Transcranial magnetic stimulation (TMS) for patients with exposure therapy-resistant obsessive-compulsive disorder (OCD): TETRO - a multicenter randomized controlled trial

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We aim to fill the gap between the 50% of patients helped by standard therapies (ERP with/without SSRIs) and the 1% receiving surgery by using a non-invasive alternative: repetitive transcranial magnetic stimulation (rTMS) to potentiate the effects...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Other condition
Study type	Interventional

Summary

ID

NL-OMON52013

Source
ToetsingOnline

Brief title
TETRO

Condition

- Other condition
- Anxiety disorders and symptoms

Synonym
obsessive-compulsive disorder

Health condition

obsessieve-compulsieve stoornis (OCS)

Research involving
Human

Sponsors and support

Primary sponsor: Amsterdam UMC
Source(s) of monetary or material Support: Ministerie van OC&W,Zorginstituut Nederland

Intervention

Keyword: exposure therapy, multi-center randomized controlled trial (RCT), obsessive-compulsive disorder (OCD), transcranial magnetic stimulation (TMS)

Outcome measures

Primary outcome

the pre-versus-post-treatment standardized mean difference (SMD) in severity of

OCD (Yale-Brown Obsessive-Compulsive Scale, version II - Y-BOCS-II; Goodman et

al. 2006). The post-treatment Y-BOCS score will be obtained at the end of

treatment, i.e, after 20, 24 or 28 sessions.

Secondary outcome

- Response (>=35% reduction on Y-BOCS-II) and remission (Y-BOCS-II<=12) as

established through international expert opinion (Mataix-Cols et al. 2016)

- Standard Mean Difference (SMD) on the Clinical Global Impression (CGI)

severity scale

- Clinical Global Impression (CGI) improvement scale

- Quality of life (EQ-5D-5L)

- Societal costs, measured through the iMTA Productivity Cost Questionnaire

(iPCQ) and the iMTA Medical Consumption Questionnaire (iMCQ)

- Depression, measured using the Beck Depression Inventory (BDI) at baseline,

post-treatment and follow-up. In addition we will administer a visual analogue

scale (VAS) for depression at these same time points, plus every week during treatment, to monitor the effects of treatment on severity of depressive symptoms.

- Anxiety, measured using the Beck Anxiety Inventory (BAI) and a VAS; following the same procedure and rationale as for depression.

- Tolerability of the treatment and side effects, using an in-house questionnaire developed as part of the ongoing TIPICCO trial.

Exploratory outcomes and/or influencing factors:

- Patient adherence to treatment protocol, as measured using the Patient Exposure and Response Prevention Adherence Scale (PEAS; Simpson et al. 2010)

- Difference between responders and non-responders on circadian rhythm and sleep disorders at baseline as defined by the Holland Sleep Disorders Questionnaire (HSDQ) (Donse et al. 2018).

- Structural brain network characteristics (using T1 and diffusion weighted scans) to predict treatment response / relapse

- Functional resting-state and task-based (during emotional processing) brain network characteristics (using echo-planar imaging) to predict treatment response / relapse

- Neuroplasticity effects as measured with structural and functional MRI (pre-post treatment) and blood-derived biomarkers (BDNF and epigenetics)

- Variation in the exact stimulation location as ascertained and recorded by neuronavigation in relation to treatment outcome.

- Contribution of demographic and clinical variables (sex, age, medication status) and pre-existing comorbidities (i.e. comorbid tics, depression,

anxiety, autism) to the variance in treatment outcome.

- In OCD patients with comorbid tics: tic severity, measured using the Yale Global Tic Severity Scale (Y-GTSS, Leckman et al 1989).

- Variation in treatment expectancy (7-items credibility and expectancy questionnaire (CEQ, Devilly & Borkovec 2000)) and blinding success (1-item question *in which condition do you think you were?*) in relation to treatment outcome.

