Investigating the role of the medial prefrontal cortex in the consolidation of schematic associative memories using Transcranial Magnetic Stimulation.

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Primary Objective: We aim to investigate the possibility of erasing multimodal memories by applying repetitive TMS to a somatosensory region that represents part of the memory trace. Specifically, we expect that application of the stimulation…

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

Summary

ID

NL-OMON41744

Source
ToetsingOnline

Brief title
Modulating schematic consolidation with TMS

Condition

- Other condition

Synonym
na

Health condition

neurowetenschappelijk onderzoek

Research involving

Human

Sponsors and support

Primary sponsor: Radboud Universiteit Nijmegen
Source(s) of monetary or material Support: ERC Grant (Neuroschema)

Intervention

Keyword: Consolidation, Memory, Schema, TMS

Outcome measures

Primary outcome

The main study parameters are item recognition (d-prime) performance and associative memory (% correct) performance on day 3. Specifically, we expect that application of the stimulation protocol to the somatosensory hand representational area in the critical window of cortical plasticity immediately after reactivation leads to a selective impairment for later retrieval of specifically those associations that are reactivated (compared to sham stimulation). We also aim to investigate how targeting the mPFC with the cTBS protocol after reactivation selectively influences the consolidation and eventual retrieval of those associative memories that are also schema-congruent. Specifically, we expect that application of the stimulation protocol to the medial prefrontal cortex region after reactivation leads to an impairment of subsequent recall of specifically reactivated schema-congruent associations.

Secondary outcome

The secondary study parameters will be word recall and recognition performance on the RDM-task for both learned words as well as critical items (non-presented

semantically associated lures). We expect that recall and recognition on the

RDM-task will display less false memories for critical items in the group that

receives stimulation to the mPFC, compared to the other groups.

Study description

Background summary

New incoming information is not encoded on a blank slate, but instead is reconciled with and incorporated into the existing body of knowledge. An extensive body of literature suggests that congruency of new information with this prior knowledge, also called schemas, can enhance later memory performance. A series of recent neuroscientific studies on this so-called schema-congruency effect in animals and humans suggest an important role for the interplay between the medial temporal lobe (MTL) and medial prefrontal cortex (mPFC). A recent proposal suggests that the mPFC drives cortical plasticity in the rest of the cortex, facilitating the integration of new information within pre-existing schemas, both upon encoding and subsequent reactivation. This is reflected in neural signals at later retrieval, such as stronger activity in the mPFC as well as connectivity between the mPFC and other neocortical associative storage areas, such that it suggests that the retrieval of schema-congruent mnemonic traces become more dependent upon representations mediated by the mPFC
In addition to correlational evidence of the relation between the mPFC and the schema-congruency effect in human memory, it would be important to manipulate the mPFC directly to further investigate the role of this region in selective processing of schema-congruent associative memories. A window of opportunity to modify the memory trace is given after reactivating associative information by partial cueing, which temporarily increases cortical plasticity of the memory trace. Several studies have shown that reactivation can strengthen the memory trace as evidenced in improved later memory performance, or that the presentation of new information after reactivation can modify or distort the memory trace. Two recent studies have applied brain stimulation after reactivation of memory traces. One found that applying electroconvulsive shocks after reactivation of a memory trace erases this memory trace,whereas another found that applying stimulation with TMS after reactivation can improve later memory. Here, we combine the TMS-induced modification of memory traces with a schema-manipulation to investigate the selective role of the mPFC in processing schema-congruent memory traces.

Study objective

Primary Objective:
We aim to investigate the possibility of erasing multimodal memories by applying repetitive TMS to a somatosensory region that represents part of the memory trace. Specifically, we expect that application of the stimulation protocol to the somatosensory hand representational area in the critical window of cortical plasticity after reactivation leads to a selective impairment for later retrieval of specifically those associative memories that are reactivated (compared to sham stimulation). We also aim to investigate how temporarily impairing processing in the mPFC with TMS after reactivation selectively influences the consolidation and eventual retrieval of those associative memories that are schema-congruent. Specifically, we expect that application of the stimulation protocol to the medial prefrontal cortex region after reactivation leads to an impairment of subsequent recall of reactivated schema-congruent associations.

