



BMJ Open Intermittent theta burst stimulation applied during early rehabilitation after stroke: study protocol for a randomised controlled trial

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ABSTRACT

Introduction Intermittent theta burst stimulation (iTBS) applied to primary motor cortex (M1) has been shown to modulate both the excitability and connectivity of the motor system. A recent proof-of-principle study, based on a small group of hospitalised patients with acute ischemic stroke, suggested that iTBS applied to the ipsilesional M1 combined with physical therapy early after stroke can amplify motor recovery with lasting after effects. A randomised controlled clinical trial using a double-blind design is warranted to justify the implementation of iTBS-assisted motor rehabilitation in neurorehabilitation from an acute ischaemic stroke.

Methods/design We investigate the effects of daily iTBS on early motor rehabilitation after stroke in an investigator-initiated, longitudinal randomised controlled trial. Patients (n=150) with hemiparesis receive either iTBS (600 pulses) applied to the ipsilesional motor cortex (M1) or a control stimulation (ie, coil placement over the parieto-occipital vertex in parallel to the interhemispheric fissure and with a tilt of 45°). On 8 consecutive workdays, a 45 min arm-centred motor training follows the intervention. The relative grip strength, defined as the grip force ratios of the affected and unaffected hands, serves as the primary outcome parameter. Secondary outcome parameters are measures of arm function (Action Research Arm Test, Fugl-Meyer Motor Scale), stroke severity (National Institutes of Health Stroke Scale), stroke-induced disability (modified Rankin Scale, Barthel Index), duration of inpatient rehabilitation, quality of life (EuroQol 5D), motor evoked potentials and the resting motor threshold of the ipsilesional M1.

Ethics and dissemination The study was approved by the Ethics Commission of the Medical Faculty, University of Cologne, Germany (reference number 15-343). Data will be disseminated through peer-reviewed publications and presentations at conferences. Study title: Theta-Burst Stimulation in Early Rehabilitation after Stroke (acronym: TheSiReS). Study registration at German Registry for Clinical Trials (DRKS00008963) and at ClinicalTrials.gov (NCT02910024).

INTRODUCTION

Stroke is a leading cause of acquired long-term disability in adults worldwide. From

Strengths and limitations of this study

- The present study is a randomised, controlled, double-blind, single-centre trial assessing the efficacy of intermittent theta burst stimulation (iTBS) in patients with acute cerebral ischaemia.
- Interventions are applied before daily physiotherapy in the first few days after stroke since previous work suggests higher neural plasticity during the acute, compared with the chronic phase.
- Patients receive iTBS during their hospitalisation warranting the adequate assessment of adverse events.
- A limitation of the study is a potential selection bias, given the patients' expected comorbidities, which may pose a risk for the application of repetitive transcranial magnetic stimulation or compromise the ability to provide informed consent.

1990 to 2010, the prevalence of stroke has reached numbers of 500–1000/100 000 people in North America and the European countries.¹ Although recent developments in the acute treatment of a stroke such as thrombolysis or thrombectomy effectively reduce both morbidity and mortality,² the majority of patients are still left with permanent motor deficits. More than 50% of stroke survivors keep a persisting impairment, affecting the patients' activities of daily living.^{3,4}

Functional recovery has been shown to arise, at least in part, from the reorganisation of functional brain networks, with intact neural structures compensating for the loss of specialised neural circuitry damaged by the lesion.^{5,6} Importantly, a focal stroke lesion also interferes with the neural processing in distant brain regions, thereby affecting the brain at a network level. In this context, neuroimaging studies have frequently reported altered brain activity in motor-related cortical areas

of both hemispheres, even for lesions affecting primarily deep white matter.^{7–9} Longitudinal data revealed that in the first days after stroke, the activity of the primary motor cortex is typically decreased, particularly in patients with severe motor deficits, despite the structurally intact motor cortex.⁸ This pattern is typically followed by a bihemispheric increase of activity, which correlates with the amount of early motor recovery. However, the best predictors of functional motor recovery are high levels of activity in the ipsilesional motor cortex early after stroke as well as the activity pattern lateralised to the ipsilesional hemisphere.^{10 11} Thus, restoring neural activation, particularly in the lesioned hemisphere seems to be essential for functional recovery after stroke.