Study description

Background summary

Obsessive-compulsive disorder (OCD) is a serious and disabling mental disorder with a lifetime prevalence of 2% (Ruscio et al. 2010). It is characterized by obsessions and compulsions and is associated with substantial comorbidity and morbidity (Stein et al. 2019). Obsessions are repetitive and persistent thoughts, images, impulses or urges that are intrusive and unwanted, and are commonly associated with anxiety. Compulsions are repetitive behaviors or mental acts, that the individual feels driven to perform in response to an obsession. 50% of patients experience initial symptoms already during childhood. Approximately 50% of patients treated with standard treatments (exposure therapy with/without medication) fail to respond fully, resulting in chronicity and poor participation in social and educational/occupational domains. Disability adjusted life years (DALY) for OCD amount to 329,684 in Europe (rate 7.9 per 10,000 DALYs, Wittchen et al. 2011). In the US, the largest contributor to the total cost incurred by OCD was lost productivity costs (74%), and not health-care costs (DuPont at al. 1995); Dutch data show that lost productivity costs from several mental disorders account for approximately 85% of total costs (Smit et al. 2006).
In this study, we aim to fill the gap between the standard treatments (exposure therapy with/without medication) on the one side and invasive end-stage strategies (brain surgery) on the other side, using a non-invasive alternative: repetitive transcranial magnetic stimulation (rTMS). Despite proven efficacy (Zhou et al. 2017; Rehn et al. 2018), rTMS for OCD is not yet covered by the Dutch insurance system while rTMS for treatment resistant depression is. In case of proven cost-effectiveness it will lead to the addition of rTMS as insured health care for patients with OCD as well.

Usual care & guidelines
The 1st choice treatment for OCD is exposure therapy with response prevention (ERP), with an effect size of 1.33 (Ost et al. 2015). Although less effective and relatively unfavorable at the long-term, the use of selective serotonergic antidepressants (SSRIs) is the pharmacological alternative. Higher doses are used for OCD than for other anxiety disorders or depression and associated with more dropout due to adverse effects. The switch to clomipramine (tricylic antidepressant) or augmentation with antipsychotics are commonly used pharmacological strategies for ERP- and SSRI-resistant patients, at the cost of additional side effects. The added effect of clomipramine or antipsychotic to ERP is limited (Foa et al. 2005; Simpson et al. 2013), while conversely ERP has a significant added value in cases that already use serotonergic or antipsychotic medication (Simpson et al. 2013). Brain surgery in the form of deep brain stimulation (DBS) or lesion surgery is a last-resort invasive treatment option that is reserved for the extreme treatment-resistant cases (<1%). This shows the enormous gap between the 50% of patients helped by ERP (with/without medication) and the 1% receiving DBS.

Existing evidence of effect, usual care
SSRIs have a small to medium effect (weighted mean difference 3.21; overall effect size d=0.43) in OCD (Soomro et al. 2008), relapse risk following discontinuation is high (Batelaan et al. 2017) and non-response following re-instating the antidepressant may occur (Bosman et al. 2018). Antipsychotic augmentation has a similar-sized effect (weighted mean difference 2.34; overall effect size d=0.4), with only 1/3 of patients with SSRI-resistant OCD showing a clinically meaningful effect (Veale et al. 2014; Bloch et al. 2006). Antipsychotics give serious side effects (e.g, weight gain and metabolic dysregulation). Within the small group of selected patients with severe refractory OCD (<1%), approximately 30-50% respond to brain surgery (Hamani et al. 2014). Possible side effects include intracerebral bleeding/infection, epilepsy, fatigue, memory problems, irritability, and disinhibition (Luyten et al. 2016).

The intervention to be investigated, rTMS
Non-invasive neuromodulation using rTMS has been used in OCD on various targets (Zhou et al. 2017; Rehn et al. 2018). Variation across studies also concerns stimulation parameters (high vs. low frequency, % resting motor threshold, number / frequency of sessions). Until recently, in most studies rTMS has been used as monotherapy. We expect better effects when rTMS is used as adjuvant therapy to ERP (as is currently also the practice in ongoing experimental rTMS studies). We here therefore propose to use low-frequency rTMS over the pre-SMA in combination with ERP.

Existing evidence of effect, rTMS
rTMS as mono-therapy has shown to be effective for OCD, with recent meta-analyses showing an effect size of 0.71 (Zhou et al. 2017) and 0.79 (Rehn et al. 2018) compared to sham stimulation. It is unknown what the additive

effect is of rTMS above the effect of ERP alone.

Anticipated cost-effectiveness
No (inter)national studies exist that assess the cost-effectiveness of rTMS in the treatment of OCD. However, OCD has a similar health-care burden as depression (Skapinakis et al. 2016) and the treatments for MDD and OCD are similar (e.g. SSRI*s, CBT and rTMS). For depression, there are three cost effectiveness studies that concluded that rTMS in the treatment of MDD is cost-effective after a single failed treatment with an antidepressant (Voigt et al. 2017; Simpson et al. 2009) and outperforms antidepressants after two failed antidepressants (Nguyen et al. 2015). TMS is thus a cost-effective treatment for depressed patients who have not received sufficient benefit from antidepressant pharmacotherapy and significant cost savings may be expected relative to the current standard of care.
Although rTMS is expected to be more expensive than usual care on the short term, we expect that the new intervention will result in higher recovery rates and better quality of life than usual care. This is expected to result in reduced OCD treatment duration and increased societal/occupational participation that will lead to reduced healthcare costs and lost productivity costs in the long term. In some cases the TMS treatment will replace the expensive and invasive alternative, i.e. brain surgery/DBS. Taken together, we expect that the new intervention is cost-effective in comparison with usual care.

