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Rationale and study design of a trial to assess rTMS add-on value for the amelioration of negative symptoms of schizophrenia (RADOVAN)

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ABSTRACT

Background: Schizophrenia is a severe and often difficult to treat psychiatric illness. In many patients, negative symptoms dominate the clinical picture. Meta-analysis has suggested moderate, but significant effects of high-frequency repetitive transcranial magnetic stimulation (HF-rTMS) on these symptoms. For treatment of depression a much shorter protocol - intermittent theta burst stimulation (iTBS) - has shown to be non-inferior to conventional high-frequency rTMS. This randomized, sham-controlled, rater-blinded clinical trial assesses the effects of conventional HF-rTMS as well as of iTBS of the left dorsolateral prefrontal cortex in comparison with sham.

Methods: The study will be conducted at two psychiatric university hospitals in Germany and at two in the Czech Republic. Assuming an effect size of 0.64 to be detected with a power of 80%, the calculated sample size is 90 patients. Primary outcome will be the difference in the Scale for the Assessment of Negative Symptoms (SANS) score between each active arm and the sham arm at end of treatment.

In addition, the trial investigates effects on depressive symptoms, cognitive performance and cigarette smoking. Recording magnetic resonance imaging (MRI) and electroencephalography (EEG) data will serve to assess whether treatment success can be predicted by neural markers and is related to specific neurobiological changes.

Discussion: This is a clinical trial directly comparing 10 Hz-rTMS and iTBS in a sham-controlled manner in treating negative symptoms of schizophrenia. If successful, this would present an interesting treatment option for a chronic and severe condition that can be applied at most psychiatric hospitals and only takes up a few minutes per day.

Trial registration number: This trial has been registered at clinicaltrials.gov, Identifier: NCT04318977.

Data dissemination: Results from the trial shall be published in peer-reviewed journals and presented at meetings and conferences.

1. Introduction

Schizophrenia is amongst the most severe psychiatric disorders, affecting up to 1% of the population and thus is of great medical as well as social importance. Despite some progress in pharmacological treatments, up to 30% of patients do not respond adequately to standard treatment or show poor adherence due to side effects [1,2].

Apart from the clinically more impressive so-called positive symptoms such as delusions or hallucinations, the clinical course is determined strongly by the so-called negative symptoms, such as affective flattening, alogia, avolition, asociality, and anhedonia. The therapeutic possibilities to control and improve negative symptoms are limited at best, and severe chronic disability is often the fate of these patients [2,3]. Thus, adding alternative modalities to the arsenal of available treatment options would be highly desirable.

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Abbreviations

CDSS	Calgary Depression Rating Scale for Schizophrenia
CGI	Clinical Global Impression
CRF	Case Registration Form
DLPFC	Dorsolateral Prefrontal Cortex
EEG	Electroencephalography
GCP	Good Clinical Practice
HDRS	Hamilton Depression Rating Scale
HF	High Frequency
iTBS	Intermittent Theta Burst Stimulation
MDI	Major Depression Inventory
MRI	Magnetic Resonance Imaging
PANSS	Positive and Negative Syndrome Scale
rTMS	Repetitive Transcranial Magnetic Stimulation
SANS	Scale for the Assessment of Negative Symptoms

Repetitive transcranial magnetic stimulation (rTMS) can non-invasively modulate neuronal activity and can be used to target specific areas of the brain. RTMS is now widely accepted as a possible treatment for depressive illness, among other conditions [4]. Efforts have been undertaken to identify potential anatomical targets to use rTMS in treating negative symptoms. Neuroimaging has been used to demonstrate reduced left-hemispheric frontal and prefrontal activity in patients with negative symptoms which was shown to be at least partially attenuated by rTMS over the left dorsolateral prefrontal cortex (DLPFC) using a HF-rTMS protocol [5,6] that is known to induce facilitatory effects on neural activity.

Sham-controlled clinical trials treating negative symptoms this way have shown mixed results. The so far largest sham-controlled, multicenter clinical trial (the "RESIS" trial) was not able to show a significant treatment effect of 10 Hz rTMS over the left DLPFC on the Positive and Negative Syndrome Scale (PANSS) ratings, depressive symptoms and cognitive functioning [7]. However, a notable number of other trials have shown promising results. The meta-analysis by Aleman and colleagues including 24 studies suggested rTMS of the DLPFC (mostly left-sided, in a few studies bilateral or right-sided) to have a mean weighted effect size of 0.64 compared to sham [8]. In light of this evidence, a European expert consensus considers high-frequency rTMS of the left DLPFC to have "possible efficacy" on negative symptoms [4]. However, considering the moderate effect sizes and contradictory results from some trials, sham control is still considered an important part of further research.