Comparable effects have been found for changes in motor-cortical excitability as probed by transcranial magnetic stimulation (TMS).¹² In parallel to the initial decrease of fMRI activity observed for ipsilesional M1,⁸ TMS studies have also found lower excitability of this region, which correlates with the severity and prognosis of motor deficits.^{13 14}

To date, first-line rehabilitative strategies for improving motor deficits are based on functional training, that is, physical or occupational therapy early after stroke.^{15 16} Such behavioural interventions have been demonstrated to facilitate neural reorganisations.¹⁷ Accumulating evidence suggests that non-invasive brain stimulation techniques such as repetitive TMS (rTMS) may enhance neuroplasticity, thereby facilitating neural reorganisation and recovery from stroke deficits.^{18 19} Particularly the observation of decreased ipsilesional excitability early after stroke has led to the hypothesis that rTMS may be capable of increasing excitability and thus aiding functional recovery.²⁰ This effect has been demonstrated for different rTMS protocols varying in stimulation frequency, pattern and the number of pulses.^{20 21} Of note, rTMS may not only aid neural reorganisation within the stimulated region, but it also modulates the activity of interconnected brain regions, for example, the dorsal premotor cortex or the supplementary motor area, as shown for both healthy subjects²² and patients with stroke.²³ Thus, rTMS applied to M1 likely results in a system-wide change of neural activity in both hemispheres. At the behavioural level, proof-of-principle studies indicate that a single session of rTMS applied to ipsilesional M1 may transiently improve motor function of the paretic hand.^{24 25} Further, a critical factor for a therapeutic effect seems to be a combination of plasticity enhancing interventions with motor training, possibly leading to a better consolidation of (re-) learnt motor skills.^{26–28}

While several rTMS studies in patients with stroke reported transient improvements in motor function, other studies failed to demonstrate lasting beneficial effects.^{29–32} A recently published large sample (n=167) trial (Navigated Inhibitory rTMS to Contralesional Hemisphere (NICHE) trial) revealed that application of inhibitory rTMS over contralesional M1 in patients with chronic stroke failed to demonstrate any beneficial effect

of contralesional 1 Hz stimulation paired with arm-motor training in patients with chronic stroke,³³ despite promising data from a relatively large number of pilot studies with small sample sizes (usually 10–20 patients). One likely reason may be the time window of intervention, which, in most studies, targeted the chronic phase after stroke. Substantial functional recovery alongside high levels of neural plasticity is observed in the acute and subacute phases after stroke.³⁴

In contrast, the effectiveness of behavioural interventions gets more and more limited if more time elapses from the onset of the stroke. This negative effect may also be true for rTMS-mediated excitatory effects and their potential to support the recovery of function and neurorehabilitation. Hence, the amplification of neuroplasticity using rTMS may be most effective during the acute and early subacute phases after a stroke. While data on neuromodulatory effects within the first few days and weeks after stroke remain scarce, recent evidence from our group indicates the lasting beneficial effects of rTMS on motor recovery in a sample of patients with stroke in the first few days after the stroke.²³ In this study, two groups of patients with early subacute stroke (each n=13, on average 7 days poststroke) received intermittent theta burst stimulation (iTBS; 600 pulses, 70% resting motor threshold (RMT)) for 5 days, either covering ipsilesional M1 or a control with the TMS coil tilted over the parieto-occipital vertex. Recovery of grip strength was stronger in the M1-stimulated group than in the control-stimulated group, with the beneficial effect persisting at least 3–6 months. As shown by fMRI before and after the rTMS intervention, patients in the verum rTMS group featured increased functional connectivity between the modulated stimulation site and a functionally related motor network, including the dorsal premotor cortex and the supplementary motor area, compared with patients in the control-stimulation group.²³ Given that without rTMS intervention, patients during the first few days after the stroke featured a loss of activity and connectivity in the ipsilesional hemisphere,^{35–37} the finding of increased connectivity with the stimulated M1 suggests that the beneficial effects of rTMS may not only result from inducing local plasticity, but also from enhancing connectivity with a functionally related motor network. Taken together, these findings support the hypothesis that rTMS may be applied in addition to physiotherapy to induce plasticity in the ipsilesional M1 and thereby promote motor outcome. Of note, the small sample size of the follow-up groups and the heterogeneity of post-interventional treatments across patients preclude a reliable estimation of the clinical use of combined iTBS and physiotherapy in patients with (sub-)acute stroke to date. While studies with similar small sample sizes corroborate a positive effect of M1-modulation by non-invasive brain stimulation after stroke,³⁰ large randomised controlled trials are widely lacking.