Added value
The proposed treatment intends to fill the gap between standard therapies (ERP with / without medication) and end-stage invasive strategies. The greatest added value will be the reduction in disease chronicity, resulting in decreased morbidity, improved quality of life, increased social and education/occupational participation and decreased healthcare and productivity costs for the society. Moreover, I will reduce demoralization in patients and therapist, who deal with these difficult to treat symptoms.

Study objective

We aim to fill the gap between the 50% of patients helped by standard therapies (ERP with/without SSRIs) and the 1% receiving surgery by using a non-invasive alternative: repetitive transcranial magnetic stimulation (rTMS) to potentiate the effects of ERP. We will establish the added value of 1Hz rTMS applied over the preSMA (versus sham rTMS) when combined with ERP in OCD patients, who show no/insufficient response to ERP (alone or combined with medication).

Study design

We propose to conduct a multi-center, double-blind, randomized, sham-controlled rTMS trial, to determine the efficacy of 1Hz rTMS over the pre-supplementary

motor area (pre-SMA) as adjuvant treatment to ERP in patients with OCD who did not respond (sufficiently) to ERP alone (with or without medication). Alongside this randomized controlled trial we will also conduct an economic evaluation. Assessments will be conducted at baseline, weekly during the 5 (to 7) weeks treatment, after last treatment session and at 3, 6 and 12 months follow-up.

PICOT:
Population: 250 adult (18 years and older) patients with treatment-resistant OCD
Intervention: 20 (or 24 or 28) sessions of 1-Hz rTMS over the pre-SMA followed by intensive ERP
Comparator: sham-rTMS with ERP
Outcomes: pre-to-post standardized mean difference in OCD severity (as measured with the Yale-Brown Obsessive-Compulsive Scale - Y-BOCS), compared to the sham condition.
Time horizon: we will measure effect of treatment before and immediately after treatment (i.e. 5, 6 or 7 weeks), and after 3, 6 and 12 months follow-up.

This is a 2-arm RCT with an active adjuvant rTMS treatment to daily ERP; the comparison condition will use sham rTMS combined with daily ERP. Treatment duration is adaptive and depending on clinical improvement (see under Intervention) and will contain 20, 24 or 28 combined rTMS-ERP sessions. Patients will undergo a baseline structural and functional MRI scan, for localizing the TMS target region using neuronavigation and for prediction analyses of response and relapse. rTMS will be performed in a single-blind fashion, as the experimenter cannot be blind to the stimulation coil; patients, ERP therapists, clinical assessors will remain blind to treatment conditions during treatment and follow-up. Outcome measures will be assessed pre-treatment and post-treatment and at 3, 6 and 12 months follow-up. A selection of the outcome measures will be assessed weekly during treatment (see outcome measures).

Intervention

Treatment will consist of almost daily (4 days/week) rTMS sessions immediately followed by a 90-minute ERP session. This offers the logistic benefit of catching up on a missed treatment during a treatment week. The treatment follows an adaptive design, offering a minimum of 20 sessions to all patients with a possible extension of 4 or 8 sessions for patients who continue to show improvement and/or are motivated to continue therapy for optimal treatment effect. The weekly improvement is measured during the treatment by a weekly administration of the YBOCS to obtain a severity score after every four individual sessions.
After the 5 weeks of combined treatment, patients who have achieved remission (YBOCS<=12) on two consecutive weeks will discontinue the treatment; patients who have at the end of week 5 reached (partial) response, defined as >=25% improvement on YBOCS score (Mataix-Cols et al. 2016), will continue, if motivated, for another week (week 6); patients who have not reached (partial)

response but feel that they can still profit from continued treatment will also continue. Patients who worsened during treatment will be discontinued. At the end of week 6 we will again monitor progress using the same criteria, allowing patients who continue to show steady (partial) response the opportunity to undergo a seventh week of treatment, amounting to a maximum of 28 sessions per participant. This design allows patients who are experiencing protracted and slowly accruing benefit from the repeated combined sessions to maximize their treatment effect; and it accounts for the slow and linear benefit of repeated rTMS sessions that has been observed in patients with OCD, who still improve at or after 20 sessions (Donse et al. 2018, Mantovani et al. 2010). The decision process on (dis)continuation will follow shared decision making; in case of doubt, the case will be discussed in the weekly indication & treatment meeting.
Previous meta-analyses have shown conflicting and inconclusive results about the efficacy of different stimulation targets in OCD (Berlim et al. 2013, Rehn et al. 2018, Zhou et al. 2017,). We base our choice of stimulation location, intensity, duration and frequency on recommendations from international guidelines and following the updated meta-analysis that we carried out (Fitzsimmons et al., in preparation). Treatment will thus consist of low-frequency (1-Hz) rTMS over the pre-supplementary motor area (pre-SMA) in time-locked combination with ERP, while either unmedicated or on a stably established dose of medication.

