# Improving executive functioning in patients with Mild Cognitive Impairment by transcranial alternate current brain stimulation

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We hypothesize that synchronous tACS in the theta range will cause an enhancement of fronto-parietal brain synchronization and improvement in EF of MCI patients.We aim to apply tACS in the theta range over the left frontal and parietal areas of...

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| **Ethical review** | Approved WMO |
| **Status** | Recruiting |
| **Health condition type** | Neurological disorders NEC |
| **Study type** | Interventional |

## Summary

### ID

NL-OMON48713

**Source**
ToetsingOnline

**Brief title**
Cognitive function in MCI after tACS

### Condition

- Neurological disorders NEC

**Synonym**
cognitive impairment, dementia, MCI, nervous system

**Research involving**
Human

### Sponsors and support

**Primary sponsor:** Universitair Medisch Centrum Groningen

**Source(s) of monetary or material Support:** ZonMW Memorabel grant Projectnumber 733050836 to B Curcic-Blake for project entitled "Mild Cognitive Impairment by transcranial alternate current brain stimulation" ; Fellowhip program of Alzheimer Nederland No WE15-2017-04 to F. Flores Vasquez

## Intervention

**Keyword:** Cognition, Mild Cognitive impairment (MCI), Neurostimulation, transcranial alternating current stimulation (tACS)

## Outcome measures

### Primary outcome

After two-weeks stimulation:

- Change in fronto-temporal synchronization (measured by resting state EEG).

- Change in working memory measured with the off-line n-back task and WAIS-WM.

- Decreased reaction time (VRRT).

### Secondary outcome

- Improvement in daily activities (IADL), functional connectivity (fMRI) during

task and rest, general executive functioning and memory performance after two

weeks of stimulation.

- Duration of effects (up to one year).

- Correlation of salivary levels of lactoferrin with change in EEG

synchronization and cognitive performance

# Study description

### Background summary

MCI is characterized by changes in cortical neural networks related to decline in EF. Executive functioning (EF) refers to the set of cognitive functions involved in controlling or guiding behaviour, involving among others attention, working memory and inhibition, in addition to planning ability and mental

flexibility (i.e. being able to switch between tasks). MCI is a prodromal phase of neurodegenerative diseases of aging. Approximately 27-49% of MCI patients develop full AD within 30 months. This is however, not limited to AD, some types of MCI develop in other forms of dementia.

In addition to the EF impairment, MCI patients have brain network changes intermediate between healthy elderly and AD patients. This is why a treatment that could improve the brain network function should be addressed also to MCI patients. By improving EF in MCI patients, one might delay the onset of neurodegenerative diseases. Working memory abilities, a critical component of EF, have been shown to contribute significantly to functional status in MCI . This affects the prognosis of MCI and AD. Furthermore, effective treatment can be used to decrease the severity of symptoms in AD and other dementias. This directly reflects on the everyday functioning of MCI patients .

The deficiencies in EF in MCI patients are coupled with compromised brain functioning visible from electroencephalography (EEG). Particularly, decreased power in the theta range (6-8Hz) of the EEG during working memory and cognitive control seem to be specific for MCI patients who progress to AD. Brain oscillations and fronto-parietal synchronization in the theta range are associated with various aspects of EF. Therefore, improving the fronto-parietal theta synchronization in patients with MCI has the potential to improve EF.

tACS affects brain function such as memory and EF in healthy adults by targeting specific brain oscillations at specific frequencies. The tACS delivered at a specific frequency affects the brain rhythms at that frequency. This is called entrainment.
We will base our two experimental conditions of tACS stimulation on the study by Polania et al. (2012) and the study by Vosskhul et al. (2015), respectively.

**Study objective**

We hypothesize that synchronous tACS in the theta range will cause an enhancement of fronto-parietal brain synchronization and improvement in EF of MCI patients.

We aim to apply tACS in the theta range over the left frontal and parietal areas of patients with amnestic MCI (aMCI) to improve their executive functioning (EF). We will assess the effect of two types of tACS by investigating brain synchronization, cognitive abilities and daily activities of patients on several time points during one year after the treatment.

