Abbreviated Title: iTBS for FMD

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Title: Phase II trial of non-invasive intermittent theta burst stimulation of the dorsolateral prefrontal cortex in functional movement disorders

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STATEMENT OF COMPLIANCE

The trial will be carried out in accordance with International Conference on Harmonisation Good Clinical Practice (ICH GCP) and the following: p

- United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 312, and/or 21 CFR Part 812)

National Institutes of Health (NIH)-funded investigators and clinical trial site staff who are responsible for the conduct, management, or oversight of NIH-funded clinical trials have completed Human Subjects Protection and ICH GCP Training.

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the Institutional Review Board (IRB) for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. In addition, all changes to the consent form will be IRB-approved; an IRB determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

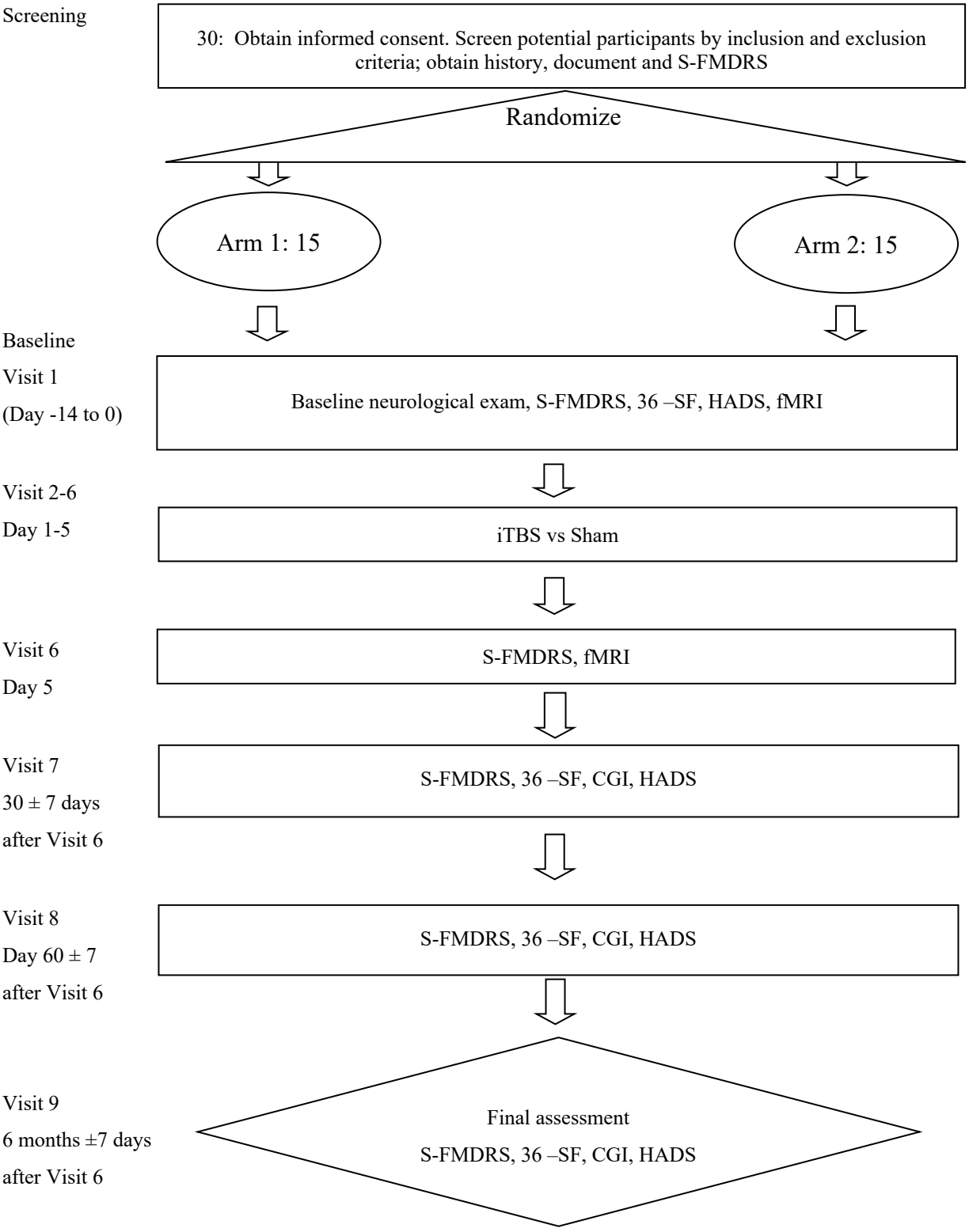
1. PROTOCOL SUMMARY

1.1. SYNOPSIS

Title:	Phase II trial of non-invasive intermittent theta burst stimulation of the dorsolateral prefrontal cortex in functional movement disorders
Study Description:	The purpose of this protocol is to investigate efficacy of intermittent theta burst stimulation (iTBS) targeting the left dorsolateral prefrontal cortex (DLPFC) in patients with functional movement disorders (FMD). Participants will be randomly assigned to receive either active iTBS or sham stimulation of the left DLPFC for 5 consecutive daily sessions.
Objectives:	Primary Objective: To investigate efficacy of iTBS of the left DLPFC on motor symptoms in patients with FMD Secondary Objectives: To investigate efficacy of iTBS of the left DLPFC on mood symptoms and its effect on fronto-amygdala circuit on functional neuroimaging

