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Understanding mild cognitive impairment through multimodal biomarkers and brain stimulation

Submission date 26/05/2026	**Recruitment status** Recruiting	[_] Prospectively registered [_] Protocol [X] Statistical analysis plan [_] Results [_] Individual participant data [X] Record updated in last year
Registration date 22/09/2026	**Overall study status** Ongoing	
Last Edited 22/09/2026	**Condition category** Mental and Behavioural Disorders	

Plain English summary of protocol
Not provided at time of registration

Contact information

Type(s)
Scientific, Principal investigator, Public

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Study information

Scientific Title
Investigating the Mechanisms of MIld Cognitive Impairment using Multimodal BiomarkERs and Non-InVAsive Brain Stimulation (MINERVA): a study in older adults with mild cognitive

impairment and healthy controls comparing active and sham theta transcranial alternating current stimulation on homeostatic plasticity, neurophysiological biomarkers, and cognitive performance

Acronym
MINERVA

Study objectives
Overall Study Objective:
The main objective of this study is to explore the role of homeostatic plasticity in the onset and progression of mild cognitive impairment (MCI) using transcranial magnetic stimulation (TMS), while simultaneously examining its relationship with multimodal biomarkers (MRI, EEG, blood NF-L, and tau protein) and assessing the effect of theta transcranial alternating current stimulation (theta-tACS) on behavioral and physiological changes.

Specific Objectives:
1. To evaluate the role of homeostatic plasticity in healthy and MCI subjects using a TMS algorithm that incorporates facilitative preconditioning with tDCS and rTMS and to correlate these findings with cognitive performance and multimodal MCI biomarkers.
2. To evaluate the predictive value of active versus sham theta-tACS on behavioral and physiological changes associated with MCI development, with a particular focus on the modulation of homeostatic plasticity parameters.

Ethics approval required
Ethics approval required

Ethics approval(s)
Approved 14/08/2025, The Ethical Committee of National Institute of Mental Health (Topolová 748, Klecany, 250 67, Czech Republic; +420 (0)283088312; martin.bares@nudz.cz), ref: 113/25

Primary study design
Interventional

Allocation
Randomized controlled trial

Masking
Blinded (masking used)

Control
Placebo

Assignment
Parallel

Purpose
Diagnostic, Treatment

Study type(s)

Health condition(s) or problem(s) studied

Diagnosis and treatment of mild cognitive impairment (MCI) in older adults

Interventions

Observational Phase:
Participants (older adults with Mild Cognitive Impairment [MCI] and healthy age-matched controls) undergo a series of baseline diagnostic measurements. These include cognitive performance testing (Montreal Cognitive Assessment [MoCA] and computerized tests: Paired Associate Learning Task, Digit Span, Tower of London), structural magnetic resonance imaging (MRI; 3D T1 and 3D T2-FLAIR), resting-state electroencephalography (EEG), and blood sample collection for neurofilament light chain (NF-L) and tau protein analysis. Additionally, participants undergo transcranial magnetic stimulation (TMS) measurements to assess cortical excitability and homeostatic plasticity, utilizing short intracortical inhibition (SICI), intracortical facilitation (ICF), and long intracortical inhibition (LICI) protocols, paired with anodal transcranial direct current stimulation (tDCS) and repetitive TMS (rTMS) preconditioning.

Interventional Phase:
Participants with MCI are randomly allocated to one of two parallel groups using a permuted block design with a fixed block size of 4.

Active Intervention Group:
Participants receive active theta transcranial alternating current stimulation (theta-tACS). The stimulation is applied via round conductive rubber electrodes at the F3-F4 EEG electrode positions. A current of up to 2 mA peak-to-peak (based on individualized current density estimation) at 4 Hz is administered for 20 minutes per session.

Control Group:
Participants receive placebo (sham) tACS. Electrodes are placed in the same F3-F4 positions, but the current remains close to 0 mA, except for a 90-second duration at the beginning and end of the session to mimic the physical sensation of active stimulation.

Administration and Follow-Up:
For both interventional arms, the schedule consists of 3 sessions per week, totalling 12 sessions over a 4-week period. After initial training in the laboratory, subsequent tACS applications are self-administered by the participant at home with online assistance from a researcher. All participants (both MCI and healthy controls) undergo follow-up cognitive testing at 1 year post-intervention.

Description of Visits:
Screening Visit (V-1) [Day -20 to -1]
The following procedures/assessments will be performed:
1. Signed informed consent
2. Confirmation of inclusion and exclusion criteria
3. Demographic data collection
4. Anamnesis (environmental factors) and complete Medical History
5. Documentation of medication (check for adequate maintenance medication)
6. Assessment of Montreal Cognitive Assessment (MoCA) scale

Between Screening Visit and Day 1, an MRI examination (Visit M) will be performed as a separate procedure prior to the baseline.

Baseline Visit (V0) [Day 0 to 1]
The following procedures/assessments will be performed for all participants:

1. Documentation of medication
2. Assessment of MoCA scale
3. Cognitive tests
4. EEG measurement
5. TMS measurement (including preconditioning tDCS and rTMS)
6. Blood collection

WP2 (MCI group only):
Randomization (permuted block design with a fixed block size of 4 to active or sham tACS group)
The tES questionnaire and potentially the first tACS session may occur during this visit.

Intervention Visits (T1 – T12) [Days 2 – 30]
Applies only to WP2 (MCI group)
The following procedures/assessments will be performed:
1. Study treatment administration (tACS)
2. tES questionnaire (recording of side/adverse events)

Intervention: 12 sessions in total (three sessions per week)

Intervention parameters:
Duration: 20 minutes/session
Area of stimulation: F3-F4 EEG electrode positions
Patient position of application: sitting position
Active group: 2 mA peak-to-peak current intensity, frequency 6 Hz - 80 Hz.
Sham group: Current close to 0 mA, except for a 90s ramp-up/ramp-down duration at the beginning and the end of the session.