Study design

In this study, we regard multisensory congruency with prior knowledge as a pre-existing schema. We manipulate this congruency with prior knowledge to investigate its influence on the retrieval of associative memories. Associative information will be learned (day 1) in a visuotactile learning paradigm where participants study visual motifs that are itself randomly associated with object word-fabric combinations that are either schema-congruent (a leather fabric paired with the word 'jacket') and schema-incongruent (a lace fabric paired with the word 'umbrella') (as in van Kesteren et al., 2010, 2013). This paradigm is extended by including a reactivation procedure on the day after encoding (day 2) as a method to selectively manipulate cortical plasticity of the trace well into the consolidation process. Half of the associative triplets will be reactivated by means of tactile exploration of fabrics and probing for retrieval of object words, which will temporarily render the corresponding associative memory trace labile (or modifiable). We then use this as a window of opportunity to selectively interfere with the consolidation process by applying continuous theta-burst stimulation (40 sec) with a MC-B70 butterfly coil (Magventure, stimulator is MagVenture, MagPro X100 with Magoption) for stimulation of deeper brain regions. We use three separate groups here (between-subject manipulation), as the memory paradigm cannot be repeated multiple times across the same participants. Participants will be randomly assigned to these three groups. The stimulation protocol will be applied to the mPFC in one group. Alternatively, the stimulation protocol with the same coil and stimulator will be applied in another group to the somatosensory cortex as a task control. The stimulation control will be formed in a third group by stimulating the primary motor cortex on the cortical midline (the area that represents leg motor movements), which is presumed not to have any effect on the task. We use this form of stimulation control instead of the usual stimulation of a medial control site over the vertex, as the underlying cortex of the vertex has a presumed function in declarative memory.
One day after the experimental intervention (day 3), we test memory by

performing a recognition memory test on the visual motifs, as well as an associative memory task probing participants to select the correct corresponding object word associated with the visual motif. We therefore employ a 3 by 2 by 2 factorial design with a between group factor (stimulation site), and two within group factors (respectively reactivation and schema-congruency) as independent factors. The outcome (dependent) measures will be recognition memory (d-prime) and associative memory (% correct).

Intervention

We will employ an off-line rTMS-protocol with the intention to produce short-term effects on the functioning of the target regions. The intervention will consist of a standard continuous theta-burst stimulation (cTBS) procedure, consisting of a total of 600 pulses administered across 40 sec. The stimulation protocol is patterned, and consists of bursts of 3 pulses at 50 Hz, and each burst itself is repeated at a frequency of 5Hz. The stimulation intensity will be anchored in all three experimental groups relative to 80 % of the measured active motor threshold from the tibialis anterior, following previous studies. The reason for using aMT as measured from the tibialis anterior muscle instead of a distal hand muscle, is that the representational motor area for the tibialis anterior effector is located at a similar depth in the interhemisperic fissure to our target location in the medial prefrontal cortex. During the intake, we will determine the active motor-evoked threshold (aMT) of the tibialis anterior as well as the first dorsal interosseous, as measured by electromyographic recordings in response to single TMS-pulses delivered to the appropriate motor hotspots in the primary motor cortex following the method of limits. Specifically, during moderate contraction of the tibialis anterior muscle respectively the first dorsal interosseous, the aMT will be determined as the minimal stimulation intensity at which 5 out of 10 pulses evokes a visible motor-evoked potential (MEP) on the electromyographic recordings. The intensity at which the protocol of cTBS is applied is defined at 80% of the aMT of the tibialis anterior, unless the intensity defined in this manner falls above 120 % of aMT of the first dorsal interosseous. In the latter case, we will employ a stimulation intensity for the cTBS-protocol that is anchored below 120% of the aMT of the first dorsal interosseous. We use this precautionary upper threshold of stimulation intensity, as the single case that is known (out of 4,500 total cases) where the application of cTBS induced a tonic-clonic seizure used a threshold of approximately 120 % of the aMT as measured by electromyographic recordings on the first dorsal interosseous. The cTBS-intervention will be delivered twice, once at the intake session to determine tolerability, and later in the reactivation session (day 2) as an experimental intervention (see study design). Depending on the experimental group, the stimulation will be delivered to the medial prefrontal cortex (navigated by anatomical midline landmarks moving the coil two-third the direction from vertex to the nasion, somatosensory cortex (by neuronavigating to anatomical somatosensory region corresponding to the finger representations, or primary motor cortex (by neuronavigating to the midline motor cortex

representing the leg area).