Endpoints:	Primary Endpoint: Relative change in Functional Movement Disorder Rating Scale (S-FMDRS) from the baseline to 1 month after iTBS vs sham: 100 *(S-FMDRS at one-month – S-FMDRS at baseline)/ S-FMDRS at baseline Secondary Endpoints: • S-FMDRS immediately after, 2 months and 6 months after the treatment • HADS at 1 month, 2 months and 6 months after the treatment • DLPFC-amygdala functional connectivity • Amygdala BOLD response to emotional stimuli
Study Population:	Thirty male and female participants with FMD between 18-80 years of age
Phase:	2
Description of Sites/Facilities Enrolling Participants:	Protocol activities will occur at the OP5 clinic and 7SW clinic at the NIH clinical center.
Description of Study Intervention:	Transcranial magnetic stimulation (TMS) is a noninvasive procedure that uses magnetic fields to stimulate certain brain target. iTBS is a specific protocol of repetitive transcranial magnetic stimulation (rTMS) which is expected to increase cortical excitability of the targeted brain region. 600 pulses of iTBS vs sham stimulation will be delivered to the left DLPFC in 5 consecutive daily sessions using a Magstim Rapid machine (Magstim Co., Whitland, South West Wales, UK) equipped with a standard figure-8 coil.
Study Duration:	36 months
Participant Duration:	6-7 months

1.2 SCHEMA


Screening
30: Obtain informed consent. Screen potential participants by inclusion and exclusion criteria; obtain history, document and S-FMDRS
Randomize
Arm 1: 15
Arm 2: 15
Baseline
Visit 1
(Day -14 to 0)
Baseline neurological exam, S-FMDRS, 36 –SF, HADS, fMRI
Visit 2-6
Day 1-5
iTBS vs Sham
Visit 6
Day 5
S-FMDRS, fMRI
Visit 7
30 ± 7 days
after Visit 6
S-FMDRS, 36 –SF, CGI, HADS
Visit 8
Day 60 ± 7
after Visit 6
S-FMDRS, 36 –SF, CGI, HADS
Visit 9
6 months ±7 days
after Visit 6
Final assessment
S-FMDRS, 36 –SF, CGI, HADS

1.3 SCHEDULE OF ACTIVITIES (SOA)

Procedures	Screening/ Enrollment*	Baseline Visit 1* Day -14 to day 0	Study Visit 2 Day 1	Study Visit 3 Day 2	Study Visit 4 Day 3	Study Visit 5 Day 4	Study Visit 6 Day 5	Study Visit 7** Day 30 +/-14 day After Visit 6	Study Visit 8** Day 60 +/-14 day After Visit 6	Final Study Visit 9** Day 180 +/-14 day After Visit 6
Informed consent	X									
Demographics	X									
Medical history	X									
Randomization	X									
Physical exam	X									
Vital signs	X	X								
Height	X	X								
Weight	X	X								
MRI		X					X			
Urine pregnancy test [a]		X	X	X	X	X	X			
TMS			X	X	X	X	X			
S-FMDRS	X	X					X	X	X	X
36-Item Short Form Survey (SF-36)		X						X	X	X
Hospital Anxiety and Depression Scale (HADS)		X						X	X	X
Clinical Global Impression scale (CGI)								X	X	X
Adverse event review and evaluation			X	X	X	X	X	X	X	X

[a]: Urine pregnancy test (women of childbearing potential).
*Screening and baseline visit 1 can be done on the same day if possible. The interval between screening and baseline visit should be no more than 28 days.
**The timing of Visit 7 through 9 is based off of the date of the last treatment session.

2. INTRODUCTION

2.1 STUDY RATIONALE

Functional movement disorder (FMD), a type of conversion disorder, refers to neurologic symptoms of involuntary movements that are not explained by other neurologic diseases. FMD is more commonly encountered in the outpatient clinic than Parkinson's disease or multiple sclerosis(1), is associated with similar levels of disability and distress(2), and has poor long-term outcome (3). Currently, effective treatments for FMD are lacking due, at least in part, to incomplete understanding of the neurobiological mechanisms underlying this disorder. Most therapeutic interventions for FMD have focused on physical or cognitive behavioral therapy but those may not be tailored to its neurobiology(4). Therefore, there is imperative need to develop new therapeutic approaches for FMD given its prevalence, disease burden, and the paucity of treatment options.

2.2 BACKGROUND

Advances in neuroimaging studies have offered the opportunity to identify several neural alterations associated with FMD. Previous studies have shown a potential role of upstream limbic influences, as well as top-down regulation of frontal regions on motor activity in FMD patients. Voon and colleagues (5) observed that subjects with FMD compared to controls showed altered functional connectivity between the amygdala and the supplementary motor area (SMA), a key region for motor planning. This suggests an abnormal interaction between limbic structures and motor programming regions. Interestingly, findings from this study also indicate that FMD patients had greater amygdala activity and impairments in habituation in response to both positive and negative salient stimuli presented during a fMRI task. Another fMRI study also showed increased amygdala activation to sad and fearful faces in patients with conversion disorder compared to healthy controls (Aybek 2015 PLoS One). In this study, amygdala hyperactivity was associated with abnormal activation in frontal emotional control areas in addition to motor planning (SMA) and sensory integration regions (right temporo-parietal junction). More recently, using a larger sample and more homogenous phenotype, increased connectivity between left amygdala and left middle frontal gyrus was identified in functional tremor patients compared to essential tremor and healthy control(6).

Taken together, these findings converge to indicate that FMD might be associated with dysfunctions in emotional regulation, as indicated by increased amygdala reactivity to emotional stimuli, which in turn could be related to dysfunctions in prefrontal motor control functioning. Emotion regulation is thought to result from an intricate interplay between automatic bottom-up appraisals of a given stimulus in emotion processing limbic regions, such as the amygdala, and top-down stimulus appraisal by mostly dorsal frontal control regions such as the dorsolateral prefrontal cortex (DLPFC)(7, 8). DLPFC is part of fronto-parietal cognitive control networks implicated in effortful (i.e. explicitly applied) reappraisal by cognitively reframing the affective meaning of emotionally valenced stimuli in more neutral terms(8, 9).

