PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Intermittent Theta Burst Stimulation applied during early rehabilitation after stroke: Study protocol for a randomized controlled trial
AUTHORS	Hensel, Lukas; Grefkes, Christian; Tscherpel, Caroline; Ringmaier, Corinna; Kraus, Daria; Hamacher, Stefanie; Volz, Lukas; Fink, Gereon

VERSION 1 – REVIEW

REVIEWER	Thomas Nyffeler Luzerner Kantonsspital
REVIEW RETURNED	30-Sep-2019

GENERAL COMMENTS	The protocol is very interesting, scientifically credible and presented in an appropriate context; the design is ethically and procedurally sound.

REVIEWER	Vincenzo Di Lazzaro Universita Campus Bio-Medico di Roma, Unit of Neurology, Neurophysiology, Neurobiology, Department of Medicine
REVIEW RETURNED	15-Oct-2019

GENERAL COMMENTS	This is a very interesting study. I have the following comments. The control group will be stimulated over different areas. Because it cannot be ruled out an effect of this form of stimulation in stroke patients, I don't think that this is a good control condition, it would be better to use a sham stimulation. iTBS uses intensities below motor threshold thus, this can be done easily with a sham coil. It would be better to use ARAT score instead of hand grip as primary outcome. The authors should report whether patients with no recordable MEP will be excluded from the study ore stimulated at the maximal stimulator output.

REVIEWER	Dr. Moisés León Ruiz Clínica San Vicente, Madrid, Spain
REVIEW RETURNED	30-Oct-2019

GENERAL COMMENTS	Everything is perfect. Congratulations. Thank you very much indeed

VERSION 1 – AUTHOR RESPONSE

Reviewer 1

The protocol is very interesting, scientifically credible and presented in an appropriate context; the design is ethically and procedurally sound.

We thank the reviewer for the positive assessment of our protocol.

Reviewer 2

This is a very interesting study. I have the following comments.

1. The control group will be stimulated over different areas. Because it cannot be ruled out an effect of this form of stimulation in stroke patients, I don't think that this is a good control condition, it would be better to use a sham stimulation. iTBS uses intensities below motor threshold thus, this can be done easily with a sham coil.

We thank the reviewer for the comment addressing the choice of the control condition, which we wish to further clarify in our protocol. Importantly, while patients assigned to the study arm receive real iTBS stimulating the primary motor cortex (M1), patients assigned to the control group receive iTBS not only over another brain region (i.e., the parieto-occipital vertex) but in a different orientation with the handle of the coil pointing anterior in parallel to the interhemispheric fissure. In addition, the coil is tilted upwards about 45° to increase the coil-brain distance. This coil position still induces skin sensations and acoustic noise comparable to the M1 stimulation, but the electromagnetic field is substantially weaker and far outside the target range to excite neural tissue. We have validated this control condition in a number of experiments, and we could consistently show that this coil positioning has no detectable effect on behavior, motor excitability, or fMRI activity/connectivity levels (Cardenas-Morales et al., 2013; Nettekoven et al., 2014; Nettekoven et al., 2015; Volz et al., 2016; Diekhoff-Krebs et al., 2017).
Therefore, we are confident that this control condition comes very close to sham stimulation, ensuring that sensory and acoustic effects are comparable in both conditions, which is essential for the blinding of participants. We agree with the reviewer that an increasing number of sham coils have entered the market recently, some of which we have tested in our lab to optimize the study design. However, in 2015 when our protocol was first presented to the local ethics committee, we found that the sham coils of leading manufacturers in the market could be easily distinguished from the "real coil", predominantly by the less noisy TMS sound and absent skin sensations below the coil.
Finally, we would like to be as close as possible to the experimental parameters used in our pilot study (Volz et al., 2016 Cerebral Cortex).
To accommodate the reviewer's concern, we made the following changes in our revised manuscript that clarify the application of the control condition in the present protocol:

Abstract:
[…] We investigate the effects of daily iTBS on early motor rehabilitation after stroke in an investigator-initiated, longitudinal randomized controlled trial. Patients (n=150) with hemiparesis receive iTBS (600 pulses) applied to the ipsilesional motor cortex (M1) or a control stimulation (i.e., coil placement over parieto-occipital vertex in parallel to the interhemispheric fissure and with a tilt of 45°).