Study burden and risks

Participants will not directly benefit from their participation in the study. Transcranial magnetic stimulation (TMS) is widely used as a non-invasive brain stimulation technique, based on principles of electromagnetic induction. During stimulation the participant will likely hear the clicks of the TMS pulses and experience a slight stimulation of nerves and muscles of the head and face.

Theta-burst stimulation
A recent meta-analysis of the published literature on continuous theta-burst repetitive (TBS) stimulation concluded that both the reported symptoms and general risk of adverse events during TBS is comparable or less than other high frequency rTMS protocols. Seizure is a reported severe adverse event, but still only occurred once in over 4,500 sessions resulting in a crude risk of 0.02%. We will take precautions with regard to the one report of a cTBS-induced seizure, by using a more conservative threshold for anchoring stimulation intensity. The overall crude risk of any adverse event from occurring was estimated at 1.1%. The most commonly reported adverse event during TBS are transient headaches and neck pains, which is similar to other rTMS protocols. This adverse event was reported by less than 3% of all subjects receiving TBS.
Stimulating deeper brain regions with the butterfly coil
For this study, we are employing a butterfly coil in order to stimulate deeper regions of the neocortex. According to a recent modeling paper, stimulation of targets located approximately 4 cm or more below the skull surface is likely unsafe, due to increased intensity of stimulation at the surface of the skull. The current study will aim to stimulate target cortex within this 4cm margin, to minimize this increased risk when stimulating deeper brain regions.
Stimulation intensity will be defined with reference to a motor threshold, determined by stimulating the toe/leg representation area in the motor cortex. We will be relying on a measured motor-evoked potential by electromyography of the tibialis anterior to define the motor threshold (in contrast with other studies that required visible motor twitches) during active muscle contraction (in contrast with resting muscles), which potentially would lower the stimulation intensities used in our study. Specifically, the active motor threshold is defined as the minimal stimulation intensity where 50% (5 out of 10) pulses delivered to the central sulcus in the primary motor cortex evokes a visible motor-evoked potential as measured with electromyography of the tibialis anterior muscle. The stimulation intensity of the theta-burst protocol will be put at 80% of this active motor threshold. If the intensity defined in this manner falls above 120 % of aMT of the first dorsal interosseous, we will employ a stimulation intensity for the cTBS-protocol that is anchored at 115 % of the aMT of the first dorsal interosseous.
All subjects are screened for their relevant medical history and other safety aspects (e.g. presence of metal parts in the head). Overall, the risk and

burden associated with participation can be considered low and acceptable based on the previous literature, and we do not expect serious adverse events during the project.

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

Only healthy, competent females, 18-45 years old, with normal vision or corrected-to normal vision by means of contact lenses.

Exclusion criteria

- Serious head trauma or brain surgery
- Large or ferromagnetic metal parts in the head (except for a dental wire)
- Implanted cardiac pacemaker or neurostimulator
- Pregnancy
- Large or ferromagnetic metal parts in the body
- Claustrophobia
- Skin diseases at intended electrode sites
- Disorders of vision (i.e., deviation from *normal or corrected-to-normal vision*)
- History or current presence of any neurologic or psychiatric disease
- Any prescribed medication that can alter cortical excitability (e.g. antiepileptics, tricyclic anti-depressives or benzodiazepines) or can have an influence on the participant*s vigilance or cognitive performance within two weeks prior to participation.

Study design

Design

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

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	02-06-2015
Enrollment:	83
Type:	Actual

Ethics review

Approved WMO

Date:	06-05-2015
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	NL51484.091.14

Study results

Date completed:	11-03-2016
Actual enrolment:	55