Aims and hypotheses

Accordingly, this study aims to investigate the efficacy of combining iTBS with ipsilesional M1 versus iTBS over a parieto-occipital control site, priming physiotherapy in the early rehabilitation of patients with stroke suffering from impaired hand–motor function. Thereby, the main goal of our study is to demonstrate the effectiveness of iTBS in supporting the recovery of motor function in a sufficiently powered sample, expecting stronger rehabilitation effects on relative grip strength (primary outcome parameter) in the M1-iTBS group compared with the control-stimulation treated group. Furthermore, by assessing the secondary outcome parameters (Action Research Arm Test (ARAT), Fugl-Meyer assessment (FM)), we also test whether combining iTBS with physiotherapy during early rehabilitation may influence more complex motor functions of the impaired upper extremity. This study will be the first with a large sample of patients with early subacute stroke ($n=150$), systematically assessing clinical deficits, electrophysiological data, structural images, comorbidity, and medication before, during, and at least 3 months after the application of iTBS. We hypothesise that the combination of physical training with iTBS over ipsilesional M1 significantly enhances motor recovery after stroke compared with physical training combined with control stimulation.

METHODS

Study design, recruitment and procedure

This prospective, randomised, controlled, double-blind, single-centre trial is conducted at the Department of Neurology University Hospital Cologne, Germany. Hospitalised patients with early subacute stroke (within the first 14 days poststroke), suffering from a hand–motor deficit due to ischaemic stroke, are screened for study participation by a stroke-specialised neurologist. Eligible patients are invited to participate in the study by the investigator, who has obtained the written informed consent. Several motor scores, as well as the general neurological status and electrophysiological measures of motor-cortical excitability, are assessed on the day of enrolment (T0) and 1 day after the last iTBS intervention (T9). A longitudinal follow-up after 3–6 months (T10) assesses the after effects that extend into the chronic poststroke phase. Of note, the first postintervention assessment at T9 takes place 1 day after stimulation, and hence does not reflect immediate stimulation after-effects. All patients undergo the same experimental procedure receiving iTBS interventions before physical therapy on days T1–T8 (figure 1), the latter conducted as a routine part of the early rehabilitation programme provided by the Department of Neurology, University Hospital Cologne. This programme (total duration of 300 min/day) includes daily physiotherapy, occupational therapy and speech therapy for at least 2 weeks. This timeframe determines the duration of the iTBS intervention phase, which aims at eight stimulations on consecutive workdays. Note that