For treatment of depression, there is evidence that a shortened protocol of 'facilitating' rTMS, so called intermittent theta burst stimulation or iTBS [9] is not inferior to the conventional rTMS treatment protocol, but due to the much shorter duration allows to treat a greater number of patients in shorter time [10]. Therefore, it is our goal to investigate whether the effects of rTMS on negative symptoms of schizophrenia could also be shown for iTBS using the protocol implemented by Blumberger et al. Though using different treatment conditions, studies investigation the application of iTBS in patients with negative symptoms have shown promising results by using e.g. four week [11] or two week neuro-navigated treatment [12].

In the era of individualized medicine it would be of great interest if treatment success can be anticipated by evaluating certain markers before even initiating treatment. There is preliminary evidence that structural MRI data can be used to predict response to rTMS in schizophrenia [13]. However, there is no such evidence yet regarding functional MRI data and iTBS treatment.

Electrophysiological investigations were able to show abnormal oscillatory EEG activity as well as evoked potentials in patients suffering from schizophrenia with negative symptoms [14]. One approach to investigate resting state EEG activity is by detection of brain activity and its development over time by so-called EEG microstates. They basically reflect the immediate state of the scalp neuronal activity due to the potential field. These states are stable over a short period of time and can be used to examine large scale brain networks [15]. Previous research usually detected 4 to 5 microstates (named A, B, C, D, and E) in both healthy people and patients with psychiatric disease [16] and already suspected EEG microstates as a marker for schizophrenia [17]. It has been demonstrated that microstate C occurs significantly more often, whereas the appearance of microstate D is reduced in this major psychiatric condition compared to healthy volunteers [17,18].

Neuroimaging experiments highlighted the connection of microstate C with the salience network [19] and the anterior default mode network [16] which was found to be dysfunctional [20,21]. Changes in this microstate were also observed after antipsychotic treatment [22]. EEG microstates could be another suitable marker for the assessment of interventions in schizophrenia.

Another potential EEG marker might be represented by TMS evoked potentials or offline effects of single sessions of rTMS on EEG markers. These were observed to be altered in patients with schizophrenia [23,24]. Furthermore, TMS evoked potentials were suggested as a suitable additional method for the evaluation of interventions in schizophrenia and other psychiatric conditions [25] and could potentially predict response to a specific treatment.

Extensive use of nicotine is highly prevalent in patients with schizophrenia and is a contributing factor to the high morbidity and shorter lifespan in this population. Previous studies have suggested that rTMS might be helpful in reducing nicotine craving and number of cigarettes smoked [26], and we will examine nicotine craving and usage of our treated patients.

2. Methods

2.1. Design of the trial and study sites

The RADOVAN trial is a cooperative randomized controlled trial carried out at four study centers. Recruitment of patients and analysis of pooled data is carried out at the Psychiatric departments of Regensburg, Aachen (both Germany), Brno and Ostrava (both Czech Republic).

2.2. Study population, inclusion and exclusion criteria

Participants will be recruited from the in- and outpatient populations of the abovementioned hospitals. Male and female patients aged 18–75 years will be eligible if they have a diagnosis of schizophrenia according to ICD-10 criteria as well as M.I.N.I. interview with predominantly negative symptoms and a SANS scale of at least 35, have taken stable medication over the last two weeks and are able and willing to give written informed consent to the study.

Key exclusion criteria include existing contraindications for treatment with rTMS (e.g. cardiac pacemaker, ferromagnetic implants, history of epileptic seizures), current comedication with lorazepam >2 mg or diazepam >10 mg daily, the presence of severe somatic medical condition or psychiatric comorbidity not compatible with study treatment, current marked abuse or dependence on alcohol or illegal drugs as well as pregnancy or lactation. Further contraindications are involuntary detention at psychiatric hospital, insufficient knowledge of German or Czech language respective to the treatment center and finally previous treatment with rTMS.

3. Intervention

Patients will be randomized to one of four treatment groups. Each group will receive a four week treatment period with five treatments a week (Monday to Friday), amounting to 20 treatment sessions. Stimulation site, the left DLPFC, will be determined via the F3 position of

10–20-EEG-system. One group will receive verum stimulation with a 10 Hz HF-rTMS protocol, consisting of 4 s-"on"- and 26 s-"off"-periods to a total of 3000 stimuli. Intensity will be set to 120% of resting motor threshold. One group will receive verum stimulation with the iTBS protocol, again with 120% of resting motor threshold for a total of 600 pulses per session, resulting from 20 repetitions of one theta burst "train".

