Applying transcranial magnetic stimulation concurrently with functional MRI: investigating disturbed transcallosal signalling in patients

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

Summary

ID

NL-OMON36283

Source
ToetsingOnline

Brief title
concurrent fMRI/TMS

Condition

- Schizophrenia and other psychotic disorders

Synonym
auditory verbal hallucinations, schizophrenia

Research involving
Human

Sponsors and support

Primary sponsor: Divisie Hersenen

Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: brain stimulation, fMRI, network, TMS

Outcome measures

Primary outcome

The main study parameters for experiment 1 are functional brain networks evoked with TMS. Such a network consists of maps of induced percent signal change in BOLD MR images over the entire brain. In experiment 2 the main outcome is the difference in percent signal change between patients and controls along connections in the language network. See also chapter 5 of the protocol text.

Secondary outcome

not applicable

Study description

Background summary

Transcranial magnetic stimulation (TMS) is a technique to safely and reversibly stimulate brain areas in human patients or healthy volunteers. Using a coil with a high current, a brief magnetic field pulse perpendicular to the surface of the head is generated that penetrates the skull almost unattenuated. In the brain, this brief magnetic pulse then generates a current locally that interferes with neuronal processing.
This technique is increasingly used to diagnose or even treat neurological and psychiatric disorders. However, at present the exact effects TMS has on the brain are unclear. Recent research shows that not only the brain areas directly underlying the TMS coil are affected, but entire connected neuronal networks. Furthermore, local cortical architecture can alter the deployed current considerably.
Very recently, it became possible to apply TMS during functional MRI scanning. This allows researchers to follow the effect TMS has on brain activation, in order to verify whether the intended TMS treatment or diagnosis is indeed having the effect on brain activation that is often assumed. The dept. of

Psychiatry at the UMCU recently assembled a concurrent fMRI/TMS setup.

Study objective

The objectives of this proposal are twofold. First, we intend to test the feasibility of the new concurrent fMRI/TMS setup on real brains of a small group of healthy volunteers. That is, can we indeed evoke fMRI BOLD responses in several functional networks in the brain with TMS? The setup has been extensively tested on phantoms, and all technical issues have been solved (see section 5.2.2 of the protocol text). Second, we aim to investigate the (dys)functioning of two pathways in a small group of schizophrenia patients. The first part of the proposed research will give us a fundamental new insight to what the actual effects of TMS on brain function are, and allow us to improve brain stimulation techniques and possible future treatments such that the brain areas of interest are influenced in the most efficient way possible. In a small group of healthy volunteers we will stimulate (pre)motor and language regions known to be incorporated in a functionally coupled cerebral network. The aim of these experiments is to establish whether we can indeed visualize TMS induced proximal and distal brain activation in these established motor networks. Besides yielding scientifically interesting results on the nature of these networks, these experiments will allow us to further optimize our concurrent fMRI/TMS setup. When the concurrent fMRI/TMS setup yields reliable activation in known networks, our first objective is achieved. We will report to a Data Safey Monitoring Board (DSMB), established for this particular study, about the outcome of this first concurrent fMRI/TMS pilot study when 5 out of 10 subjects and 10 out of 10 subjects have been tested before proceeding with the second objective (see also section 9.3 of the protocol text). As we are aware of the fact that this is a new technique within the UMC Utrecht, we want to give the DSMB the opportunity to judge on the application of this technique after the experiences of a small number of volunteers (mainly the applicants and 5 of naive subjects recruited externally) are fully evaluated. In the second part of the proposed research the objective is to investigate the functioning of two pathways in a small group of schizophrenia patients. The second objective will be carried out when the first objective, testing the new setup on healthy volunteers, is achieved. It has been hypothesized that the symptoms in a special group of schizophrenia patients, namely patients with persistent auditory verbal hallucinations (i.e., 'hearing voices'), are caused by an imbalance in neuronal pathway functioning. With the setup perfected and tested on brain networks of healthy volunteers, we can now stimulate a cortical starting point of such a possibly affected pathway, while simultaneously reading out fMRI BOLD signals at another end of such a pathway. These readout measures can then be compared to the same measures in healthy controls. The first pathways we intend to investigate this way are the transcallosal connection between the language areas of Broca and Wernicke in the left inferior frontal cortex and temporor-parietal cortex and their respective homologues in the right hemisphere. Broca*s and Wernicke's area in one hemisphere will be stimulated, and BOLD fMRI in the contralateral hemisphere

read out. Imbalances in both the transcallosal and intrahemispheric networks under investigation have been implicated as the cerebral pathology underlying auditory verbal hallucinations in schizophrenia. Testing these hypotheses in vivo for the first time can greatly improve our understanding of this disabling disease and offer new therapeutic interventions in the future.

Study design

The study is comprised of 2 experiments, and is a combination of an observational study (fMRI) with an 'invasive' component (TMS). The first study is a feasibility study of this new technique on 10 healthy volunteers. The second study is a study on schizophrenia patients and matched controls, testing hypotheses on disturbed transcallosal signaling in these patients (see above paragraph).

Study burden and risks

The risk associated with participating in an fMRI/TMS experiment is minimal. It is not considered greater than when doing an fMRI or TMS experiment in isolation. The potential risks of bringing a TMS coil into the bore of an MRI scanner have been eliminated by the special setup that is designed by the applicants (see methods, chapter 5 of protocol text). A comparable setup has been in use for at least 8 years at University College London (UCL). This group advised us regarding our setup, most parts are identical as at UCL. In the first study 10 subjects will be tested during brief visits. 5 of these subjects will be the applicants and co-workers that are used to such experiments. 5 subjects for experiment 1 will be recruited from campus, to guarentee objective reports of feasibility and burdon by questionaires. The patients are recruited in-house, and matched controls recruited externally. For potential risks of fMRI and TMS, the usual precautions are taken (proper screening, see D5).

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

Healthy volunteers:
- for experiment 1: between age 18-40yr.
- for experiment 2: matched with available patient group with respect to age (18-65yr), gender and education;Patients:
- between age 18-65yr
- diagnosed with schizophrenia according to DSM IV will be included.
- able to lie in an MRI scanner and prevent head movements for a short period of time (about 15 minutes)

Exclusion criteria

The following list of exclusion criteria is for both controls and patients, unless noted.
- non-removable metal objects in head/body
- pregnancy
- history of closed- or open head injury
- history of psychiatric illness (healthy controls only)
- history of neurological illness or endocrinological dysfunction
- history of epilepsy
- occurrence of epilepsy in 1st degree family
- use of medication other than anticonceptive or paracetamol (healthy controls only)
- drug or alcohol abuse over a period of six months prior to the experiment
- intake of alcohol, caffeine or nicotine containing products within 4 hrs prior to the scanning sessions.
- claustrofobia

Study design

Design

Study type:	Observational invasive
Intervention model:	Other
Allocation:	Non-randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Basic science

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	23-05-2011
Enrollment:	70
Type:	Actual

Ethics review

Approved WMO Date:	29-04-2011
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	28-02-2012
Application type:	Amendment
Review commission:	METC NedMec

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	NL33472.041.10