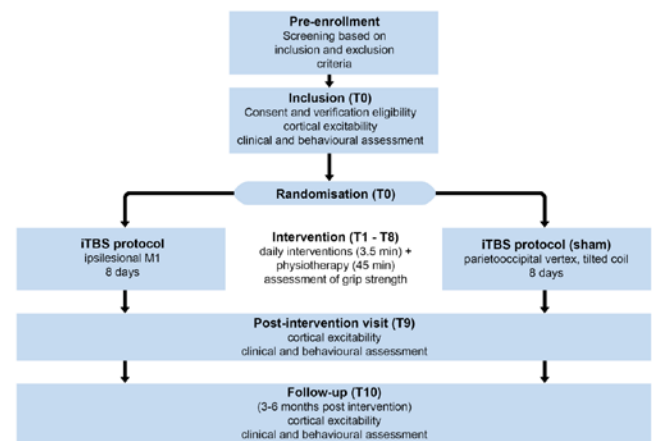


Figure 1 Flow chart of study procedure. iTBS, Intermittent theta burst stimulation.

the intended stimulation period is longer than the five stimulations employed in our pilot study²³ in order to increase the total stimulation dose. In case eight stimulations cannot be performed due to organisational reasons (eg, transfer of the patient to another rehab centre), a minimum of five stimulations is necessary to be included in the final analysis.²³ A stimulation period longer than 8 days was not considered feasible without delaying further medical plans or subsequent treatment after transfer to a rehabilitation centre. Importantly, both groups receive the same amount of motor training, with cohorts solely differing in receiving M1-iTBS or control-iTBS before the physiotherapy session (see below). Details on trial characteristics based on the WHO trial registration dataset are provided in table 1.

Patient and public involvement

The study was designed based on the available literature related to optimising motor recovery in patients with stroke using iTBS, as described in the introduction. There was no public involvement in the study design.

iTBS protocol

As a predominantly facilitatory rTMS protocol, iTBS has been rendered safe and effective, increasing cortical excitability in healthy subjects³⁸ and in patients with acute stroke.³⁹ One session of iTBS consists of 3 pulses delivered at a frequency of 50 Hz every 200 ms during 2 s (10 bursts), which are repeated every 10 s for a total duration of 3.5 min (600 pulses).³⁸ 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 the 10–20 electroencephalography (EEG) system. Importantly, to prevent effective stimulation of cortical tissue in the control condition, the handle of the coil is placed parallel to the interhemispheric fissure pointing to the front. Besides, the coil is tilted upwards at about 45°, touching the skull not with the centre but with the