Methods (iTBS protocol)

For patients assigned to the study arm receiving an effective intervention, the protocol is applied over the ipsilesional M1, whereas patients in the control group receive iTBS over the parieto-occipital vertex, corresponding to the POz location of a 10-20 EEG system. Importantly, to prevent effective stimulation of cortical tissue in the control condition, the handle of the coil was placed parallel to the interhemispheric fissure pointing to the front. Besides, the coil was tilted upwards about 45°, touching the skull not with the center but with the rim to increase the coil-brain distance. This procedure induces similar acoustic and tactile effects as M1 stimulation without leading to a change of motor behavior, motor cortical excitability, or neural activity as measured with fMRI (Cardenas-Morales et al., 2013; Nettekoven et al., 2014; Nettekoven et al., 2015; Volz et al., 2016; Diekhoff-Krebs et al., 2017).

2. It would be better to use ARAT score instead of hand grip as primary outcome.

We agree with the reviewer that the ARAT score is a valid and robust measure for motor performance after stroke. Nevertheless, the following arguments guided our decision to select relative grip strength as the primary outcome parameter:
i) Grip force represents a fundamental feature of recovered hand motor function, which can be measured in an easy and quick but highly standardized fashion, even in severely affected patients still unable to perform more complex grasping movements;
ii) It is rather robust against compensatory movement strategies as the primary movement direction (finger flexion) cannot be significantly modified by recruiting
other (e.g., more proximal) muscle groups. Therefore, increases in grip strength predominantly reflect restitution of neurological function rather than compensation achieved via learning alternative movement pattern as it might be the case for the ARAT.
iii) Variation in grip strength has been directly related to M1 activity (Dettmers et al. 1995). Therefore, as the intervention aimed at enhancing M1 activity, we assume that grip strength represents a sensitive behavioral marker.
iv) Relative grip strength can be easily assessed at the bedside within 1-2 minutes in contrast to the ARAT score, which needs up to 10-15 min, depending on the deficit. Hence, grip strength is better suited for a day-by-day assessment.
v) The design of the present study is based on our previous work (Volz et. al, 2016), demonstrating an effect of iTBS on relative grip strength. We, therefore, aimed to maintain the primary outcome parameter comparable to the proof-of-principle study. However, we hope that the implementation of the ARAT as a secondary outcome parameter will allow us to estimate the effect of iTBS on motor recovery for future studies.

To point out the above-mentioned rationale and the need to explore iTBS effects in alternative measures such as the ARAT or the Fugl-Meyer Scale, we modified the paragraph ‘Outcome measures’ in our Methods section.

Methods (Outcome measures)
The primary endpoint of this study is relative grip strength defined as of the maximum grip strength of the affected (paretic) hand compared to the unaffected hand, assessed three to six months after the intervention, i.e., in the chronic phase post-stroke. While motor recovery after stroke may be assessed with several measures, we selected grip strength based on the following rationale: First, relative grip strength represents a fundamental feature of hand motor function. Second, the assessment of grip strength can be conducted efficiently at the bedside, even in severely affected patients. A stroke leading to hemiparesis typically reduces grip strength. In turn, recovery of grip strength usually precedes the recovery of other motor domains such as dexterity or movement speed [49].

Furthermore, improvements in grip strength predominantly reflect the restitution of neurological function as grip strength is less dependent on alternative movement strategies such as compensatory movements. Besides, grip strength is mediated by contralateral M1 activity [50]. Therefore, given that in the present study iTBS is applied to enhance M1 activity, grip strength seems to be a sensitive readout to monitor improvements of M1. Finally, as the present study is designed based on a pilot study that also used grip force as the primary outcome parameter [24], we aimed at reproducing the beneficial effects of iTBS on the recovery of grip force. Besides, we further assess the impact of iTBS on the motor recovery in other parameters frequently used to study motor performance after stroke. These secondary endpoints […]

3. The authors should report whether patients with no recordable MEP will be excluded from the study ore stimulated at the maximal stimulator output.

We thank the reviewer for pointing out the need to clarify this critical issue. Since acute stroke patients often show no recordable MEPs early after stroke, we argue that it is critical to include those patients in the study too. Therefore, in line with our pilot study (Volz et al., 2016), patients with no measurable MEP receive iTBS at the maximal intensity that may be safely applied with the SuperRapid2 system (50% MSO).

Methods (iTBS protocol)
As shown in our proof-of-principle study [24], stimulation thresholds may exceed the maximum stimulator output (MSO) in case of a severe disruption of the corticospinal tract leading to no recordable MEPs. Here, the stimulation intensity is set to 50% MSO, which represents the upper limit for 50-Hz stimulation using a standard Magstim SuperRapid2 stimulator and which has been proven to be safe.

Reviewer 3

Everything is perfect. Congratulations.

We are grateful for the appreciation of our work and thank the reviewer for the positive evaluation.