The DLPFC is critically involved in cognitive regulation of emotion and reappraisal of emotional stimuli regardless of valence(10). It has been posited that the DLPFC participates in emotion regulation and reappraisal via top-down inhibitory connections to the amygdala(11). Previous studies on reappraisal of negative affect have reported reappraisal-dependent coupling

between the DLPFC and the amygdala(12, 13). In patients with major depressive disorder, top-down endogenous effective connectivity from the DLPFC to the amygdala was greatly impaired compared to healthy controls(14). In addition to its role in emotion regulation, the DLPFC is also functionally connected to the motor system. Functional connectivity data demonstrated lower functional connectivity of the SMA with bilateral DLPFC in FMD patients during internally generated actions relative to externally generated actions (5). Multiple sources of evidence suggest a role for the DLPFC in higher order guidance of internally generated action selection. The DLPFC is activated during the selection between movements (15-17), and the DLPFC and parietal cortex are believed to be involved in selecting the action-target representation (16, 18). Also, the DLPFC is critically implicated in attention, and FMD patients exhibit dysfunctions in adaptation of attentional process, as previously discussed. These findings suggest that the DLPFC could be critically implicated in the emotion dysregulation, motor symptoms, and behavioral manifestations characterizing FMD.

DLPFC rTMS for treatment of major depressive disorder has been shown to increase amygdala blood flow and decrease amygdala response to negative faces (19). One study showed an increase in DLPFC global connectivity and induction of negative DLPFC amygdala connectivity which was correlated with clinical benefit with DLPFC rTMS (20). Another study using tDCS also showed that DLPFC tDCS reduced amygdala activity supporting a causal role for prefrontal regulation of amygdala function(21). Together, these studies suggest that decreased local inhibition around the DLPFC would enhance inhibitory regulation from the DLPFC to the amygdala. Increasing DLPFC activity in FMD patients may improve emotion processing and reduce motor symptoms by counteracting amygdala hyperactivity.

Intermittent theta burst stimulation (iTBS) is a specific repetitive transcranial magnetic stimulation (rTMS) protocol that effectively increases cortical excitability of the targeted brain region after a relatively short stimulation period (22-26). iTBS has been approved by U.S. Food and Drug Administration (FDA) for treatment of depression(27). iTBS involves pulses being applied in bursts of three at high frequency (50 Hz) with an inter-burst interval of 200 ms (5 Hz, which is in the range of theta frequency). In iTBS, 2 s of theta burst trains (30 pulses) are repeated every 10 s for 190 s, with a total number of 600 pulses. iTBS protocols offer the advantage of delivering a high number of pulses in a short period (1-3 minutes), allowing for multiple sessions within the same day, to achieve more pronounced effects than regular rTMS protocols, without increasing the risk of adverse events. This is supported by the results of several studies investigating the antidepressant efficacy of iTBS (28). For major depressive disorder, iTBS has been proved to be as safe and effective as high frequency rTMS (29). A recent meta-analysis reviewed 10 randomized-controlled trial for treatment of depression using iTBS (30). Various stimulation intensities were used ranging from 80% to 120% of resting motor threshold (RMT). The seminal paper (THREE-D trial) used 120% RMT for both iTBS and 20 Hz rTMS and found no difference in efficacy and safety(29).

Studies suggest that multiple sessions of iTBS, referred to as accelerated iTBS, to give a higher dose of stimulation, referred as accelerated iTBS, and to improve the efficacy of iTBS leading to a better and faster response without compromising safety (31-34). Different accelerated iTBS protocols have been used with variable stimulation intensity and doses. Baeken et al. used 5 sessions of 1,620 pulses/session a day for 4 days and reported no significant difference in adverse events between active vs sham group(31). Standford Accelerated Intelligent

Neuromodulation Therapy, which uses 10 daily sessions of iTBS (1,800 pulses per session at 90% RMT), was tested on 22 treatment-resistant depression patients, and they reported no serious adverse events(33). The only side effects were fatigue and some discomfort at the stimulation site. Kaster et al. performed 3 sessions of iTBS, total of 1800 pulses a day using 120 % RMT(34), which is a very similar stimulation protocol as in our study, and reported safety and toleratbility as well.

To explore the feasibility of accelerated iTBS on DLPFC in FMD patients, we conducted a pilot phase I study (17-N-0160) of two consecutive daily sessions of iTBS on DLPFC on 6 FMD patients(35). Although it was a small sample size pilot study, it demonstrated a significant improvement in functional movement disorder rating scale (S-FMDRS) after two sessions of iTBS(Fig.1). Moreover, iTBS on DLPFC resulted in decreased amygdala response to arousal stimuli and decreased in functional connectivity between DLPFC and amygdala (Fig.1). This result not only enhanced our understanding of the neural basis of FMD, but also provided a basis to take a step forward for potential therapeutic intervention for FMD. However, this feasibility study was not designed to assess long term benefit of iTBS in FMD patients. Also, this study was done as an open-label experiment, hence we could not assess placebo effect. In addition, increasing evidence suggest that a dose-dependent mechanism plays a crucial role in determining local and distal neuromodulatory effects, and in causing significant clinical changes(33). Therefore, we needed to design a study to test this intervention for a longer duration in a randomized placebo-controlled manner.