Table 1 1 Trial characteristics based on WHO trial registration dataset

Data category	Trial information
Primary registry and trial identifying number	German Clinical Trials Register (DRKS) DRKS-ID: DRKS00008963
Date of registration in primary registry	16 February 2016
Secondary identifying numbers	ClinicalTrials.gov (NCT02910024)
Source(s) of monetary or material support	The study is conducted as an investigator-initiated study supported by the Max-Delbrück Prize to GRF and by the University of Cologne Emerging Groups Initiative (CONNECT group; CG and GRF) implemented in the Institutional Strategy of the University of Cologne and the German Excellence Initiative.
Primary sponsor	University of Cologne, Albertus-Magnus-Platz 50923 Cologne
Secondary sponsor	NA
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Public title	Theta-Burst-Stimulation in early Rehabilitation of Stroke (TheSiReS)
Scientific title	Theta-Burst-Stimulation in early Rehabilitation of Stroke (TheSiReS)
Country of recruitment	Germany
Healthy conditions(s) or problems studied	Stroke with hemiparesis, including impaired hand-motor function
Interventions	Active comparator: repetitive transcranial magnetic stimulation (rTMS) applied to the primary motor cortex of the lesioned hemisphere using the intermittent theta burst stimulation protocol (application of 3 pulses with a frequency of 50 Hz, in a theta-rhythm of 5 Hz for 2 s, repeated every 10 s, duration of one session: about 3.5 min) before physical therapy for 8 days. Sham comparator: repetitive transcranial magnetic stimulation (rTMS) in control position (tilted coil over parieto-occipital vertex) before physical therapy for 8 days.
Key inclusion and exclusion criteria	Inclusion criteria: written consent, age: 40–90 years, ischaemic stroke. hemiparesis with impaired hand-motor function. Exclusion criteria: Subjects who are legally detained in an official institute (§20 MPG), participation in a clinical trial within the last 12 weeks, electronic implants or ferromagnetic implants located in the head, neck or thorax (eg, clips, intracranial shunt, artificial heart valve, pacemaker), medication pump (eg, insulin pump), metal splinters in eye or head, pregnancy/breastfeeding, severe neurodegenerative disease, severe neuroinflammatory disease, history of seizures/epilepsy, physical addiction to alcohol, medication or drugs (excluded: nicotine), insufficient compliance, present or past malignant tumour involving the central nervous system, severe psychiatric disease, clinically manifest bilateral hemiparesis or infarcts in the primary motor cortex or along the corticospinal tract in the hemisphere ipsilateral to the hemiparesis, pre-existing cerebral infarctions with hemiparesis or pre-existing cerebral infarctions in the primary motor cortex or along the corticospinal tract, excluding microvascular changes (eg, clinically asymptomatic lacunae <1 cm), known brain lesion (surgical, traumatic), evidence for enhanced cerebral pressure, severe cardiac dysfunction, life expectancy <12 months, National Institutes of Health Stroke Scale Score (NIHSS) >20, blood glucose imbalances resistant to treatment (<50 mg/dL or >300 mg/dL), elevated blood pressure resistant to treatment (>185/110 mm Hg), systemic thrombolysis using alteplase or thrombectomy within the last 24 hours before enrolment in study, medication with benzodiazepines, high-potency antipsychotics or tricyclic antidepressants before hospitalisation or long-term during hospitalisation.
Study type	Interventional Allocation: randomised intervention model Masking: double-blind (subject, caregiver, investigator, outcomes assessor). Assignment: parallel Primary purpose: treatment
Date of first enrolment	April 2016
Target sample size	150
Recruitment status	Recruiting
Primary outcome(s)	Relative grip force (time frame: 3–6 months after enrolment)

Continued

Table 1 Continued

Key secondary outcome	<p>Relative grip force (time frame: after 8 days of intervention, and 3–6 months after enrolment).</p> <p>Action Research Arm Test (time frame: after 8 days of intervention, and 3–6 months after enrolment),</p> <p>Fugl-Meyer Motor Scale of the upper extremity (time frame: after 8 days of intervention, and 3–6 months after enrolment).</p> <p>NIHSS (time frame: after 8 days of intervention, and 3–6 months after enrolment).</p> <p>modified Rankin Scale (time frame: after 8 days of intervention, and 3–6 months after enrolment).</p> <p>Motor evoked potential induced by stimulation of the affected motor cortex as a measure of motorcortex excitability (time frame: after 8 days of intervention, and 3–6 months after enrolment).</p> <p>Resting motor threshold as measured by stimulation of the affected motor cortex as a measure of motorcortex excitability (time frame: after 8 days of intervention, and 3–6 months after enrolment).</p> <p>EuroQol 5D questionnaire (time frame: after 8 days of intervention, and 3–6 months after enrolment).</p> <p>Barthel-Index at admission and discharge in external rehabilitation facility (time frame: 3–6 months after enrolment).</p> <p>Days of rehabilitation after intervention phase (time frame: 3–6 months after enrolment).</p>
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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 behaviour, motor-cortical excitability or neural activity as measured with fMRI.^{22 23 40–42} Compared with other facilitatory rTMS protocols, the short duration of the intervention (3.5 min) enables a good integration of iTBS in training schedules even when patients are severely affected. The second advantage of iTBS is its relatively low stimulation intensity, reducing the risk of adverse reactions, particularly seizures.⁴³ The stimulation intensity of iTBS is individually adapted in each patient according to the excitability of the ipsilesional motor cortex. The original iTBS protocol, as published by Huang *et al*³⁸ set the stimulation intensity to 80% of the active motor threshold (AMT). However, assessment of the AMT requires subjects to perform constant contractions of the hand muscles which is often impossible for stroke patients with severe hand-motor weakness. The present study, therefore, set stimulation intensities to 70% of the RMT, which is independent of the patients' motor abilities. Of note, using 70% RMT instead of 80% AMT has been repeatedly demonstrated to induce comparable after effects on cortical excitability,^{22 40 44} allowing effective application of iTBS in stroke.²³ As shown in our proof-of-principle study,²³ stimulation thresholds may exceed the maximum stimulator output (MSO) in case of a severe disruption of the corticospinal tract leading to no recordable motor-evoked potentials (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.