**Study design**

To investigate effectiveness of the tACS treatment and to find the most effective stimulation type, three groups of amnestic MCI (aMCI) patients (n=90)

will randomly receive either tACS active treatment (two groups; n = 30 for each active group) or a placebo (n=30), daily for two weeks. Active group 1 will receivetACS at 6 Hz (protocol by Polania et colleagues (2012)). Active group 2 will receive tACS at the individual relevant frequency as used by Vosskuhl (2015). Synchronous tACS (1mA peak-to-peak amplitude) will be delivered on the frontal and parietal lobe symoultaneously (F3 and P3) while performing a two-letter delayed task, which is a task suitable for patients with cognitive problems and the digit span task (forward and backward condition.
We will assess the following at day 1 and month 12:
- EEG resting state (5 mins; for measuringsynchrony).
- N-back working memory task. This task will be different from the task used during tACS stimulation. In stead of using letters, numbers will be used.
- Vienna Reaction time task (VRTT)
- The Mini Mental State Exam (MMSE)
- Instrumental activity of daily living (IADL) and functional activity questionnaire (FAQ) (for daily activities).
- Face-name-associative memory test (FNAME)
- Neuropsychological evaluation (NPE) will consist of:
- 15-word memory test (immediate and delayed recall; 4 different versions).
- WAIS Digit Span test: Forward, Backward and arithmetic
- Trail making test
- Verbal fluency tasks (semantic and letter fluency).
- Stroop test
- Digit span
- Symbol digit substitution test
- Amsterdamse korte termijn geheugentest (AKTG) - short version
- Key search (BADS)
- Mild Behavioral Impairment Checklist (MBI-C) Nederlandse versie (MBI-C-NL)

We will assess the following at day 11an month 1,
- EEG resting state (5 mins; for measuringsynchrony).
- N-back working memory task. This task will be different from the task used during tACS stimulation. In stead of using letters, numbers will be used.
- Vienna Reaction time task (VRTT)
- Instrumental activity of daily living (IADL)
- Neuropsychological evaluation (NPE) will consist of:
- 15-word memory test (immediate and delayed recall; 4 different versions).
- WAIS Digit Span test: Forward, Backward and arithmetic
- Trail making test
- Verbal fluency tasks (semantic and letter fluency).
- Stroop test

- Digit span
- Symbol digit substitution test
- Mild Behavioral Impairment Checklist (MBI-C)
Nederlandse versie (MBI-C-NL)
Salivary levels of lactoferrin will be collected at day 2.
Neuroimaging
We will use fMRI (day 2 and 11) to investigate brain network functioning during working memory (n-back task, ~10 minutes) and resting state.Anatomical features (used as cofounding variables) will be assessed using a T1 scan: diffusion tensor imaging (DTI), magnetic transfer imaging (MTI) and Magnetic resonance spectroscopy. MR-scans (including fMRI) will be made both at baseline and after 2 weeks of treatment.
EEG will be recorded for approximately 10 minutes. We aim to record a segment of 5 minutes with minimum artifacts. This segment will be used for coherence analysis. Coherence will be estimated using the weighted phase lag index which has an advantage over other methods as not being affected by volume conductance of independent sources, and increased power to detect changes in phase-synchronization .
The outcomes on VRTT will be compared using repeated measures ANOVA with factors: the condition (visual or auditory) and time of stimulus (pre or post).
If participants take part in the additional session, they will undergo a more extensive EEG and psychological assessment including Cognitive Reserve Index Questionnaire and the Behavioral dysexecutive syndrome inventory.

### Intervention

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### Study burden and risks

Participants in the study will go through 13 session that will take place across 1 year. The initial step will be NPE testing (70 minutes). If the patients fulfill CI criteria, she/he will undergo the second step a pre-stimulation an MRI scanning session (60 minutes). The same day patients will undergo an EEG session (10 minutes recording and 20 minutes preparation time, total 30 minutes). After the EEG, participants will fill perform cognitive Vienna reaction time task (14 minutes). And eventually first tACS session (18 minutes stimulation and 10 minutes preparation). On the third to 10th day, participants will undergo brain stimulation (tACS or sham tDCS). The stimulation session will last 28 minutes (preparation: 10 minutes, stimulation: 18 minutes). On the 11th day, participants will undergo the brain stimulation followed by brief EEG recording, VRTT, NPE and MRI. If patients express that the second day or the tenth day last too long, we might split it in two days, Further, we will offer participants a time to relax or have lunch in between MRI and other measurements. This will be adjusted solely to decrease the burden to patients as much as possible. Maximum 20 of 90 participants, that are not