If the initial intensity is too high for the patient to tolerate, there will be the possibility of a "ramping" phase, in which intensity is dialed down to an acceptable level and then increased to target intensity as quickly as possible over the next sessions.

For each verum group (10 Hz and iTBS), there will be a sham control group. Sham treatment will consist of either a sham coil or alternatively, angulating the verum coil 45° away from the skull with otherwise identical parameters as has been done e.g. in the RESIS trial [27]. Standard care consisting of pharmacotherapy, psychotherapy and other treatments (e.g. occupational therapy, group therapies) will continue during the intervention, which is necessary especially given the possibility of sham stimulation.

3.1. Blinding

Patients are to be blinded as well as raters. Raters will not be involved in the immediate application of rTMS, which will be performed by specialized operators. Considering the difference in duration between 10 Hz and iTBS, there can be no perfect patient blinding of these two treatments. Patients who have previously undergone rTMS treatment will be excluded from the trial.

3.2. Detailed trial objectives and purpose

The primary objective of the trial is to prove whether 10 Hz-rTMS and iTBS are effective in treating negative symptoms of schizophrenia as indicated by changes in SANS score after four weeks of treatment.

Secondary objectives include evaluating the efficacy of 10 Hz-rTMS and iTBS versus sham and of 10 Hz-rTMS versus iTBS concerning the reduction of negative symptoms as measured by PANSS negative scale, the tolerability and safety of each treatment arm, the reduction of depressive symptoms as measured by Calgary Depression Rating Scale for Schizophrenia (CDSS), Major Depression Inventory (MDI) and Hamilton Rating Score for Depression (HDRS) as well as global assessment by Clinical Global Impression (CGI) and assessment of cognitive capacity as measured by digit span and a concentration test. Finally, cigarette consumption will be examined as a further secondary objective.

Furthermore, we will investigate whether treatment success is accompanied by structural and functional brain changes and can be predicted by MRI and EEG data.

3.3. Ethical issues

Patients will be extensively informed by study physicians on the risks and benefits of participating in the study, as will be their legal custodians if applicable. The study, patient information and consent forms were approved by the local ethics committees under numbers 19-1616-101 (Regensburg), 01–180919/EK (Brno), 279/2020 (Ostrava) and EK 372/19 (Aachen). Extensive literature data and long years of clinical experience have shown rTMS to be safe and well tolerated. The study will be performed in accordance with the Declaration of Helsinki and ICH Guidelines for Good Clinical Practice (GCP). The patient population in question suffers from severe chronic psychiatric illness often not adequately controlled by medication, psychotherapy or supportive measures and deserves special scientific attention to improve available treatment. As all patients are recruited from the in- and outpatient population, they all have treating physicians and therapists, ensuring their further adequate treatment after completing or dropping from the trial. Patients will be closely monitored for adverse events; severe adverse events will be reported to local ethics committees.

3.4. Visit schedule and data collection/management

Study visit (V)	V 0	V 1	V 2			V 3	V 4
Phase	**Screening**	**Baseline**	**Treatment**				**Follow-Up**
Week (W)			1	2	3	4	
Day (D)	−28 to −7	−7 to −1	5	12	19	26	90 ± 3
Informed consent	X						
Inclusion and exclusion criteria	X	X					
Demographical and medical data	X	(X)					
M.I.N.I.	X	(X)					
Comorbidities	X	(X)				X	X
Medication		X				X	X
SANS	X (≥35)	X		X		X	X
PANSS		X		X		X	X
CDSS–G		X		X		X	X
CGI		X		X		X	X
HAMD		X		X		X	X
MDI		X		X		X	X
Cognitive testing		X				X	X
Smoking habits		X				X	X
MRI		X (±)				D26 to +7	
EEG		X				X	
Motor threshold		X	(X)				
Randomization			D1 of W1				
Treatment			X	X	X	X	
Treatment side effects			X	X	X	X	X
Putative treatment modality						X	
			V 2–5 (except treatment) Possible D −1 to +3				

F(X) = if not yet done.
X (±) = can vary from V1.

Data will be collected by study physicians who are blinded to the treatment protocol. Study physicians are clinical psychiatrists with extensive experience in treating patients with schizophrenia and the clinical rating scores. Data will be entered into written Case Report Forms (CRFs) and safely stored. Data will be entered in to a digital database under a pseudonym be operators not involved in data collection for later analysis. The modalities of data handling and storage have been approved by the ethics committees.

3.5. Power and sample size justification

Assuming an effect size of 0.64 as found in the meta-analysis by Aleman and a power of 80%, and assuming a statistical significance threshold of 5%, 90 patients shall be recruited to the study.