Inclusion and exclusion criteria

Inclusion and exclusion criteria are defined in line with previous iTBS studies in stroke^{22 23} and the guidelines for the use of rTMS in clinical practice and research.^{43 45 46}

Inclusion criteria are

- ▶ Written informed consent.
- ▶ Age 40–90 years.

- ▶ Ischaemic stroke.
- ▶ Hemiparesis with impaired unilateral hand motor function.

Exclusion criteria are

- ▶ Subjects legally detained in an official institute.
- ▶ Participation in a clinical trial within the last 12 weeks.
- ▶ Electronic or ferromagnetic implants located in the head, neck or thorax (eg, clips, intracranial shunt, artificial heart valve, pacemaker, medication pump).
- ▶ Metal splinters in eye or head.
- ▶ Pregnancy/breastfeeding.
- ▶ Severe neurodegenerative disease (eg, Parkinson's disease, Alzheimer's disease).
- ▶ Severe neuroinflammatory disease (eg, multiple sclerosis).
- ▶ History of seizures/epilepsy.
- ▶ Physical addiction to alcohol, medication or drugs (excluded: nicotine).
- ▶ Insufficient compliance.
- ▶ Present or past malignant tumour involving the central nervous system.
- ▶ Severe psychiatric disease (eg, schizophrenia).
- ▶ Bilateral hemiparesis or infarcts to the primary motor cortex or the corticospinal tract in the hemisphere ipsilateral to the hemiparesis.
- ▶ Pre-existing cerebral infarctions with hemiparesis or pre-existing cerebral infarctions affecting the primary motor cortex or the corticospinal tract, excluding minor small vessel disease changes (eg, clinically asymptomatic lacunae <1 cm).
- ▶ Known brain lesion (surgical, traumatic).
- ▶ Evidence of enhanced cerebral pressure.
- ▶ Severe cardiac dysfunction.
- ▶ Life expectancy <12 months.
- ▶ National Institutes of Health Stroke Scale (NIHSS) score at enrolment >20.
- ▶ Blood glucose imbalances resistant to treatment (<50 mg/dL or >300 mg/dL).

- ▶ Elevated blood pressure resistant to treatment (RR >185/110 mm Hg).
- ▶ Systemic thrombolysis using r-tPA or thrombectomy within the last 24 hours before enrolment in the study.
- ▶ Medication with benzodiazepines, antipsychotics or tricyclic antidepressants before hospitalisation or long-term during hospitalisation.

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 with that of the unaffected hand, assessed 3–6 months after the intervention, that is, in the chronic phase poststroke. While motor recovery after stroke may be assessed with several measures, we selected grip strength based on the following rationale: first, grip strength represents a fundamental feature of hand motor function, and is typically reduced in patients suffering from stroke-induced hemiparesis. In turn, recovery of grip strength usually precedes the recovery of other motor domains such as dexterity or movement speed.⁴⁷ Second, the assessment of grip strength can be conducted efficiently at the bedside, even in severely affected patients.