rTMS parameters
The intensity of stimulation will be set at 110% of resting motor threshold, ascertained using EMG recording of the first dorsal interosseus muscle under handheld single-pulse stimulation by trained experimenters. Resting motor threshold is defined as 2 motor evoked potentials of at least 50μV peak-to-peak amplitude in a series of 4 consecutive single-pulse stimulations. In order to monitor changes in motor threshold during treatment, we will repeat the assessment of the motor threshold after 2 and 4 weeks of treatment.
In the verum rTMS condition, we will deliver 1500 continuous 1-Hz pulses to the pre-SMA, i.e. 25 minutes of stimulation under neuronavigation (see below). These protocols allow us to obtain a maximum stimulation effect while conforming to internationally published safety guidelines (Rossi et al. 2009).
The comparison group will thus receive 4 days/week sham-rTMS (using a sham coil) followed by ERP (unmedicated or on stable dose of medication for at least 8 weeks) similar to the other treatment arm. Sham-rTMS delivers TMS pulses of ineffective intensity to the brain while maintaining the scalp sensation, and therefore is considered a null-treatment, leaving possible clinical response in this group to the ERP. The location of the sham treatment will be performed over the same location, i.e. pre-SMA, to further ensure blinding of the patient to the treatment condition.
TMS coil placement using neuronavigation
Precision and specificity of the rTMS intervention will be ascertained and maintained throughout the treatment using neuronavigation (Sack et al. 2009), available in all collaborating centers. The procedure of neuronavigation

requires the use of a high-resolution T1 MRI scan, that will be registered to the patient*s head upon co-registering visible landmarks on the head of the patient with landmarks on the MRI scan. This will allow us to perform stereotaxic placement of the center of the stimulation coil on the pre-identified target. The use of neuronavigation software will additionally allow us to record the location of every single pulse of stimulation throughout the treatment, enabling us to reposition the coil during treatment if needed, and for post-hoc verification of the precise stimulation location in the subject*s individual MRI in native space, and at group level in standard space. Precision of stimulation location will therefore also be available for use in post-hoc analyses of treatment efficacy. Finally, the neuronavigation recordings are used to reposition the coil at the sequential visits with minimal time investment. The use of neuronavigation allows us to place the coil at the stimulation target with millimeter precision and resolution.
The positioning of the TMS coil on the scalp will be based on the EEG 10-20 coordinate system. In parallel we define three alternative individual MRI-based pre-SMA coordinates, using:
1) pre-identified coordinates in standard space derived from group activation studies that activate the pre-SMA. This standard target will then be converted to each patient*s individual native space, using the inversion of the conversion matrix from native to standard space. Based on the literature, the pre-defined target coordinates in standard space for the left pre-SMA are: x=-4, y=14, z=58 (Norman et al. 2019; Picard and Strick. 2001).
2) coordinate in pre-SMA with strongest anti-correlation with the amygdala during resting state
3) coordinate in pre-SMA with strongest anti-correlation with the amygdala during emotional processing (symptom provocation task).
This will allow us to post-hoc map the optimal individualized MRI-based coordinates relative to the actually stimulated coordinate in order to relate treatment success to stimulation location (distance between actual and optimal coordinate). This approach will serve to inform us on the added value of MRI-based individualized targeting using neuronavigation versus non-neuronavigated rTMS treatments. This is relevant for use in future clinical practice.

Requirements for the TMS and neuronavigation devices
In this study we will use CE-certified rTMS equipment with similar pulse shapes and pulse widths to ascertain an acceptable degree of standardization. Systems using biphasic TMS pulses and pulse widths between 280-330 µs will be deemed acceptable (this includes Magstim (330 µs), MagVenture (280 µs) and Deymed DuoMag (280 µs) systems). All the TMS systems should be outfitted with a MEP unit to quantify the motor threshold.
For the placebo condition *passive* placebo coils will be used, i.e. coils identical to the stimulation coils in appearance, but with a built-in metal plate that effectively blocks the active stimulation while maintaining mechanical scalp sensation. These placebo coils are available for the systems mentioned.

