groups: active transcranial alternating current stimulation (tACS) or placebo tACS.

The study is divided into two work packages (WP):
WP 1: Randomized controlled trial with active (n=10) and sham (n=10) groups
WP 2: Randomized controlled trial with active (n=20) and sham (n=20) groups

First, the total subject count in WP1 will be recruited, subsequently moving on to WP2.

Description of Visits:
Screening Visit (V-1)
Signed informed consent
Confirm inclusion and exclusion criteria
Complete physical examination
Complete medical history, review of concomitant medications, check the adequate maintenance treatment
Randomization

Only subjects who meet all of the inclusion criteria and none of the exclusion criteria will be eligible for enrollment into the study.
An investigator will perform a thorough medical history evaluation, mainly focused on any possible contraindications, to exclude subjects with a possible confounding condition.

Baseline Visit (V0)
WP1
The following procedures/assessments will be performed: EEG Measurement (Resting state), RBANS, TMT, WCST, PANSS, Speech abilities testing
WP2
The following procedures/assessments will be performed: EEG Measurement (Resting state, Auditory Oddball Task, Sternberg Memory Test), RBANS, TMT, WCST, PANSS, Signed informed consent for fMRI-EEG, fMRI-EEG examination, TMS Measurement

Intervention Visits (Day 1 – Day 14)
The following procedures/assessments will be performed: Confirmation of inclusion and exclusion criteria, Study treatment administration, Recording of adverse events, if any

Intervention
The intervention parameters for each session are recommended as follows:
10 applications
One session per day, five times a week
Area of stimulation: F3/F4 electrode according to the 10-20 system
Patient position of application: sitting position
6-80Hz, 2mA, 20 min duration
Concomitant cognitive testing – N-back test

End-of-Intervention Visit (V1)
WP1
The following procedures/assessments will be performed: EEG Measurement (Resting state), RBANS, TMT, WCST, PANSS, Speech abilities testing

WP2
The following procedures/assessments will be performed: EEG Measurement (Resting state, Auditory Oddball Task, Sternberg Memory Test), RBANS, TMT, WCST, PANSS, fMRI-EEG examination, TMS Measurement

Follow-up Visit (V2)
During the follow-up visit, the Investigator will question the subject if any reaction or adverse event after the treatment appeared.
WP1
The following procedures/assessments will be performed: EEG Measurement (Resting state), RBANS, TMT, WCST, PANSS, Speech abilities testing

WP2
The following procedures/assessments will be performed: EEG Measurement (Resting state, Auditory Oddball Task, Sternberg Memory Test), RBANS, TMT, WCST, PANSS, TMS Measurement

Subjects who will not respond in the acute phase of the study will be treated as usual according to their psychiatrists. If the patient withdraws consent within follow-up (late drop-out), an unscheduled visit X-FU will be carried out to exclude side effects or worsening of clinical status and to record reasons for withdrawal.

Intervention Type
Device

Pharmaceutical study type(s)
Not Applicable

Phase
Not Applicable

Drug/device/biological/vaccine name(s)
DC Stimulator Mobile (Neuroconn, Germany)

Primary outcome measure
Current primary outcome measure as of 07/05/2025:
Attention domain and Total score in the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) score at baseline (V0) and week two (V1)

Previous primary outcome measure:
Delayed memory Index measured using the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) score at baseline (V0) and week two (V1)

Secondary outcome measures
Current secondary outcome measure as of 07/05/2025:
1. Changes in cognition, measured using Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) subdomains score (Immediate memory, Delayed memory, Visuospatial abilities, Language and Attention), Trail Making Test – TMT score, Sternberg Memory Test score, Wisconsin Card Sorting Test – WCST score at baseline (V0), week two (V1), and week six (V2)
2. Changes in speech abilities, measured using reading of text, free speech production, reproduction of emotional and neutral speech, and picture description at baseline (V0), week two (V1), and week six (V2)
3. Symptom severity, measured using the Positive and Negative Syndrome Scale (PANSS) at baseline (V0), week two (V1), and week six (V2)
4. Neurophysiological changes, measured using EEG and TMS signal change at baseline (V0), week two (V1), and week six (V2)
5. Cognition changes in the RBANS Attention domain and Total score at baseline (V0) and week six (V2)

Previous secondary outcome measure:
1. Changes in cognition, measured using Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) overall score, RBANS subdomains score (Immediate memory, Visuospatial abilities, Language and Attention), Trail Making Test – TMT score, Sternberg Memory Test score, Wisconsin Card Sorting Test – WCST score at baseline (V0), week two (V1), and week six (V2)
2. Changes in speech abilities, measured using reading of text, free speech production, reproduction of emotional and neutral speech, and picture description at baseline (V0), week two (V1), and week six (V2)
3. Symptom severity, measured using the Positive and Negative Syndrome Scale (PANSS) scale at baseline (V0), week two (V1), and week six (V2)
4. Neurophysiological changes, measured using EEG, fMRI-EEG, and TMS signal change at baseline (V0), week two (V1), and week six (V2)
5. Cognition changes in the RBANS subdomains Delayed memory domain at baseline (V0) and week six (V2)

Overall study start date
01/11/2023

Completion date
31/07/2029

Eligibility

Key inclusion criteria

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

Participant type(s)
Patient

Age group
Mixed

Lower age limit
18 Years

Upper age limit
70 Years

Sex
Both

Target number of participants
60

Key exclusion criteria
1. Psychiatric comorbidity on axes I and II according to DSM-V six months before enrollment to the study except for 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

Date of first enrolment
01/04/2024

Date of final enrolment
28/02/2029

Locations

Countries of recruitment
Czech Republic

Study participating centre
National Institute of Mental Health
Topolova 748
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Sponsor information

Organisation
National Institute of Mental Health

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Sponsor type
Research organisation

Website
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ROR
https://ror.org/05xj56w78

Funder(s)

Funder type
Not defined

Funder Name
National Institute of Mental Health, Czechia

Results and Publications

Publication and dissemination plan
Data will be published in peer-reviewed journals with IF (Q1, Q2) after completion of the study. Preliminary and final results will also be communicated at scientific international conferences and to the public at educational public lectures.

Intention to publish date
31/12/2029

Individual participant data (IPD) sharing plan

After the article's publication, de-anonymized data will be made available for non-commercial academic projects. Data can be obtained by request to the corresponding author (Monika Klírová, monika.klirova@nudz.cz). The de-anonymized data files with a dictionary will be provided via a secure data transfer service.

IPD sharing plan summary

Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Participant information sheet	Bohnice Psychiatric Hospital (Psychiatrické nemocnici Bohnice; PNB) in Czech		30/01/2024	No	Yes
Participant information sheet	in Czech		30/01/2024	No	Yes
Participant information sheet	in Czech		30/01/2024	No	Yes