MRI compatible, will not undergo the MRI sessions.
Further, we might offer participants, in case of too high burden of frequent visits and if possible to research team, to deliver some tACS sessions at their home. These issues were discussed with our expert by experience. It is important to measure the post-stimulation EEG and the VRTT immediately after the last stimulation thus the final tACS has to be coupled with the post-stimulation VRTT and EEG. In addition, patients will come for follow up at months 1 and 12. In addition, before and after the stimulation, patients will fill in one questionnaire at their home - the hybrid-computer-based-executive-function test which takes 55 minutes, and they have to fill in TOPICS_MDS questionnaire that is complying with Memorabel grant requirements.

The experiment will not involve more than minimal risks for the participants. MRI is a standard brain imaging technique with no known negative effects on health. The only risks are for subjects with cardiac pacemaker and metal implants. These individuals will not be allowed to participate. In terms of burden, MRI involves lying still in a confined environment during one hour. In addition, during data acquisition, the MRI scanner makes a loud noise, and although participants are provided with earplugs, the residual noise can be a burden for some individuals. During the tACS procedure participants are exposed to a very low electrical current of 2 mA. The use of tACS to date has not resulted in adverse effects, apart from mild headache or a mild tingling sensation underneath the electrodes. Finally, EEG involves a measurement of brain currents and is not associated with any contraindication.
Salivary collection is quick and adds little extra burden to patients. In addition, participants will be offered an optional additional session that will take place before the first stimulation session and last for 2 hours.

## Contacts

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# Trial sites

## Listed location countries

Netherlands

# Eligibility criteria

**Age**
Adults (18-64 years)
Elderly (65 years and older)

## Inclusion criteria

Diagnosis of aMCI based on neurologists evaluation.
Age >=50 years
aMCI will be defined as having a verbal memory score 1.5 standard deviations below the normative control values on both sub-scales.
Signed written informed consent.

## Exclusion criteria

1. History of psychiatric or neurological illness other than MCI
2. Metal implants (e.g., pacemaker, heart valves, vascular clips, eye-implants, copper containing intra-uterine devices, non-removable piercing, cerebral implants)
3. Any risk of having metal particles in the eyes
4. Tattoos containing iron oxide (often found in red pigments)
5. Claustrophobia
6. Alcohol or drug abuse
7. Excessive intake alcohol (>2 units per day);
8. Recent use of alcohol (2 days before the EEG and/or fMRI measurement).
9. Refusal to be informed of structural brain abnormalities that could be detected using MRI during the experiment
10. Severe scalp skin lesions
11. Color blindness

# Study design

## Design

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| Study type: | Interventional |
| Intervention model: | Parallel |
| Allocation: | Randomized controlled trial |
| Masking: | Double blinded (masking used) |
| Control: | Active |
| Primary purpose: | Treatment |

## Recruitment

NL

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| Recruitment status: | Recruiting |
| Start date (anticipated): | 08-11-2018 |
| Enrollment: | 90 |
| Type: | Actual |

# Ethics review

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| Approved WMO Date: | 30-08-2018 |
| Application type: | First submission |
| Review commission: | METC Universitair Medisch Centrum Groningen (Groningen) |
| Approved WMO Date: | 13-11-2018 |
| Application type: | Amendment |
| Review commission: | METC Universitair Medisch Centrum Groningen (Groningen) |
| Approved WMO Date: | 07-05-2020 |
| Application type: | Amendment |
| Review commission: | METC Universitair Medisch Centrum Groningen (Groningen) |

# Study registrations

## Followed up by the following (possibly more current) registration

No registrations found.

## Other (possibly less up-to-date) registrations in this register

No registrations found.

## In other registers

| Register | ID |
|---|---|
| CCMO | NL64677.042.18 |