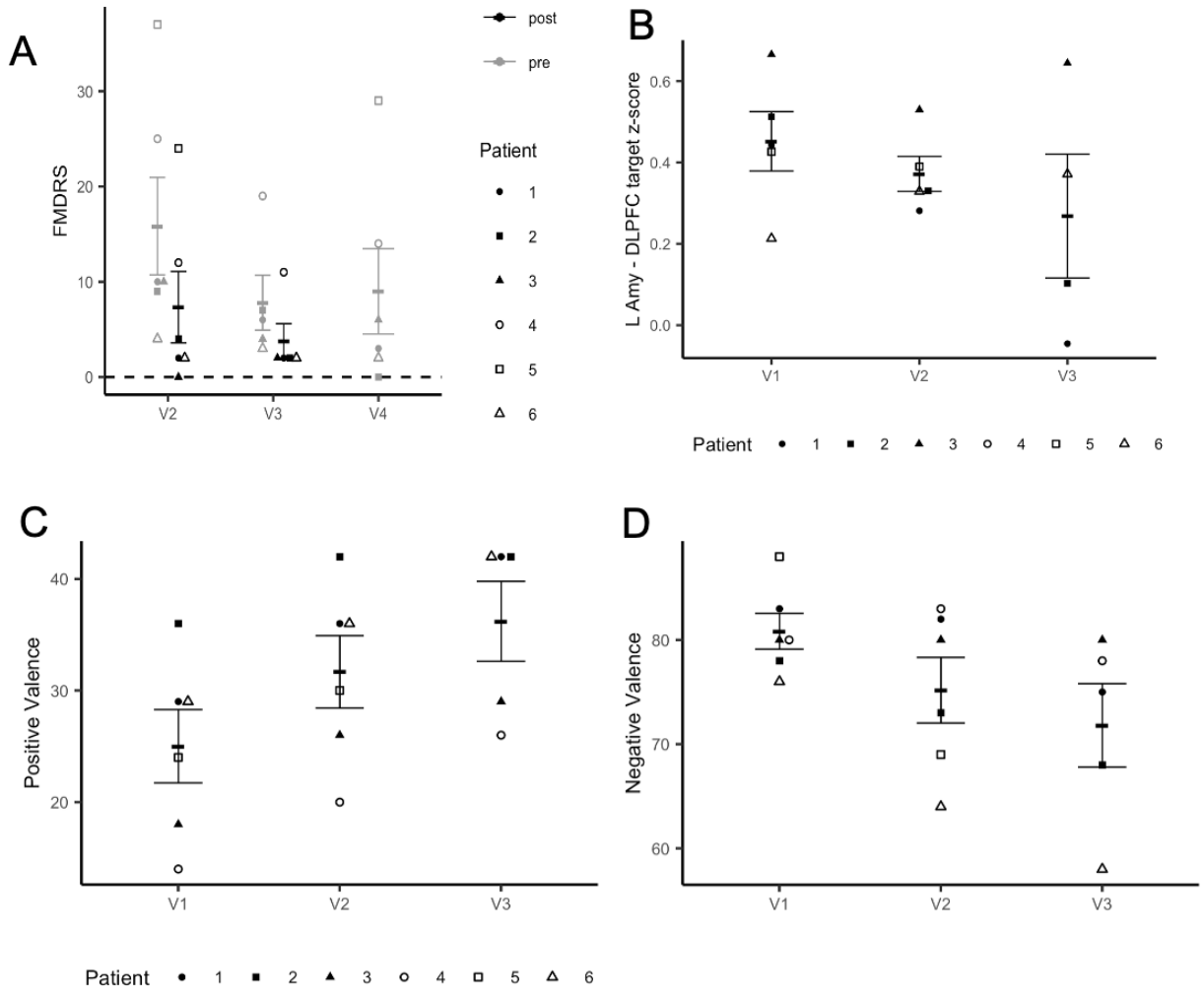


Figure 1. A. Changes in Simplied-Functional Movement disorder Rating Scale (S-FMDRS) B. Changes in resting state functional connectivity between the individualized dorsolateral prefrontal cortex (DLPFC) target and the left amygdala. C&D. Changes in positive and negative valence.

Several TMS studies have focused on motor cortex (M1) as a target of rTMS for FMD patients(36). Garcin et al. showed that one session of low frequency rTMS on motor cortex resulted in greater than 50% improvement in motor symptoms in FMD that lasted 19.8 months on average(37). However, this result was criticized by lack of control arm and suggestive message from the study team presenting rTMS as highly effective treatment for FMD, therefore question of placebo effect was raised. The same group of investigators performed a single session of rTMS either on motor cortex or spinal nerve root and found equally effective result from both stimulation targets(38). They concluded that TMS effect might be due to cognitive-behavioral rather than cortical modulation (although, of course, peripheral stimulation can influence the cortex). TMS on M1 at above RMT will generate a motor evoked potential which is perceived as a quick muscle jerk. This can demonstrate temporary restoration of normal motor function (interruption of a tremor or movement of a paralyzed arm), therefore it may present

cognitive and higher motor system with a possibility of to relearn motor function. To address this question, a randomized double-blind controlled study was performed using 5 daily sessions of low frequency rTMS on M1 at 90% of resting motor threshold in FMD patients(39). This study showed that benefit in motor symptoms as measured by decrease in S-FMDRS was seen in both active and sham groups at 1 month, but it remained at 6 months and 12 months only in active stimulation group. However, mood symptoms did not improve in either group.

Conceptually, FMD is considered as disorders of high-order motor control at the upstream of motor cortex. Abundant data suggest limbic dysfunction as key pathophysiology for FMD that lead to impaired motor control(40). We have been trying to localize the region where the limbic-motor regulation dysfunction might occur in FMD. Our previous study showed that SMA-DLPFC connectivity was decreased in FMD patients during movement selection(5). The same study showed that SMA activity was decreased in FMD patients during motor initiation while limbic region activity was increased compared to healthy controls. SMA can be considered as another potential target for neuromodulation treatment for FMD. However, considering that SMA-limbic pathway is not well understood currently, and that we have more data available about efficacy and safety of DLPFC iTBS, we decided to choose DLPFC as the iTBS target for our current study.

Based on on the mechanistic theory of the treatment and the pilot data, this new protocol has been written. In this phase II trial, we aim to study the efficacy of 5 consecutive daily sessions of iTBS over the left DLPFC in FMD patients on behavioral and motor changes, by assessing mood scales and qulity of life as well as FMD motor symptoms.

2.3 Risk/Benefit Assessment

Known Potential Risks

Risks of TMS

In August 2018, FDA approved iTBS for treatment of refractory depression. Since then, iTBS has been widely used across the country and well tolerated with considerable benefit for patients with medically refractory depression. Our protocol will use similar intensities, durations and frequencies that have been vigorously tested in previous research studies and have been used widely in clinical practice. According to the expert guidelines on safety and recommendations for TMS use, iTBS is considered safe with a frequency and intensity that will be used in our study(41).