End-of-Intervention Visit (V1) [Day 30 ± 2]
The following procedures/assessments will be performed:
1. Assessment of MoCA scale
2. Cognitive tests
3. EEG measurement
4. TMS measurement (including preconditioning tDCS and rTMS)
5. Blood collection
6. WP2 (MCI group only): Side/adverse effect questionnaire (tES questionnaire) completion (if not fully completed at the end of T12).

WP2: Follow-up Visit (V2) [1-year FU]
The following procedures/assessments will be performed:
1. Documentation of medication
2. Assessment of MoCA scale
3. Cognitive tests

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

Phase
Not Applicable

Drug/device/biological/vaccine name(s)
HDCStim stimulator (NeuroConn)

Primary outcome(s)
1. Homeostatic plasticity assessed by changes in motor evoked potential (MEP) amplitude in MCI patients compared to healthy controls, measured using single-pulse TMS measurements - peak-to-peak amplitude of MEPs recorded via surface electromyography (EMG) of the right first dorsal interosseous (FDI) muscle, before and after facilitatory preconditioning (anodal tDCS and 5 Hz rTMS) at baseline

2. Homeostatic plasticity assessed by changes in MEP amplitude in MCI patients measured using single-pulse TMS measurements - peak-to-peak amplitude of MEPs recorded via surface electromyography (EMG) of the right first dorsal interosseous (FDI) muscle, before and after facilitatory preconditioning (anodal tDCS and 5 Hz rTMS) at baseline and 4 weeks (immediately post-intervention)

Key secondary outcome(s)
1. Cognitive performance measured using global cognitive status assessed by the Montreal Cognitive Assessment (MoCA) and specific cognitive domains (memory, executive functions, attention) measured via computerized tasks: Spatial Paired Associate Learning Task (S-PALT), Digit Span (DS) at baseline and at 4 weeks (post-intervention)

2. EEG spectral power and connectivity measured using resting-state electroencephalography (EEG) recording using a 64-channel system, focusing on spectral power changes (specifically in theta and alpha bands) and functional connectivity measures to assess neural oscillation normalization, at baseline and at 4 weeks (post-intervention)

3. Plasma levels of neurodegeneration biomarkers measured using concentrations of neurofilament light chain (NF-L) and Tau protein (total tau and p-tau181) measured from peripheral blood samples through Single Molecule Array (Simoa) technology at baseline and at 4 weeks (post-intervention)

4. Structural brain changes and white matter integrity measured using magnetic resonance imaging (MRI) assessing hippocampal volume and periventricular white matter hyperintensities (WMH) using 3D T1-weighted and 3D T2-FLAIR sequences at baseline and at 4 weeks (post-intervention)

Completion date
01/06/2029

Eligibility

Key inclusion criteria
MCI:
1. Males and females aged 65 years and older with single- and multiple-domain amnestic MCI
2. Meet Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-V) criteria for Mild Neurocognitive Disorder as determined by Structured Clinical Interview for DSM-V (SCID-5)
3. The mental ability to understand and sign the Informed Consent Form
4. Montreal Cognitive Assessment (MoCA) score from 19 to 25

Age-matched controls:
1. Healthy males and females aged 65 years and older without single- and multiple-domain amnestic MCI and without subjective cognitive decline
2. The mental ability to understand and sign the Informed Consent Form
3. MoCA score ≥26

Healthy volunteers allowed
Yes

Age group
Senior

Lower age limit
65 Years

Upper age limit
100 Years

Sex
All

Total final enrolment
0

Key exclusion criteria
1. Psychiatric comorbidity on axis I and II according to DSM-V 6 months before enrolment in the study
2. Personality disorder that makes participation in the trial difficult
3. History of substance dependence in the last year except for nicotine
4. Contraindications of TMS and tES: history of epilepsy or any neurologic condition likely to increase risk of seizure, mass brain lesions, cerebrovascular accident, metal in the head, a history of major head trauma with unconsciousness longer than 5 minutes), skin diseases (contraindications to tES)
5. Subjects with severe somatic disorders (cardiovascular disease, neoplasms, endocrinological disorders, etc)
6. Subjects treated with electroconvulsive therapy less than 3 months before enrollment or suffering from neurologic disorder (e.g., epilepsy, head trauma with loss of consciousness) and subjects using any treatment which can strongly affect EEG
7. Substantial suicidal risk as judged by the treating psychiatrist
8. Sensory and motor impairment precluding the participation on computer tests
9. Claustrophobia

Date of first enrolment
01/06/2026

Date of final enrolment
01/06/2028

Locations

Countries of recruitment
Czech Republic

Germany

Sponsor information

Organisation
National Institute of Mental Health

ROR
https://ror.org/05xj56w78

Funder(s)

Funder type

Funder Name
Ministry of Health of the Czech Republic

Results and Publications

Individual participant data (IPD) sharing plan
The datasets generated during and/or analysed during the current study will be available upon request and will be published as a supplement to the results publication. Data will be made available following study completion through the European Open Science Cloud (EOSC) Portal (https://eosc-portal.eu/) in accordance with FAIR principles. Data will be stored pseudonymised in RedCap (NIMH) and secuTrial® (UMG) databases, accessible only to authorised personnel in compliance with EU GDPR. Data types include behavioural data, assessment scales, electrophysiological data (EEG, TMS), MRI/fMRI, and physiological data.

IPD sharing plan summary
Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Statistical Analysis Plan			26/05/2026	No	No