Randomized controlled trial of neurostimulation treatment for apathy in schizophrenia

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Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Schizophrenia and other psychotic disorders
Study type	Interventional

Summary

ID

NL-OMON41353

Source
ToetsingOnline

Brief title
Neurostimulation as a treatment of apathy with vulnerability for psychosis

Condition

- Schizophrenia and other psychotic disorders

Synonym
apathy, listlessness, psychosis

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Groningen
Source(s) of monetary or material Support: Ministerie van OC&W,Vici Grant (453 □ 11 □ 004)

Intervention

Keyword: apathy, neurostimulation, schizophrenia

Outcome measures

Primary outcome

The main study parameter concerns the changes in the level of apathy as indexed by the Apathy Evaluation Scale (AES) before and after neurostimulative treatment, and the amount of spontaneous motor behaviour as measured by the Acti-meter. Another important parameter concerns the changes after treatment in the blood oxygenation level dependent (BOLD) response. This concerns the BOLD response at the level of individual brain areas, as well as their functional dynamic interactions. Furthermore, changes in frontoparietal connectivity after tDCS or rTMS treatment are used as a measure of neuroplasticity.

Secondary outcome

Not applicable

Study description

Background summary

Apathy concerns a quantitative reduction of voluntary, goal-directed behaviours that impairs daily functioning. It is a prominent and severely debilitating aspect of several psychiatric disorders, most notably schizophrenia. Surprisingly, little is known regarding the neurobiological basis of these symptoms. Moreover, currently no treatment for these symptoms is available. In this study we will investigate the effectiveness of several treatment options including transcranial Direct-Current Stimulation (tDCS), repetitive Transcranial Magnetic Stimulation (rTMS), and rTMS in combination with Behavioural Activation Therapy (BAT) to treat apathy in schizophrenia patients. By identifying involved neural networks and implementing the treatment study, contributions may be made to novel treatment strategies that will ultimately improve patients* lives. The results might also have implications for

understanding apathy in patients with depression, brain damage and neurodegenerative diseases.

Study objective

The main objective is to investigate whether tDCS and rTMS treatment targeting the right dorsolateral prefrontal cortex (rDLPFC) reduces apathy in schizophrenia patients, and whether tDCS and / or rTMS increases activity of the dorsolateral PFC * striatal circuit (including the parietal cortex), that has been shown to be involved in apathy. By reactivating this circuit we aim to reduce apathy and associated impairments of executive functions. The secondary objective of the study is to evaluate responses to BAT in combination with rTMS. A tertiairy aim of the study is to provide insights into which patients are more likely to benefit from neurostimulative treatment. Applying near-infrared spectroscopy (NIRS) before, during, and after the first neurostimulative treatment session will enable us to investigate whether baseline frontoparietal connectivity is predictive of the clinical response to neurostimulation. By comparing the response to rTMS treatment measured by NIRS within group of healthy subjects to patients will help us define compare it to normal, healthy, brain information processing, as a reaction to rTMS treatment and point deficiencies in patients.

Study design

The proposed study includes tDCS, rTMS, (f)MRI, and NIRS techniques. The entire study exists of five phases. Within the first phase demographic data are acquired, neuropsychological tests are performed, interviews are held, and MRI scanning takes place for structural, and fMRI scans. The neuropsychological tests and interviews serve to measure the level of apathy and possible comorbidities. The fMRI scans are necessary to evaluate resting state connectivity, and brain activation during the execution of tasks that involve the DLPFC * striatal circuit. During the second phase, participants receive either real or placebo neurostimulation (tDCS or rTMS) for a duration of two weeks. Closely before, during and shortly after the treatment (tDCS, rTMS, or rTMS plus BAT), spontaneous motor behaviour will be recorded by means of an Acti-meter. This provides a secondary measure of apathy. The third phase is similar to the first phase. This session also includes applying apathy rating scales, neuropsychological tests, and an (f)MRI study. The last two phases are included as a follow-up to measure potential short and long-term effects after treatment. These follow-up sessions take place four weeks, and 10 weeks after finishing the (neurostimulative) treatment or sham stimulation. During these follow-up sessions apathy will be indexed through questionnaires, interviews, and spontaneous motor behaviour.