Seizures: The greatest concern with iTBS treatment is the possibility of inducing a seizure. TMS has substantial published guidelines (1996, 2008 and 2020 International Consensus Safety Guidelines), which describe the maximum safe duration of an rTMS train based on intensity and frequency of the stimulation (41, 42). Since the issuance of these guidelines, the incidence of TMS-induced seizures worldwide has been very low, estimated as “rare” with low-frequency (< 1 Hz) rTMS and < 1% with high-frequency (> 1 Hz) rTMS (43). With regard to theta burst stimulation (TBS), a seizure has only been reported once in a 33 year old man receiving continuous TBS (44). The seizure was transient and self-limited. In a meta-analysis of over 65 studies testing TBS for different indications (depression, stroke, Parkinson’s disease, dystonia, etc.), the crude risk of seizure per session of TBS was calculated as approximately 0.02%. (45). There have been no reports of any subject developing epilepsy or repeated spontaneous seizures after rTMS and TBS (43, 45, 46). rTMS and TBS do not appear to pose any hazard to the brain

beyond that of electric stimulation, which has been in clinical use for decades. The World Health Organization task group and the Food and Drug Administration concluded that brief exposure to static magnetic fields up to 2 Tesla have no adverse effects on human health (47). The previous TMS Safety guidelines advised caution in the application of TMS in persons taking medications known to lower seizure threshold. However, the currently available data showing low seizure rate no longer support this recommendation(41).

Risk Minimization: Participants will be thoroughly monitored during the study to guard against potential negative effects of iTBS. Furthermore, to avoid the risk of stimulating at an improper intensity, iTBS stimulation intensity will be adjusted per motor threshold established directly prior to application of iTBS. All staff administering iTBS will be trained in BLS and nursing staff and/or a physician will be present while iTBS sessions are in progress.

Headache, Scalp Pain and Dizziness : Mild headache responding readily to non-opioid analgesics is the most common side-effect of iTBS reported in depression treatment trials (45). It may result from direct stimulation of superficial facial muscles or nerves, as magnetic stimulation may cause an uncomfortable facial twitch (48). Headaches usually go away promptly with nonprescription medication, such as acetaminophen.

In one study testing the antidepressant effects of iTBS in 60 patients, dizziness and/or nausea was reported in seven subjects receiving different protocols of active TBS (continuous and intermittent). The authors noted that most patients with dizziness had received a sequence from continuous to intermittent TBS (4/7, 57.1%), whereas only a small portion of patients suffered from dizziness when intermittent TBS was given first (49). A small number of reports also described focal pain, discomfort, and other minor symptoms (45).With regard to scalp pain, transient scalp pain may occur with stimulation at higher intensities and frequencies. The coil may heat up with prolonged use, raising the risk of scalp burns (50).

Risk Minimization and management: Coil heating will be avoided in the present study by using a cooled coil and by allowing the coil to cool off between treatment sessions. Acetaminophen or other medications may be provided for treatment of pain, if necessary. Nursing staff and/or a physician will be present while iTBS sessions are in progress.

Hearing Impairment: Rapid excitation of the stimulation coil produces clicks that have resulted in a transient increase in the auditory threshold of human subjects (42). This should not occur if earplugs are used. Loo and colleagues (48) have measured auditory thresholds with rTMS which we will use for our iTBS administration. Auditory thresholds were measured before and after 30 sessions of rTMS have been assessed given over 6 weeks in a depression treatment trial. All participants wore earplugs during stimulation. No significant mean changes in hearing threshold were detected. Two participants showed small bilateral increases in threshold at mid to high frequencies, which returned to previous levels when retested 1 month later. FDA guidelines require testing of auditory threshold only if participants receive rTMS at a frequency higher than 1 Hz for four or more weeks. Auditory threshold will not be monitored in the current proposed study.

Risk Minimization and management: The subjects will be fitted with earplugs to wear during the study to protect their hearing from the noise of the magnet. Investigators will ask each subject to report immediately any loosening or detachment of a subject's earplug during application of

iTBS. If subject reports or if an investigator observes that a subject's earplug has loosened or fallen out, investigators will immediately stop applying iTBS.

Dental Pain: To date, dental pain following iTBS has not been reported. Nevertheless, in a single case report, a 57-year-old women being treated for major depressive disorder reported a pulsating, localized dental twinge in the region of the upper left jaw associated with left dorsolateral prefrontal cortex rTMS (51). The pain disappeared during the inter-train interval but emerged again during the next train of stimuli. The pain was dependent on the stimulus intensity and remained despite repositioning of the coil. The cause of the pain is unclear, but may be due to stimulation of the trigeminal nerve by the rTMS magnetic field (51). Given the similar coil placement, and the use of active iTBS in our study, risk of dental pain should be considered.

Risk Minimization and management: If a participant reports dental pain, iTBS will be stopped. Acetaminophen or other medications may be provided for treatment of pain, if necessary.

Magnetic Stimulation-Induced Manic Effects: Regarding iTBS, hypomanic or manic effects have not been reported in trials assessing the antidepressant efficacy of iTBS.

Nevertheless, it should be noticed that mania has been induced in a small number of healthy and depressed subjects by high-frequency rTMS to the left dorsolateral prefrontal cortex. Nedjat and Folkerts (52) reported hypomanic symptoms after a single session of rTMS in three female subjects without a prior history of mood disorder. Stimulation parameters were comparable to those used in depression treatment studies and studies of mood changes in healthy subjects.

Two subjects with unipolar depression have shown manic changes with rTMS treatment. George et al. (53) reported mild hypomania in a patient with refractory recurrent unipolar depression. This female patient had responded well to previous shorter courses of rTMS but became hypomanic after nine treatment sessions in the third course. The hypomanic symptoms resolved when rTMS was reduced to treatment every second day. Sakkas et al. (54) reported on a 55-yr-old depressed male who became hypomanic for the first time after 3 weeks of twice daily rTMS to the left dorsolateral prefrontal cortex and concomitant citalopram. Over the following week, medication was stopped, but rTMS continued. His symptoms deteriorated into mania and rTMS was also stopped. Five months later, a second course of 2 weeks of twice-daily rTMS also resulted in hypomania. rTMS may also have a therapeutic effect in mania, with high-frequency application to the right prefrontal cortex (55).