Furthermore, improvements in grip strength predominantly reflect the restitution of neurological function as grip strength is less dependent on alternative strategies such as compensatory movements. Besides, grip

strength is mediated by contralateral M1 activity.⁴⁸ 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 design is based on a pilot study that also used grip force as the primary outcome parameter,²³ 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 comprise different measures of gross and fine upper limb function assessed by the ARAT⁴⁹ and the FM⁵⁰ of the upper extremity, stroke severity measured by NIHSS, general disability (modified Rankin Scale)⁵¹ and quality of life (EuroQol 5D including the visual analogue scale). Moreover, in order to obtain electrophysiological measures of corticospinal integrity, MEP and the RMT of the ipsilesional M1 are included as secondary endpoints. Finally, to account for the differences in rehabilitation treatments between completion of the intervention (T9) and the follow-up assessment (T10), we document the performance in activities of daily living assessed by the Barthel scale as well as the duration of stay in external rehabilitation facilities.

In sum, these tests provide a detailed assessment, monitoring the clinical and electrophysiological condition of patients before and after iTBS (table 2).

Table 2 : Overview of data collection and study timings

Study period	Pre-enrolment	T0	T1	T2	T3	T4	T5	T6	T7	T8	T9	T10
Visits												
Screening (in-/exclusion criteria)	X											
Written informed consent		X										
Randomisation		X										
Medical history	X	X										
Neuroimaging (MRI/CT)	X											
TMS-intervention (M1 iTBS/control iTBS)			X	X	X	X	X	X	X	X		
Physiotherapy			X	X	X	X	X	X	X	X		
Assessment of adverse events		X	X	X	X	X	X	X	X	X	X	X
Relative grip strength	X	X	X	X	X	X	X	X	X	X	X	X
Documentation of medication		X	X	X	X	X	X	X	X	X	X	X
Neurological examination	X	X									X	X
Electrophysiological examination (RMT, MEPs)		X									X	X
Upper limb motor function (ARAT, FM)		X									X	X
Stroke severity (NIHSS)		X									X	X
Disability (mRS)		X									X	X
Quality of life (EQ-5D)		X									X	X
Assessment of external rehabilitation time												X

ARAT, Action Research Arm Test; EQ-5D, EuroQol 5D including the visual analogue scale; FM, Fugl-Meyer Motor Scale of the upper extremity; iTBS, intermittent theta burst stimulation; MEPs, Motor evoked potentials; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; RMT, resting motor threshold.

Randomisation and stratification

After obtaining informed consent, randomisation is performed using the 24/7 online randomisation tool ALEA (FormsVision BV, Abcoude, NL). Patients are allocated 1:1 into the intervention groups, receiving 'verum' or 'control' iTBS. In order to balance groups for potential confounding factors, randomisation is stratified based on patients' age (≤ 68 , > 68 years), motor impairment (relative grip strength $< 10\%$, $10\% - 70\%$, $> 70\%$) and stimulation intensity ($\leq 50\%$, $> 50\%$ maximal stimulator output), as these factors are known to impact motor recovery post-stroke.^{52 53}

Statistical analysis

After data collection, confirmatory and descriptive analyses will be conducted. In our proof-of-principle study, we obtained data from a smaller sample²¹ which revealed, 3–6 months after the intervention, an increase in grip strength of $38.1\% \pm 28.7\%$ in patients treated with iTBS versus $26.2\% \pm 11.7\%$ in the control-stimulation group. Thus, the observed strength of the effect amounted to 0.54. Using an unpaired, two-sided t-test with a type I error of 5% and a power of 80%, a sample of 110 patients is required (calculated using the software G*Power V.3.1.7). Assuming a dropout rate of 25% based on the cohort of Volz *et al* (2016), an estimated sample of 150 recruited patients is needed.

Variables are analysed descriptively using mean, SD, quantiles (0, 25, 50, 75, 100), or count and frequency, respectively. The final statistical analysis is carried out with an intention to treat) collective including all patients who received at least one intervention (verum or control) with a subsequent grip strength testing, to assess the safety and efficacy of iTBS. Moreover, a supportive analysis is performed based on the 'per protocol' collective which includes all patients who underwent at least five²³ interventions (verum or control) and provided grip force measures at baseline and at 3–6-month follow-up.