For neuronavigation several systems and approaches exist. In this study we will include only CE-certified systems that achieve coil placement using frameless stereotaxy, guided by an infrared-emitting and receiving stereoscopic camera. Available setups in the participating centers are Brainsight (Brainbox Ltd, UK) and TMSnavigator (Localite, Germany).

Study burden and risks

Patients will receive a minimum of 20 and maximum of 28 sessions of rTMS (30 minutes per session) adjuvant to ERP (90 minutes per session), 4 days/week for 5 (to 7) weeks. Prior to treatment they will get an MRI (max 1 hour). Screening is 1 hour, baseline assessment takes half a day (3.5 - 4 hours). Pre-treatment, weekly during treatment, and post-treatment and at 3, 6 and 12 months follow-up, they will be assessed for about 1 hour.

Benefits experimental group: severity of OCD (and comorbid affective) symptoms will probably decrease.
Benefits sham group: severity of OCD (and comorbid affective) symptoms will probably decrease, even in this group, thanks to the intensive ERP program (4 days/wk).
Risks experimental group: rTMS-related side effects, see paragraph of side effects (see below).
Risks sham group: risk of suboptimal treatment effect, due to fact that they only receive intensive ERP.

Side effects of rTMS
TMS is considered safe and generally tolerable. When following the international safety guidelines (Rossi et al. 2021), the risk to induce an epileptic convulsion is extremely low. Hearing protection is achieved by wearing ear plugs during stimulation. Possible adverse events of TMS have been frequently mentioned but a validated checklist to monitor and quantify adverse effects does not exist. We recently performed a pilot study with the aim to systematically objectify possible adverse events of rTMS during treatment for OCD, using an in-house-made questionnaire (currently used in ongoing proof-of-concept RCT in OCD as part of the VIDI project of OA van den Heuvel). This questionnaire consists of three parts, assessing possible adverse events during, directly after and during the days after an rTMS-treatment session. We see that adverse events, or co-occurrences, during treatment in OCD patients are rare, and consist mostly of headache, local scalp pain and sleepiness. Frequency and severity of these adverse events differs widely between subjects, and has not led to subjects withdrawing from our earlier trials.

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

- OCD as current primary diagnosis
- Age 18 and older
- Yale-Brown Obsessive-Compulsive Scale (YBOCS) score of 16 or higher.
- Insufficient response to state-of-the art exposure therapy with response prevention (ERP) and/or drop-out from ERP due to extreme anxiety/avoidance
- The following comorbid disorders are allowed (as long as OCD is the current primary diagnosis): depression, other anxiety disorders, ADHD, tic/Tourette*s disorder, eating disorders, personality disorders, autism spectrum disorder (when this does not dominate the clinical profile, i.e. is not main diagnosis).
- Commitment to actively undergo intensive exposure therapy (both supervised during ERP sessions, as well as unsupervised at home)
- Unmedicated (for at least 8 weeks) or stable dosage of psychotropic medication (for at least 8 weeks), involving serotonergic antidepressants (SSRI, SNRI, clomipramine). Other psychotropic medication that is allowed (provided dosage is stably established for at least 8 weeks): methylphenidate,

mood stabilizers, antipsychotic drugs
- Ability to participate in frequent treatment sessions (4 days/week, for 5 (or 6, or 7) weeks) at one of the 5 sites nearest to their home and/or work
- Ability to participate in pre-treatment MRI session (for neuronavigation) at one of the 3 academic sites nearest to their home and/or work
- Capacity for providing informed consent

Exclusion criteria

- OCD patients with hoarding as main symptom dimension
- The following comorbid disorders (current diagnosis) are not allowed: psychotic disorders, bipolar disorder, autism spectrum disorder (when this dominates the clinical profile, i.e. is diagnosed as main disorder), substance use disorder
- Active suicidal thoughts and intent to act on it
- Chronic use of benzodiazepines is not allowed
- Cochlear implant
- (History of) epilepsy
- Pregnancy
- Extreme claustrophobia or metallic objects in or on the body, preventing from participation in MRI session
- Space-occupying lesion on MRI
- Previous rTMS treatment (for blinding reasons)

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:	Recruiting
Start date (anticipated):	16-05-2022

Enrollment:	250
Type:	Actual

Ethics review

Approved WMO Date:	10-03-2022
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	23-03-2022
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	10-06-2022
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	05-07-2022
Application type:	Amendment
Review commission:	METC Amsterdam UMC

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	https://clinicaltrials.gov/ct2/show/NCT05331937
CCMO	NL78930.029.21