Intervention

Three of the five patient groups (25 patients per group) will receive either tDCS, rTMS, or rTMS + BAT treatment. The remaining two patient groups are included as placebo control groups, and will receive either *sham* tDCS or sham rTMS stimulation. The site of stimulation for tDCS and rTMS will be the right dorsolateral prefrontal cortex.

Study burden and risks

Firstly, interviews are held, and the patients are asked to fill in questionnaires. This will take approximately 150 minutes. Secondly, patients will undergo (f)MRI scanning, during which participants have to perform two tasks, in addition to a resting state scan and an anatomy scan. This (f)MRI session will take approximately 60 minutes. Thirdly, a tDCS, rTMS, or rTMS plus BAT treatment will be administered. Neurostimulative treatment will be given once a day for two weeks, five days per week. One group of patients will receive an additional BAT for ten weeks, after finishing the rTMS treatment. During the first and last neurostimulative treatment session, NIRS will be applied simultaneously. Shortly after treatment another appointment is made, whereby the neuropsychological evaluation and (f)MRI scan will be repeated. These two sessions will take approximately 130, and 60 minutes respectively. Four weeks, and again ten weeks after treatment the neuropsychological interviews, questionnaires, and assessment of motor behaviour (not the neuropsychological tests) will be repeated to assess possible short and long term effects of treatment (tDCS, rTMS, or rTMS plus BAT). These last sessions will approximately take 100 minutes.

Concerning the fMRI scanner, participants will be exposed to a field strength of 3 Tesla and scanner noise. Thus far, there is no evidence to suggest that exposing humans to a magnetic field of this strength has a negative influence on health. With regard to the noise, earplugs and headphones will be provided. During the tDCS procedure participants are exposed to a very low electrical current of 2 Ma. The use of tDCS to date has not resulted in significant adverse effects, apart from mild headache or a mild tingling sensation underneath the electrodes. During the rTMS procedure participants are exposed to a magnetic field strength of 1.5 Tesla. The application of TMS is considered safe and useful as a treatment strategy as long as it is given within recommended guidelines. The proposed study excludes high risk patients and all parameters are well within international safety guidelines. However, the risk of inducing a seizure cannot be fully excluded, so several safety procedures will be taken. Lastly, the NIRS technique is considered non-intrusive and safe. It does not involve strong magnetic fields or radio frequency pulses. It also requires less rigid stabilization of the head and body. The applied light intensities for the proposed study are considered safe for adults.

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

Patients:
- At least 18 y.o.a.
- Diagnosis schizophrenia, according to DSM IV
- Minimum score AES (27)
- Written informed consent
Healthy subjects:
- At least 18 y.o.a.
- written informed consent

Exclusion criteria

fMRI:
-Metal implants (pacemaker, heart valves, vascular clips, eye-implants, copper containing intra-uterine devices, or non-removable piercing)
- Any risk of having metal particles in the eyes due to manual work without proper eye protections - Tattoos containing iron oxide (often found in red pigments)
- (suspected) Pregnancy
- Claustrophobia
- Refused to be informed (via the general practisioner of the patient) of structural brain abnormalities that could be detected during the experiment;TMS:
- Diagnosis of epilepsy, or a personal or first degree family history of epileptic seizures
- Medications associated with increased seizure risk
- Brain surgery
- Neurological problems in the past or at present
- Intracerebral implants;tDCS:
- Metal implants inside the skull or eye
- Severe scalp skin lesions;Treatment of tDCS of rTMS within the past year.;Relative contra-indications for tDCS:
- A history of previous seizures or predisposing factors that might increase seizure risk such as neuromodulatory medication
Additional exclusion criteria for healthy subjects:
History of psychiatric or neurological illness

Study design

Design

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

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	15-10-2013
Enrollment:	150
Type:	Actual

Ethics review

Approved WMO Date:	04-09-2013
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	20-12-2013
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	07-04-2014
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	21-04-2015
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	24-06-2015
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Not approved Date:	19-08-2016
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	07-11-2016
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
Other	3805 (NTR)
CCMO	NL43310.042.13