Integrating motivation, cognition and action: cortical control of striatal processing

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Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Other condition
Study type	Interventional

Summary

ID

NL-OMON36652

Source
ToetsingOnline

Brief title
Cortico-striatal circuits and motivation, cognition and action

Condition

- Other condition

Synonym
not applicable

Health condition

niet van toepassing

Research involving
Human

Sponsors and support

Primary sponsor: Radboud Universiteit Nijmegen
Source(s) of monetary or material Support: Radboud Universiteit Nijmegen;TOPtalent beurs (DGCN)

Intervention

Keyword: Cortex, Motivation-cognition interface, Striatum, Theta Burst Stimulation

Outcome measures

Primary outcome

Reaction times, error rates and brain activity (fMRI BOLD response) will be used to test whether cTBS over the OFC, dlPFC, and PMC will uniquely affect performance on the (interaction between) 3 components of the task and whether the BOLD response is altered in the VS, CN, or putamen, respectively and the interaction between the striatal regions.

Secondary outcome

In order to assess functional connectivity patterns between the striatal and cortical areas, we will obtain resting state scans before and after cTBS intervention.

We aim to test whether the cTBS effects are confined to those cortico-striatal loops predicted to be affected on the basis of known anatomy in non-human primates. Furthermore, this will enable us to investigate whether cTBS influences cortico-striatal circuits only when those circuits are taxed by a particular task, or whether those effects influence the ongoing pattern of functional connectivity in the cortico-striatal system, irrespective of task performance.

Study description

Background summary

Dopamine in the striatum is an important mechanism for the mediation between motivation, cognition, and action. Neuroanatomical (animal) data have revealed an arrangement of spiraling connections between the midbrain and the striatum that seems perfectly suited to subserve a mechanism by which dopamine can direct information flow from ventral/ ventromedial (VS), via central (caudate nucleus; CN), to dorsolateral (putamen) regions of the striatum. Moreover, these striatal regions are connected to distinct cortical areas [orbitofrontal (OFC), dorsolateral prefrontal (dlPFC), and premotor cortex (PMC), respectively] through cortico -striatal circuits.

Transcranial magnetic stimulation (TMS) of particular cortical areas is known to affect dopamine release in distinct striatal regions. Therefore, with a particular TMS protocol (continuous Theta Burst Stimulation; cTBS) we will decrease the excitability of the OFC, dlPFC and PMC to infer the connections to the VS, CN and putamen. We hypothesize that desensitizing these cortical areas uniquely affects task-related brain activity in the distinct striatal areas and the area(s) it projects to and behavioral performance on the functions associated with these areas (i.e. the VS, CN and putamen are involved in reward processing- cognitive flexibility - motor control, respectively).

We hypothesize that stimulation of particular parts of the human cortex changes task-related brain activity in distinct striatal areas and performance on the distinct components of a rewarded-task switching paradigm. This paradigm measures cognitive flexibility, which is previously shown to improve after anticipation of high (vs. low) reward.

This effect is thought to depend on individual differences in baseline levels of striatal dopamine and the results will confirm that the interaction between motivation, cognition, and action is mediated by dopamine in the striatum, as will be measured with the dopamine transporter genotype (DAT1/SLC6A3).

Study objective

The main objective is to assess the effect of decreasing cortical excitability on task performance and striatal BOLD response as well as the effects on the striatal areas that are connected through ventral - dorsal spiraling connections.

We will also assess whether these hypothesized effects are mediated by striatal dopamine, by taking into account individual differences in baseline levels of striatal dopamine.

We furthermore look at cTBS induced changes in cortico-striatal connectivity with resting state functional Magnetic Resonance Imaging (fMRI).

Study design

The study will consist of four sessions, each separated by at least a week. During the first session, the motor threshold (MT) will be determined (to determine the stimulation intensity in the later TMS-sessions) and a structural MRI-scan will be made (in order to localize the TMS coil in the other TMS-sessions). Furthermore, during this first session, a short cTBS protocol (10 sec.) will be applied on the PMC and OFC at a low intensity (at first 10% and later 80% of the aMT). By this means, subjects can indicate whether they would like to proceed with the experiment.

The study consists of one intake session and three experimental sessions in which the excitability of three cortical regions will be inhibited with an off-line TMS protocol by administering cTBS in counterbalanced order (within-subject). To investigate the effects of cortical cTBS on task-related brain activity in the striatum while participants perform a rewarded-switch task during the measurement of brain activity with fMRI. Differences in connectivity will be measured with high resolution resting state scans. The off-line effects of cTBS will last approximately 60 minutes.

To measure the effects of cortical cTBS on task-related brain activity in the striatum while participants perform a rewarded-switch task, we will measure the task related BOLD-response with fMRI. Differences in connectivity will be measured with resting state fMRI.

All participants will perform the task -related scan and resting state scan twice during each session, once after cTBS and once without the application of cTBS (i.e. before cTBS or more than 1 hour after its application).

Intervention

During the intake session, participants will become accustomed to the sensation of cTBS. During the following three experimental sessions, each participant will receive continuous theta-burst stimulation of 600 pulses (three 50Hz pulses every 200 ms) at 80% of the active motor threshold for 40 seconds over the left OFC, left dlPFC and left PMC.

Furthermore, during this first session, a short cTBS protocol (10 sec.) will be applied on the PMC and OFC at a low intensity (at first 10% and later 80% of the aMT).

Study burden and risks

TMS is not painful at the level of intensity used in this project (i.e. at 80% of active motor threshold). According to previous literature, it might be possible that, in rare cases, participants could report a (light) headache, which could be treated easily with paracetamol. On the basis of incidental epileptic seizures triggered by TMS in early 90*s, safety-guidelines were established to set up the maximum duration of TMS stimulation (Wassermann, 1998; Anderson et al., 2006; Rossi et al., 2008; Oberman et al, 2011). Therefore, our protocols will follow these safety TMS guidelines. Furthermore, all participants will be pre-screened for relevant medical history, epilepsy, drug abuse, head trauma, neurological or psychiatric illness, pregnancy, heart disease, cardiac pacemakers, medication pumps, tricyclic antidepressants, neuroleptics and a family history of neurological illness, psychiatric illness or epilepsy. Because the risk associated with participation can be considered negligible and the burden can be considered minimal, we do not expect adverse events during the project.

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, right handed participants (males and females) age 18-35 years. All participants will have normal or corrected to normal vision.

Exclusion criteria

Contra-indications for TMS and fMRI: drug abuse, head trauma, neurological or psychiatric illness, pregnancy, heart disease, claustrophobia, cardiac pacemakers, metal objects in the body, medication pumps, tricyclic antidepressants, neuroleptics and a family history of neurological illness, psychiatric illness or epilepsy.

Study design

Design

Study type: Interventional

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Other

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	19-10-2011
Enrollment:	40
Type:	Actual

Ethics review

Approved WMO

Date:	24-08-2011
Application type:	First submission

Review commission: CMO regio Arnhem-Nijmegen (Nijmegen)

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	NL33905.091.11