We are aware of six reports of mania induced by rTMS in patients with bipolar disorder ((56), (57), (58), (59), (54)), even while taking mood-stabilizing medications. In a trial of right prefrontal rTMS for post-traumatic stress disorder, two patients developed a manic episode after the third session (60) One patient was randomized to 1 Hz rTMS and one to 10 Hz. Another subject in this trial developed a 'mild rage attack, probably related to the stimulation'. There is a single case report of high-frequency left prefrontal rTMS inducing transient persecutory delusions in a depressed, non-psychotic subject (61).

In all the above cases, the psychiatric side-effects induced by rTMS were transient, resolving with the cessation of rTMS or rapidly responding to pharmacological treatment.

Risk Minimization: Although it has not been reported that iTBS induced hypomanic or manic effects, preliminary evidence suggests that the side effects and safety profile associated with TBS is comparable to that of other rTMS modalities. Therefore, in our participants will be informed

of the small risk of transient mania or hypomania associated with magnetic stimulation of the DLPFC, informed of early symptoms to look out for, and instructed to contact the study physician if they believe they are experiencing any such symptoms. Furthermore, participants with current psychosis or severe depressive episode and/or suicidal ideation will be excluded from this study.

Additional precautions to minimize risk from iTBS:

Magnetic stimulation: iTBS uses magnetic pulses, and could therefore interfere with the function of pacemakers, implanted pumps or stimulators. Moreover, the use of magnetic pulses over the head could affect metallic objects inside the eye or skull. The effects of magnetic stimulation on fetal development are unknown.

Risk minimization: Participants will undergo TMS/iTBS safety screening and will be excluded from participation if they have pacemakers, implanted pumps or stimulators, and metal objects inside the eye or skull. If they have a question about any metal objects being present in their body, they will be prompted to inform the physician. In addition, all magnetic objects (for example, watches, coins, jewelry, and credit cards) must be removed. Women of childbearing potential will have apregnancy test prior to each iTBS session and each day of an MRI scan, and pregnant women will be excluded.

Risks of MRI:

People are at risk for injury from the MRI magnet if they have pacemakers or other implanted electrical devices, brain stimulators, aneurysm clips (metal clips on the wall of a large artery), metallic prostheses (including metal pins and rods, heart valves, and cochlear implants), permanent eyeliner, implanted delivery pump, or shrapnel fragments. Welders and metal workers are also at risk for injury because of possible small metal fragments in the eye of which they may be unaware.

Risk Minimization: The patients are screened using the NMR center safety screening form prior to the study and will not receive an MRI scan if the screen is positive. Women who are pregnant may not undergo a research MRI. All women of childbearing potential will have a pregnancy test performed, which must be negative, before proceeding. Individuals with fear of confined spaces may become anxious during an MRI. There are no known long-term risks or consequences of MRI scans. The length of scan varies from 45 min to 90 min maximum.

KNOWN POTENTIAL BENEFITS

Potential benefits of iTBS

Study participants for TMS studies have some chance for individual benefits. In placebo-controlled trials, some portion of participants have a chance to benefit from the active intervention, but empirical research has shown that those allocated to inactive treatment arms may also benefit to some extent, e.g. from the placebo effect and/or intensified monitoring and care(41). Placebo effect is usually short lasting whereas iTBS effect is expected to last longer period. iTBS of DLPFC has been approved by FDA for treatment of medically refractory depression (33) and obsessive compulsive disorder(62), and it has been studied in other psychiatric disorders such as post traumatic stress disorder(63) with promising results.

ASSESSMENT OF POTENTIAL RISKS AND BENEFITS

Currently, effective treatment options for FMD are lacking. A number of clinical trials using physical therapy, cognitive behavioral therapy, and hypnotherapy showed significant benefit, however, patients are expected to be actively engaged for these types of therapy in order to gain benefit(4). In addition, physical or behavioral therapy need to be specially protocolized for FMD which may not be readily available for many of FMD patients(64). There is no effective pharmacological intervention for FMD to date. Therefore, there is an imperative need to develop a new and accessible treatment for FMD patients. Given major chronic disability that FMD patients suffer along with lack of effective standard treatment options, minor risk from non-invasive TMS can be justified. Also, by using a new target of DLPFC as opposed to M1 in previous studies, our study can enhance our understanding in cortical pathways of FMD symptom genesis.

3. OBJECTIVES AND ENDPOINTS

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
Primary		
To demonstrate efficacy of DLPFC iTBS for FMD	The relative change of S-FMDRS from baseline to 1 month after iTBS vs sham stimulation	S-FMDRS has high inter-rater reliability and good sensitivity to change in FMD motor symptoms
Secondary		
• To investigate whether DPLFC iTBS affects fronto-amygdala resting state functional connectivity • To explore whether DLPFC iTBS changes emotional processing • To evaluate long term benefit of DLPFC iTBS on FMD • To test whether DLPFC iTBS improves mood in FMD patients	• S-FMDRS immediately after, 2 months and 6 months after the treatment • HADS at 1 month, 2 months and 6 months after the treatment • DLPFC-amygdala functional connectivity • Amygdala BOLD response to emotional stimuli	• S-FMDRS has high inter-rater reliability and good sensitivity to change in FMD motor symptoms • HADS is a popular tool in clinical practice and research that measures both anxiety and depression • Both amygdala BOLD response to emotional stimuli and fronto-amygdala functional connectivity have been associated with FMD and thought to play a pathophysiological role

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
Tertiary/Exploratory		
• To examine subjective benefit of DLPFC iTBS perceived by patients and clinicians • To test whether DLPFC iTBS improves quality of life in FMD patients • Relationship between imaging measures (DLPFC-amygdala connectivity and amygdala activity) and clinical response (S-FMDSR and HADS)	• CGI at 1 month, 2 months and 6 months after the treatment • SF-36 at 1 month, 2 months and 6 months after the treatment • Correlation between imaging measures and clinical responses	• CGI provides a readily recognizable and universally known efficacy measure as a summary measure, and has been widely used in numerous clinical trials as outcome measure regardless of type of diseases • SF-36 is a well-researched self-reported quality of measure related to health • Investigating correlationg between imaging measures and clinical response will be helpful to understand the mechanism of potential clinicl benefit.

