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Transcranial direct current stimulation (tDCS) in the treatment of neuropsychiatric symptoms of post-COVID syndrome (long COVID)

Submission date
01/04/2022

Recruitment status
No longer recruiting

Registration date
06/05/2022

Overall study status
Completed

Last Edited
28/02/2024

Condition category
Mental and Behavioural Disorders

[_] Prospectively registered
[_] Protocol
[X] Statistical analysis plan
[X] Results
[_] Individual participant data

Plain English summary of protocol

Background and study aims
The post-acute sequelae of SARS-CoV-2 infection (PASC) is a syndrome of persistent symptoms after COVID-19 lasting more than one month. Neuropsychiatric (NP) symptoms, including functional impairment, cognitive dysfunction, and emotional dysregulation are among the most common manifestations of PASC. Non-invasive brain stimulation (NIBS) could be a treatment method for post-acute and chronic stages of COVID-19. The first clinical results suggest the therapeutic potential of transcranial direct current stimulation (tDCS) in influencing PASC symptoms.
Transcranial direct current stimulation (tDCS) uses constant, low direct current delivered via electrodes on the head to stimulate activity in brain cells.
The aim of the project is to conduct a study to evaluate the efficacy and safety of tDCS in the treatment of PASC. The study will further map the side effects of tDCS (such as a tingling or burning during tDCS application) and electroencephalographic (EEG) changes.

Who can participate?
Adults aged 18-75 years with a history of COVID-19 and mental disorders

What does the study involve?
The study includes clinical examinations of post-covid symptoms, cognitive testing, EEG, and tDCS treatment.
The study will evaluate the symptoms of PASC before, at the end of the tDCS treatment phase of the study (after 4 weeks), and after a four-week follow-up

What are the possible benefits and risks of participating?
The possible benefit is neuropsychiatric symptoms amelioration of the post-acute sequelae of Covid (PASC).
The possible risks are TDCS adverse effects such as tingling, mild burning, itching at the place of tDCS application during stimulation, or transient headache and a feeling of fatigue immediately after tDCS application.

Where is the study run from?
National Institute of Mental Health (Czechia)

When is the study starting and how long is it expected to run for?
November 2021 to December 2023

Who is funding the study?
Czech Health Research Council (Agentura Pro Zdravotnický Výzkum České Republiky)

Who is the main contact?
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Contact information

Type(s)
Principal investigator

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Additional identifiers

Clinical Trials Information System (CTIS)
Nil known

ClinicalTrials.gov (NCT)
Nil known

Protocol serial number
NU 22-D-133 of the MH, CR

Study information

Scientific Title
Transcranial direct current stimulation (tDCS) as a therapeutic intervention for post-acute sequelae of SARS-CoV-2 (PASC)

Study objectives

Current study hypothesis as of 10/11/2023:
1. DLPFC-tDCS will lead to a significant reduction in the overall Fatigue Impact Scale (FIS) score after four weeks of treatment and in subsequent monitoring (FU-4W) compared to placebo-tDCS.
2. DLPFC-tDCS will lead to a significant reduction in the overall Post-COVID-19 Symptom Assessment Questionnaire (A-PASC) score and in A-PASC score in the domains of functional abilities, emotional symptoms, and cognitive functions after four weeks of treatment compared to placebo-tDCS.
3. DLPFC-tDCS will lead to a significant reduction in overall Patient Health Questionnaire (PHQ-9) and General Anxiety Disorder (GAD-7) scores after four weeks of treatment and in subsequent monitoring (FU-4W) compared to placebo-tDCS.
4. DLPFC-tDCS will lead to a significant increase in performance compared to placebo-tDCS in the Digit Span and Digit Symbol Substitution tests after four weeks of treatment and in subsequent monitoring (FU-4W).
5. DLPFC-tDCS will lead to a significant increase in quality of life scores in all domains as measured by the Assessment Quality of Life questionnaire (AQoL-6D) at the end of treatment and in subsequent monitoring (FU-4W) compared to placebo-tDCS.
6. DLPFC-tDCS will lead to significant qEEG changes compared to placebo-tDCS, namely the change in EEG microstates and functional connectivity after two weeks of treatment and at the end of treatment.
7. The change in total FIS, A-PASC, PHQ-9, and GAD-7 scores at the end of treatment will correlate with qEEG changes (EEG microstates, Θ-functional connectivity) at the end of treatment.