The primary endpoint, that is, the change in grip strength after 3 months (T10), is analysed using a linear mixed model with repeated measurements, in which the factors group (verum, control), time, group x time and strata at baseline (age, motor impairment, stimulation intensity) will be entered. Moreover, the model will account for the number of data points obtained during the intervention phase (T1–T9). The primary hypothesis is addressed using a customised test (contrast) to compare the change from baseline (T0) to 3–6 months (T10) between the two treatment groups. Mean difference, the corresponding 95% CI, and the p-value (two-sided) will be presented.

All secondary variables will be analysed similarly or using unpaired t-tests or Mann-Whitney U tests. Serious adverse events (SAE) are listed. Subgroup analyses will be performed for randomisation stratification variables and length of rehabilitation therapy. The current version of SPSS statistics (IBM Corp) will be used for the statistical analyses.

Blinding

The study is carried out using a double-blinded design, in which neither the patients nor the testing physicians nor statisticians are aware of the intervention arm (verum or control). As applying iTBS over different stimulation sites (depending on the patients' intervention arm) implies that physicians performing the intervention cannot be blinded, the intervention team needs to be separated into blinded physicians performing patient recruitment and examinations, and unblinded physicians exclusively applying iTBS. Thereby, we ensure that both patients and investigators are blinded during the assessment of outcome parameters through the entire study procedure. In case of an emergency unblinding, investigators at the department of neurology have access to sealed envelopes labelled with the patients' randomisation numbers. To maintain the quality of the trial, a patient's allocation should only be unblinded in exceptional circumstances when knowledge of the actual treatment is essential for the management of the patient.

Safety

The exclusion criteria of the present trial follow the latest safety recommendations for rTMS,^{43 46} thereby reducing the risk of adverse events (AEs) or reactions to iTBS to a minimum. AEs or SAEs are assessed throughout observation period of the study, including all scheduled visits T0–T10. All events are reported to the federal authorities (Federal Institute for Drugs and Medical Devices, BfArM). In our pilot study,²³ no SAE occurred, especially no focal or generalised seizures.

Documentation and quality assurance

All data assessed during the trial are documented promptly after data acquisition and entered into the electronic case report form (eCRF) by the responsible investigators. Regular monitor inspections ensure high quality of documentation and correct implementation of the study protocol. The Clinical Trials Centre Cologne (CTCC Cologne) is responsible for the monitoring. Besides the initiation visit at the beginning and the closeout visit at the end of the study, monitoring visits are performed, on average, after every tenth patient included. Thus, at least 15 visits are scheduled. Monitoring visits include a review of source data documented in the eCRF, written consent, inclusion and exclusion criteria.

Data collection and management

CTCC Cologne performs the data management. The commercial online software TrialMasterTM (OmniComm.com) is used as a data management system, ensuring data safety with a firewall and backup system, including multiple data storage sites. The database was developed and validated by CTCC Cologne.

All data collectors are stroke-specialised neurologists who have been trained in good clinical practice. After the investigators enter the data into the eCRF, CTCC Cologne reviews the data for completeness and plausibility. The

data manager and investigators resolve discrepancies and implausible entries.

Only researchers involved in the data collection, management and data analysis will have access to the final dataset. However, the principal investigator allows direct access to all source data and documents at monitoring and inspection from federal authorities (Federal Institute for Drugs and Medical Devices, BfArM).

Ethics and dissemination

The study was approved by the Ethics Commission of the Medical Faculty/University of Cologne (reference number: 15-343). The amendments leading to the current version (V.3, 15 November 2018) were made to increase the number of patients eligible for the study. Before entering the study, all participants are informed that their participation is entirely voluntary, and that their withdrawal of consent is possible at any time without further consequences. All requirements regarding the well-being, insurance, rights, and privacy of participants are fulfilled. The study findings will be reported at conferences and in peer-reviewed journals.

Trial status

At the time of submission, recruitment has not been completed.

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