Transcranial Alternating Current Stimulation (tACS) as a novel treatment option: a proof of concept study in Adult Classic Galactosemia

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Main objective: We propose a proof of concept study to apply noninvasive brain stimulation, specifically tACS, for the first time to adult CG patients with the aim to find stimulation protocols that improve their motor and language performance by…

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Metabolic and nutritional disorders congenital
Study type	Interventional

Summary

ID

NL-OMON49032

Source
ToetsingOnline

Brief title
Non Invasive Brain Stimulation in Adolescent Classic Galactosemia

Condition

- Metabolic and nutritional disorders congenital
- Movement disorders (incl parkinsonism)

Synonym
classic galactosemia, GALT deficiency

Research involving
Human

Sponsors and support

Primary sponsor: Medisch Universitair Ziekenhuis Maastricht
Source(s) of monetary or material Support: Galactosemia Foundation

Intervention

Keyword: classic galactosemia, Motor and language impairments, non invasive brain stimulation, Transcranial Alternating Current Stimulation

Outcome measures

Primary outcome

Language/speech task

Reaction times and accuracy will be compared pre, during and post stimulation within the CG group and between groups. To validate a relation of theta and beta oscillation on language problems, we will compare the EEG theta and beta power spectrum of CG and healthy controls during the active language task and in resting state data. To investigate the relation between tACS and brain oscillation we will compare theta and beta power in pre and post stimulation EEG. To validate a relation of speech behavior and tACS we will investigate the relation of theta power pre-post difference and behavior pre-post difference in both groups of participants.

Secondary outcome

Not applicable

Study description

Background summary

The brain is one of the major target organs affected in classic galactosemia (CG). Patients suffer from speech and motor problems among others. These

problems are related to observed changes in functional and anatomical brain networks compared to healthy controls. Cognitive and motor functions are driven by neuronal oscillation in certain frequency bands, with language syllables-theta (5-8 Hz) and motor-beta (15-30Hz) rhythm. In this proof of concept study, we propose to (1) investigate for the first time which frequency bands are affected in adult CG compared to healthy controls. We also propose to (2) apply one form of non-invasive brain stimulation (NIBS), namely transcranial alternating current stimulation (tACS) which can entrain brain oscillations in individual and relevant frequencies such that they result in behavioral improvement. NIBS has shown to have therapeutic efficacy in various neurological and psychiatric disorders. It has not yet been applied in CG. TACS is our method of choice as it*s possible to change oscillations during a longer period of time, compared to TMS and tDCS.
We compare brain oscillation and tACS efficiency of CG adults and matched healthy controls. 25 participants per group will have three sessions, two with real stimulation, one with sham. Sham stimulation is used to assess the efficacy of active stimulation and placebo effects. Each session consists of three elements referred to as pre, during, and post stimulation. In the pre stimulation part of the session, we quantify behavior (speed and accuracy) and electroencephalography (EEG) oscillation profiles per individual. With regard to behavior we measure reaction times and accuracy for selected language tasks. With regard to brain oscillation, we acquire EEG at rest as well as during the execution of the active language task. For each individual, we decompose the obtained EEG signal into frequency bands and compare the frequency power spectrum of CG and healthy controls. This benchmarking procedure allows us to define *relevant frequencies*. Frequencies are *relevant* when their power clearly differ between CG and controls or when they clearly modulate during an active task. During the stimulation, participants perform the same task as in the pre session while we simultaneously apply tACS or sham in the relevant frequency and record behavioral performance. TACS should now entrain the cortical brain oscillation network relevant for that task and should lead to behavioral improvement. During post stimulation, behavior and EEG will again be quantified immediately after stimulation, again for resting state and active tasks.
To investigate whether tailored stimulation driven entrainment results in optimization of behavior we analyze tACS induced behavioral change by comparing pre, during and post tACS stimulation performance within and across groups. We also quantify tACS induced pre-post changes in the EEG frequency power spectrum within and across groups. In addition, we correlate behavioral and EEG change to investigate their relation. The proof of concept study contributes to a first understanding of brain oscillation in CG and to tACS as treatment in CG. The proposed research requires and provides interdisciplinary expertise from the medical and cognitive neuroscience point of view.

Study objective

Main objective:

We propose a proof of concept study to apply noninvasive brain stimulation, specifically tACS, for the first time to adult CG patients with the aim to find stimulation protocols that improve their motor and language performance by positively influencing their brain oscillatory profiles. Thereby we hypothesize that tACS can entrain oscillations in individual and relevant frequencies such that they result in improvements of their motor and language performance.

Secondary objectives:
1) Benchmark group and individual brain oscillations in CG for the first time and compare them to those of healthy controls. Hopefully, this can give us more insight into the impact of CG on the brain function and information transfer.
2) We apply these individualized frequencies with tACS to entrain the relevant brain oscillation. In addition, we apply in a separate session a sham stimulation to test for placebo effects.
3) We compare EEG and behavior pre and post stimulation to quantify the effect and efficiency of tACS in CG.

Study design

We propose a pre/during/post stimulation mixed design in CG and healthy controls. Control participants will be matched for age and gender. All participants have two sessions **real stimulation** and one with a **sham stimulation**. The patients will have an extra session to conduct neuropsychological tests.

Intervention

The intervention consists of tACS at beta and theta frequency to hopefully ameliorate the motor and speech problems in patients with CG.

Study burden and risks

TACS is an extremely well tolerated treatment form of NIBS with a very small risk of side effects. Mild side effects include headache, fatigue and prickling and burning sensations during the tACS. Patients will receive a sham and real stimulation and will perform language tasks.
We expect that the burden of participating in this study will be low, because the EEG and tACS are accompanied by a very small risk of side effects. During the sessions, they receive good guidance. Concerning discomforts, a conductive paste is applied to the tACS and EEG electrodes to stick them to the scalp of the patient. After the session has ended the patient
will be given the opportunity to wash his/her hair. Moreover, the only difference between the study and control group is the first session, in which the patients will be tested with neuropsychological tests and the healthy controls won*t. However, there is no difference in the burden between the study and control group, since the interventions are the same.

Personal benefits are not expected, but results pointing to normalization of the EEG frequencies with improvement in the motor/language task, favors the use of this technique as potential treatment in classic galactosemia patients with motor and language problems.

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

Patient group:
The patient may participate in the study, if they meet these criteria:
- Adult age: 18 years or older
- GALT enzyme activity below 10% and/or GALT gene severe disease causing mutations
- Motor sequencing and/or word productions problems

- Documented motor and language impairments
- Capable of giving informed consent
- The participants are screened pre and post intervention using standardized tests. Participants with abnormal scores in cognitive and/or motor domains are eligible.

Control group:
Healthy controls are included if they meet the following criteria:
- Adult age: 18 years or older
- No motor, language and/or cognitive impairments
- Capable of giving informed consent

Exclusion criteria

- Motor and language problems due to other causes
- Eczema
- Psoriasis
- Epilepsy

Study design

Design

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

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	02-12-2020
Enrollment:	50
Type:	Actual

Medical products/devices used

Generic name:	transcranial alternating current stimulation and electro-encephalography
Registration:	Yes - CE intended use

Ethics review

Approved WMO Date:	11-03-2020
Application type:	First submission
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	15-07-2021
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)

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	NL71109.068.19
Other	Status: candidate op website: www.trialregister.nl