Previous study hypothesis:
1. DLPFC-tDCS will lead to a significant reduction in the overall Fatigue Impact Scale (FIS) score after 4 weeks of treatment and in subsequent monitoring (FU-4W) compared to placebo-tDCS.
2. DLPFC-tDCS will lead to a significant reduction in the overall Post-COVID-19 Symptom Assessment Questionnaire (A-PASC) score and in A-PASC score in the domains of functional abilities, emotional symptoms, and cognitive functions after 4 weeks of treatment and in subsequent monitoring (FU-4W) compared to placebo-tDCS.
3. DLPFC-tDCS will lead to a significant reduction in overall Patient Health Questionnaire (PHQ-9) and General Anxiety Disorder (GAD-7) scores after 4 weeks of treatment and in subsequent monitoring (FU-4W) compared to placebo-tDCS.
4. DLPFC-tDCS will lead to a significant increase in performance compared to placebo-tDCS in the Digit Span and Digit Symbol Substitution tests after 4 weeks of treatment and in subsequent monitoring (FU-4W).
5. DLPFC-tDCS will lead to a significant increase in quality of life scores in all domains as measured by the Assessment Quality of Life questionnaire (AQoL-6D) at the end of treatment and in subsequent monitoring (FU-4W) compared to placebo-tDCS.
6. DLPFC-tDCS will lead to significant qEEG changes compared to placebo-tDCS, namely a reduction in mean theta (Θ) band concordance, EEG micro-states, and Θ-functional connectivity after 2 weeks of treatment and at the end of treatment.
7. The change in total FIS, A-PASC, PHQ-9, and GAD-7 scores at the end of treatment will correlate with qEEG changes (decreased Θ concordance; EEG microstates, Θ-functional connectivity) at the end of treatment.

Ethics approval required
Ethics approval required

Ethics approval(s)

approved 16/11/2021, National Institute of Mental Health Ethics Committee (Topolova 748, , Klecany, 250 67, Czech Republic; +420 (0)283 088 312; ek@nudz.cz), ref: č.j.169/21

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

Primary study design
Interventional

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Post-acute sequelae of SARS-CoV-2 infection (PASC)

Interventions
Patients included in the study will be examined by FIS, A-PASC, AQoL, PHQ, GAD-7, and Clinical Global Impression (CGI) questionnaires to determine neuropsychiatric symptoms and the current symptom severity at study entry, at initiation, during (after 2 weeks), at the end of 4 weeks of tDCS treatment and with an interval of 4 weeks after. Attention-oriented cognitive tests (computer variant) (Digit Span - forward span), working memory (Digit Span - backwards span) and psychomotor tempo (Digit Symbol Substitution Test) will be performed at the beginning and subsequent follow-ups. In addition, three EEG examinations will be performed during the study (before the start of tDCS, after two weeks of tDCS, and at the end of tDCS treatment).
Patients will be randomly allocated according to permuted block design to one of two intervention groups: active anodal tDCS or placebo anodal tDCS.
Each tDCS session (active or placebo) will last 30 minutes. A total of 20 tDCS sessions will be administered to patients over four weeks.
The HDCStim programmable stimulator (Newronika, Italy) available for a double-blind design will be used for the application of tDCS.

Intervention Type
Device

Phase
Not Applicable

Drug/device/biological/vaccine name(s)
HDCStim programmable stimulator (Newronika, Italy)

Primary outcome(s)
Current primary outcome measure as of 10/11/2023:
Czech version of the “Fatigue Impact Scale“ (FIS) score after the acute phase of the study

Previous primary outcome measure:
Czech version of the “Fatigue Impact Scale“ (FIS) score after the acute phase of the study and after the 4W-FU

Key secondary outcome(s))

Current secondary outcome measure as of 10/11/2023:
1. The change in the following measurements after the acute phase of the study and after the 4W-FU:
1.1. Functional ability, cognitive functions, and emotional symptoms subscales of the “Post-COVID-19 Symptoms Assessment Questionnaire” (A-PASC)
1.2. Self-assessment scales of depressive and anxiety symptoms (PHQ-9; GAD-7)
1.3. Cognitive testing focused on attention, working memory, and psychomotor pace
1.4. Quality of life monitoring based on the AQOL-6D questionnaire
2. Evaluation of tDCS side effects during tDCS treatment by the investigator
3. Electrophysiological (EEG) parameters associated with PASC and their changes after the intervention (specifically EEG and functional connectivity will be evaluated)

