Tracing the origin of psychosis in schizophrenia - A repetitive TMS/neuroimaging study of frontostriatal interaction

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The objective of this study is to directly test, in humans, the hypothesis that reduced prefrontral control leads to dysregulation of the striatum.

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

Summary

ID

NL-OMON37137

Source
ToetsingOnline

Brief title
Tracing the origin of psychosis in schizophrenia

Condition

- Schizophrenia and other psychotic disorders

Synonym
schizophrenia

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Utrecht
Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: frontostriatal system, functional MRI, repetitive TMS, schizophrenia

Outcome measures

Primary outcome

The main study parameter is brain activity in the frontostriatal system, as measured with functional magnetic resonance imaging.

Secondary outcome

Secondary study parameters associated with task performance (reaction time, accuracy), structural MRI (number of white matter fibers between areas, white-matter integrity), repetitive TMS (intensity of stimulation) and abnormalities in candidate genes for dopamine receptors.

Study description

Background summary

Schizophrenia is characterized by positive symptoms (i.e. psychotic episodes characterized by delusions and hallucinations) and negative symptoms (i.e. decline in cognitive and social functioning and emotional blunting). Positive symptoms are associated with abnormal function of the striatum, whereas negative symptoms have been related to dysfunction of the prefrontal cortex. It has been hypothesized that the deficits underlying positive and negative symptoms are linked, in that prefrontal regulation of the striatum fails due to dopamine disfunctioning, giving rise to psychosis and related symptoms. Although supported by several findings, direct evidence from human studies for this hypothesis is still lacking.

Study objective

The objective of this study is to directly test, in humans, the hypothesis that reduced prefrontral control leads to dysregulation of the striatum.

Study design

Using neuroimaging techniques and repetitive transcranial magnetic stimulation we will localize prefrontal regions that are involved in controlling activity in the striatum (Study 1 and Study 2). Besides, we will clarify frontostriatal activation patterns on fMRI by investigating underlying genetic mechanisms in dopaminereceptors that may be responsible for these effects. The effects of frontal suppression on striatal activation will then be investigated in healthy siblings of schizophrenia patients and healthy control subjects (Study 3).

Intervention

In the Pilot study and Study 3, healthy siblings of schizophrenia patients and healthy control subjects are randomly assigned to an experimental or control subgroup. The experimental subgroups will receive repetitive transcranial magnetic stimulation over prefrontal regions, whereas the control groups receive stimulation over a brain region that does not interact with the frontostriatal system. In Study 2, healthy control subjects will take part in both the experimental and control conditions. In the two experimental conditions subjects will receive rTMS over prefrontal regions. In the control condition subjects will receive sham rTMS. The order of rTMS treatment (i.e. experimental vs control) is counterbalanced across subjects. For gene investigation there will be blood collection of healthy controls only, whereas blood collection of schizophrenia patients and their siblings already has been performed under a different protocol (04-003).

Study burden and risks

The burden of this study differs per experiment and study group. Studies will take at maximum two and a half hours per day. Furthermore, only non-invasive techniques will be used. Given careful screening, there are no known risks associated with magnetic resonance imaging. When severe abnormalities will be noticed on the magnetic resonance scans, a radiologist will be asked for advise, Repetitive transcranial magnetic stimulation is also a safe technique, but some, generally mild, adverse events have been identified, including headache. More severe adverse events associated with repetitive transcranial magnetic stimulation (e.g. tinnitus and (pseudo)seizures) are rare. To minimize the risk of severe adverse events we will take extensive safety measures. First, subjects will be screened carefully for contraindications to transcranial magnetic stimulation. Second, repetitive transcranial magnetic stimulation will be applied in compliance with international safety guidelines that have been approved by the National Institute of Neurological Disorders and Stroke and the National Institute of Health. Third, repetitive transcranial magnetic stimulation will be administered by technicians or investigators who have been trained as *first responders* in order to render appropriate care in the event of a seizure. They are under supervision of an appropriately trained and licensed physician who will be immediately available if necessary. Fourth, repetitive transcranial magnetic stimulation will be performed in a medical

setting with appropriate emergency facilities to manage seizures and their consequences, located at the Department of Clinical Neurophysiology at University Medical Center Utrecht. Finally, we will conduct repetitive transcranial magnetic stimulation experiments in healthy volunteers only. Subjects can leave the study at any time for any reason if they wish to do so without any consequences. Besides financial remuneration, no immediate benefits are to be expected from participation in this study. In the long run, increased understanding of brain function and the aetiology of schizophrenia may contribute to diagnosis, early detection, and prediction of treatment outcome. Blood collection is a safe technique with very mild adverse events, as haematomas in inner elbow.

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

All subjects:
- Right-handedness
- Written informed consent;Specific for schizophrenia patients:
- DSM-IV diagnosis of schizophrenia
- Age between 18 and 45;Specific for healthy siblings of patients with schizophrenia:
- Age between 30 and 45;Specific for healthy volunteers:
- Age between 18 and 45

Exclusion criteria

All subjects:
- Ferrous objects in or around the body (e.g. braces, glasses, pacemaker, metal fragments)
- Drug or alcohol abuse over a period of six months prior to the experiment
- History of closed- or open-head injury
- History of neurological illness or endocrinological dysfunction
- Claustrofobia
- Major medical history
- Chronic use of medication
- History of epilepsy
- History of epilepsy in first-degree relatives
- Incapability of giving an informed consent
- Symptoms indicative of schizophrenia;Specific for women:
- Pregnancy;Specific for healthy siblings of patients with schizophrenia:
- History of psychiatric illness;Specific for healthy volunteers:
- History of psychiatric illness
- First-degree family member with psychiatric illness

Study design

Design

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

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	04-02-2008
Enrollment:	168
Type:	Actual

Ethics review

Approved WMO Date:	17-07-2007
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	16-02-2010
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	11-10-2011
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)

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	NL16890.041.07