4. STUDY DESIGN

4.1 OVERALL DESIGN

This is a single site phase II randomized, placebo-controlled, double-blind trial of DLPFC iTBS in FMD. Twenty-six patients with FMD will be randomized to either iTBS or sham stimulation for 5 consecutive daily sessions. Stratified randomization method will be applied using baseline S-FMDRS as covariate. Participants will be followed for 6 months after the intervention in this study. Interim analysis will be performed to adjust number of subjects required for study power. To minimize bias, patients and clinicians who will be obtaining outcome measures will be blinded to type of intervention (iTBS vs sham) until the study is closed.

We hypothesize that DLPFC iTBS will be efficacious to decrease abnormal movements in FMD patients at 1 month after 5 daily sessions of intervention. Furthermore, we hypothesize that DLPFC iTBS will improve mood and quality of life in FMD patients.

4.2 Scientific Rationale for Study Design

In order to demonstrate biological benefit from DLPFC iTBS, a placebo arm is included in this study. To differentiate placebo effect from biological effect, long term follow up is implemented up to 6 months. FMD patients may be subject to placebo effect due to its characteristic of suggestibility. A previous study using rTMS on M1 for functional tremor patients demonstrated clinical benefit in the sham stimulation group as well as rTMS group, but the benefit did not sustain longer than 1 month in the sham group(39).

4.3 Justification for Dose

iTBS parameter that will be used in our study is in line with well-studied, clinically used, FDA-approved stimulation parameters for major depressive disorder(65).

5. STUDY POPULATION

5.1 Inclusion Criteria

In order to be eligible to participate in this study, an individual must meet all of the following criteria:

1. Stated willingness to comply with all study procedures and availability for the duration of the study
2. Male or female, aged 18-80
3. Diagnosis of functional movement disorder made by a neurologist
4. Agreement to adhere to Lifestyle Considerations (see section **0**) throughout study duration
5. Ability of subject to understand and the willingness to sign a written informed consent document.

5.2 Exclusion Criteria

An individual who meets any of the following criteria will be excluded from participation in this study:

1. Current psychosis or active suicidal ideation
2. History of epilepsy with the exception of febrile seizure
3. Patients with psychogenic non-epileptic seizure without comcomitant functional movement disorder
4. Any significant neurological disorders other than FMD including but not limited to multiple sclerosis, stroke, Parkinson's disease, space occupying brain lesion
5. Alcohol or substance use disorder
6. *Patients who are on Buproprion (Wellbutrin)
7. **Patients with moderate to severe cardiac disease
8. Any psychiatric, medical or social condition due to which, in the judgment of the PI and after any consults if indicated, participation in the study is not in the best interest of the patient.
9. Pregnancy

*Buproprion is associated with dose-related seizure risk and there is a case report of decreased cortical motor threshold on a subject taking high dose of Buproprion(66). Therefore, patients who are on Buproprion will be excluded from the study. Rare incidences of syncope have been

reported(67) which can be difficult to differentiate from seizure. Patients with moderate to severe cardiac disease will be excluded from the study as a measure of precaution.

**Moderate to severe cardiac disease will be determined by the standard of care clinical process of reviewing the medical records and reviewing the medical history during the screening visit. A review of cardiac history is covered in this process.

The eligibility of all subjects based on a review of their medical history, including those presenting with cardiac disease, will be determined by protocol investigators.

5.3 Inclusion of Vulnerable Participants

Participation of NIH Staff or family members of study team members

NIH staff and family members of study team members may be enrolled in this study as this population meets the study entry criteria. Neither participation nor refusal to participate as a subject in the research will have an effect, either beneficial or adverse, on the participant's employment or position at NIH.

Every effort will be made to protect participant information, but such information may be available in medical records and may be available to authorized users outside of the study team in both an identifiable an unidentifiable manner.

The NIH Frequently Asked Questions (FAQs) for Staff Who are Considering Participation in NIH Research will be made available. Please see section **0** for consent of NIH Staff.

5.4 Inclusion of Pregnant Women, fetuses or neonates

Not Applicable

5.5 Lifestyle Considerations

During this study, participants are asked to:

1.) Avoid sleep deprivation and
2.) Heavy alcohol consumption (more than 1 drink a day) during 5 daily sessions of iTBS.

5.6 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical trial but are not subsequently assigned to the study intervention or entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants, to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event (SAE).

Individuals who do not meet the criteria for participation in this trial (screen failure) may be rescreened. Rescreened participants should be assigned the same participant number as for the initial screening.

5.7 Strategies for Recruitment and Retention

Thirty FMD patients will be recruited into the study with the number of evaluable subjects anticipated to be 24 considering a 20% drop-out rate. It is anticipated that accrual will be

completed in 18-24 months. NIH clinical center will be the only site of enrollment. FMD subjects will be recruited from patients assessed at the HMCS Clinic of NINDS/NIH, from the HMCS database, and from protocol 07-N-0190. Patients who have previously participated in protocol 07-N-0190 will be contacted over the telephone and offered participation in the study. Any procedures done under protocol 07-N-0190 will be repeated under the current protocol even if the same procedures were done (ie. FMDRS, HADS, fMRI etc.). The study will be advertised at the regional movement disorder meetings as well as on the patient support groups website. There is no direct solicitation of NIH employees/staff for recruitment by supervisors or co-workers.

COSTS

Subjects are not expected to pay any costs for the study. However, the patient will be responsible for payment if hospitalization or transfer to other hospitals is required due to unexpected complications.