Previous secondary outcome measure:
1. The change in the following measurements after the acute phase of the study and after the 4W-FU:
1.1. Functional ability, cognitive functions, and emotional symptoms subscales of the “Post-COVID-19 Symptoms Assessment Questionnaire” (A-PASC)
1.2. Self-assessment scales of depressive and anxiety symptoms (PHQ-9; GAD-7)
1.3. Cognitive testing focused on attention, working memory, and psychomotor pace
1.4. Quality of life monitoring based on the AQOL-6D questionnaire
2. Evaluation of tDCS side effects during tDCS treatment by the investigator
3. Electrophysiological (EEG) parameters associated with PASC and their changes after the intervention (specifically qEEG concordance, EEG microstates, and functional connectivity will be evaluated)

Completion date
31/12/2023

Eligibility

Key inclusion criteria
Current participant inclusion criteria as of 10/11/2023:
1. Male and female outpatients aged 18-75 years with a history of COVID-19 and monitored by an outpatient physician for mental disorders (anxiety, mood disorders, sleep) within the PASC
2. PCR RNA SARS-CoV-2 negativity at screening/study entry
3. Duration of symptoms >1 and ≤24 months after detection of COVID-19
4. The mental ability to understand and sign the Informed Consent Form
5. Presence of neuropsychiatric PASC symptoms as determined by A-PASC with a minimum overall score ≥25 (cognitive score, emotional and functional impairment)
6. FIS questionnaire score ≥40
7. Psychopharmacological medication (if used) at a stable dose ≥4 weeks.

Previous participant inclusion criteria:
1. Male and female outpatients aged 18-75 years with a history of COVID-19 and monitored by an outpatient physician for mental disorders (anxiety, mood disorders, sleep) within the PASC
2. PCR RNA SARS-CoV-2 negativity at screening/study entry
3. Duration of symptoms >1 and ≤18 months after detection of COVID-19
4. The mental ability to understand and sign the Informed Consent Form
5. Presence of neuropsychiatric PASC symptoms as determined by A-PASC with a minimum

overall score ≥25 (cognitive score, emotional and functional impairment)
6. FIS questionnaire score ≥40
7. Psychopharmacological medication (if used) at a stable dose ≥4 weeks.

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 years

Upper age limit
75 years

Sex
All

Total final enrolment
33

Key exclusion criteria
1. Contraindications of tDCS (skin disease, superficial injury, and fracture or infraction of skull in the stimulation area, epilepsy, metallic plates in the head)
2. History of any other DSM-IV axis I diagnosis prior to COVID-19, except for:
2.1. Depressive disorders, anxiety disorders, and sleep disorders that may be present in the history, but with at least 6 months of documented remission of symptoms
2.2. Disorders associated with the use of addictive substances at least 6 months before entering the study
3. Pregnancy or breastfeeding
4. Patients with severe and/or unstable somatic disorders (cardiovascular disease, neoplasms, endocrinology disorders, etc)
5. Patients suffering from a serious neurological disorder (eg epilepsy, head injury with loss of consciousness)

Date of first enrolment
15/03/2022

Date of final enrolment
31/12/2022

Locations

Countries of recruitment
Czech Republic

Study participating centre
National Institute of Mental Health
Topolova 748
Klecany
Czech Republic
250 67

Sponsor information

Organisation
Czech Health Research Council

Funder(s)

Funder type
Research council

Funder Name
Agentura Pro Zdravotnický Výzkum České Republiky

Alternative Name(s)
Czech Health Research Council, AZV ČR

Funding Body Type
Government organisation

Funding Body Subtype
Local government

Location
Czech Republic

Results and Publications

Individual participant data (IPD) sharing plan
Available on request
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IPD sharing plan summary
Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article		25/01/2024	28/02/2024	Yes	No
Participant information sheet	Participant information sheet	11/11/2025	11/11/2025	No	Yes
Statistical Analysis Plan			13/11/2023	No	No