3.6. Randomization

Patients will be randomized by the study center in Regensburg via block-wise randomization using a computer generated randomization system. Patients will be randomized in blocks of 6, with 2 patients randomized to active 10 Hz-rTMS, 2 patients to active iTBS, 1 patient to sham 10 Hz-rTMS, and 1 patient to sham iTBS.

The randomization procedure will be performed by staff that are not involved in any actual interaction with patients. The information about treatment allocation will be sent via email to the TMS operators at the different study sites. In addition, a general information about the date of the randomization will be sent by email to the TMS operators and raters of the respective study site.

3.7. Statistics

The analysis of primary and secondary outcome measures will be done with the intention to treat sample. Bias of missing patients due to protocol violations will be controlled by replication of analyses with the per protocol sample. Missing values will be replaced by the last observation carried forward and backward method and are allowed up to 10% of missing visits for all patients. Inductive statistics will be used in this case which was shown to come up with comparable results in contrast to mixed effects model analyses in the case of 6.6% missing values [28]. Independent variables for analyses will be treatment arm, time point of clinical visits, and center of the study.

3.8. Recruitment

To the current date, eleven patients have been enrolled.

4. Discussion

In summary, this is a clinical trial directly comparing 10 Hz-rTMS and iTBS in a sham-controlled manner in treating negative symptoms of schizophrenia. If successful, this would present an interesting treatment option that can be applied at most psychiatric hospitals and only takes up a few minutes of patients' and hospital staffs' time per day.

Results from previous studies have been heterogenous. Meta-analysis by Aleman [8] revealed a significant but moderate effect of rTMS when compared to sham. Heterogeneity of results suggests that identifying moderating variables and predicting factors of treatment success is the next step in clarifying the role of rTMS in the treatment of negative symptoms of schizophrenia. We chose a treatment duration of four weeks. This is longer than in most previous studies and is also the duration chosen, amongst others, by Zhao et al. in their rather verum-favorable trial [11] and which is also the minimum duration used in the Blumberger trial in depression [10].

There are several limitations with the study:

The pulse pattern and duration of HF-rTMS and iTBS are of course, at least in principle, intelligible by the patient. However, this is a fundamental problem when comparing different rTMS protocols. Sham will consist of the verum coil angulated 45° away, which generates some skull sensation with minimal cerebral effects as discussed by e.g. Cordes et al. for the RESIS trial [27]. Establishing sham conditions has been and will always be an issue in rTMS studies. Patients with previous rTMS experience will be excluded from study participation, and patients will be asked to guess which treatment they have received in an effort to evaluate blinding success. We will also refrain from informing patients about the technical details of the protocols as far as not necessary for informing about safety issues.

Clinical rating scales of course do not exhaustively characterize the symptoms and disabilities the patients face. However, by using an array of diverse testings including cognitive assessments, we hope to get a good picture of patient's overall condition.

Concomitant usage of antipsychotic is expected to be almost 100% in the study population, and occasional usage of antidepressants is expected to occur. Medication use will be documented. Medication is expected to be stable the two weeks before commencing treatment by the physician's judgement. At least, frequent change of medication is not that common in schizophrenia with predominant negative symptoms as in other, more acute conditions.

5. Conclusion

To summarize, we hope to further elucidate the efficacy and tolerability of HF-rTMS and iTBS in the treatment of negative symptoms of schizophrenia, and to find clues to which markers might predict treatment success in the individual patient.

Ethics approval

The study, patient information and consent forms were approved by the local ethics committees under the following approval numbers: Regensburg University Ethics Committee [19–16], Ethics Board of the University Hospital Brno (01–180919/EK), the Ethics Committee of FN Ostrava (279/2020) and Ethics Committee of the Medical Faculty of RWTH Aachen University (372/19).

Written informed consent was and will be obtained from the participants.

Consent for publication

Not applicable.

Data availability

All data generated for the protocol is available from the authors upon reasonable request.

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Author contributions

BL, LU and TP conceived of the study outline. All of the authors detailed the design of the study, recruit, rate and support participants and handle and interpret the data, all at their respective study site. KS and LR prepared the case registration forms. TH prepared and submitted the manuscript for publication. All authors proofread and approved the manuscript.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: BL receives royalties from Springer for edited books, received research grants from the company Neuromod as well as from national (DFG, BMBF) and European institutions (EU), received speaker's honoraria and advisory panel payments from Neuromod, Desyncra, Decibel Tx and Servier. SS received funding from the European Union's Horizon 2020 research and innovation program under the Marie Sklodowska-Curie grant [agreement number 722046]. TH has had travel expenses paid for by Nexstim plc. All other authors have no competing interests or disclaimers to declare.

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