COMPENSATION

Patients will be compensated for time and research-related inconveniences in accord with NIH guidelines as follows:

Compensation for time (Outpatient Visits)	
First hour of visit	$20
Each additional hour	$10
Compensation for inconveniences	
Research MRI	$100 per visit
Questionnaires	$25 per visit
Surface EMG	$20 per visit
TMS, repetitive	$150 per visit

Payment (check) will be mailed to participants after they complete the protocol, or by direct deposit if available. If participants are unable to finish the study, they will be paid for the portion of the study completed. NIH employees must either participate outside of work hours or take leave in order to receive compensation. Payment will be made at termination of study participation. If any procedure needs to be repeated in a separate visit, the procedure and visit will be compensated at the same time and discomfort/inconvenience rates listed above.

6. STUDY INTERVENTION

6.1 STUDY INTERVENTIONS(S) ADMINISTRATION

STUDY INTERVENTION DESCRIPTION

According to 21 CFR 812.3 (m) and FDA "Information Sheet Guidance for IRBs, Clinical Investigators, and Sponsors: Significant Risk and Nonsignificant Risk and Nonsignificant Risk Medical Device Studies January 2006 (accessible at http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM126418.pdf), the use of

TMS in the study is a Non-signficant Risk study. 21 CFR 812.3(m) enumerates four criteria for a Significant Risk Device Study; none of these apply to this study:

1. is intended as an implant and presents a potential for serious risk to the health, safety, or welfare of a subject;

   TMS is NOT implant.

2. is purported or represented to be for a use in supporting or sustaining human life and presents a potential for serious risk to the health, safety, or welfare of a subject;

   TMS is NOT for use in supporting or sustaining human life.

3. is for a use of substantial importance in diagnosing, curing, mitigating, or treating disease, or otherwise preventing impairment of human health and presents a potential for serious risk to the health, safety, or welfare of a subject; or

   The investigational use of TMS is NOT of substantial importance in diagnosing, curing, mitigating, or treating disease, or otherwise preventing impairment of human health and presents a potential for serious risk to the health, safety, or welfare of a subject.

4. otherwise presents a potential for serious risk to the health, safety or welfare of a subject

a) *The use of the legally marketed standard MRI system will be performed under operating conditions below each of the limits (field strength, Specific Absorption Rate, time rate of change of gradient fields and sound pressure levels) deemed to be significant risk by the FDA as stated in the FDA guidance document, Criteria for Significant Risk Investigations of Magnetic Resonance Diagnostic Devices. Siemens 3T MR Skyra system, including the head coil, is classified as an FDA approved device. This device will used as marketed.*

   The Magstim Rapid2 Therapy System is legally marketed, indicated for "the treatment of Major Depressive Disorder in adult patients who have failed to achieve satisfactory improvement from prior antidepressant medication in the current episode." The Magstim Air Film Coil is legally marketed as "a stimulating coil solely intended for use with the Magstim® Rapid2 Stimulating Unit for the purposes of peripheral nerve stimulation. The Air Film Coil is an accessory of the Magstim® Rapid2 Unit." Both are used in combination in rTMS. Their use in this study is not within the labeled indications. The major risk of rTMS and cTMS is the risk of seizure. Brief, self-limited, seizures were seen in early studies, before limits were established for combinations of delivery parameters. However, this risk has been reduced to the order of one in every 50,000 sessions. For rTMS, safety guidelines have been developed (Wassermann, 1998) and updated (Rossi, Hallett, Rossini, & Pascual-Leone, 2009). These guidelines were incorporated into FDA's Class II Special Controls Guidance Document: Repetitive Transcranial Magnetic Stimulation (rTMS) Systems in Table 2. Maximum Safe Train Duration (seconds) Limits for Avoiding Seizures.

The rTMS and and 1-Hz Stimulation in this study are below the limits defined in these documents. Furthermore, the study subjects are a lower risk since subjects with any neurological or psychiatric disorders, history of seizure are excluded.

Over the past 20 years, the FDA has generally waived pre-IDE inquiries for TMS/rTMS studies on an NSR device basis.

All subjects will wear hearing protection.

The protocol will comply with the abbreviated IDE requirements under 21 CFR 812.2(b), available at:

https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfCFR/CFRSearch.cfm?fr=812.2

The subject will be seated in a chair and encouraged to relax. Inidividual MRI scan will be uploaded in Neuronavigation system (BrainSight Navigation System - (Rogue Research, Montreal, QC, Canada) to preset the stimulation target in DLPFC that has the highest connectivity to amygdala. The BrainSight program enables the coil to be placed at precise cortical targets on the individual's 3-dimensionally rendered brain MRI with less than one millimeter error, and enables the research team to dynamically move the coil to account for slight head movements during the procedure.

Surface EMG electrode will be placed on the first dorsal interossei (FDI) muscle and its signal will be recorded and analyzed by software Signal (Cambridge Electronic Design Limited, Cambridge, UK). Before TMS experiment begins, earplugs will be inserted. Magstim Rapid machine (Magstim Co., Whitland, South West Wales, UK) equipped with D70 Air Film Coil (AFC) will be used for the study intervention. MagStim Rapid system was approved by FDA as class II medical device.

First, single pulse stimulation will be delivered to motor cortex to find the hotspot which produces the highest amplitude of MEP in FDI. Once the hotspot is marked, RMT will be determined using an adaptive hunting method(68). 120 % of RMT will be used for DLPFC iTBS. Neuronavigation software will be used to ensure that stimulations will be given on the predetermined target. The coil will be angled at 45 degree angle perpendicular to the left DLPFC. iTBS will be applied in bursts of three at high frequency (50Hz) with an interburst interval of 200 ms (5Hz, which is in the range of theta frequency) (Figure 1). Total of 600 pulses will be given for 190 seconds and this session will be repeated 3 times with at least 15 minutes between each session in one day. The set of 3 sessions will be repeated 5 times in 5 consecutive days. Control group will receive sham stimulation. The AFC Sham coil looks identical to its active version, replicates operational sounds, and delivers a very shallow magnetic field to mimic the sensation of magnetic stimulation.

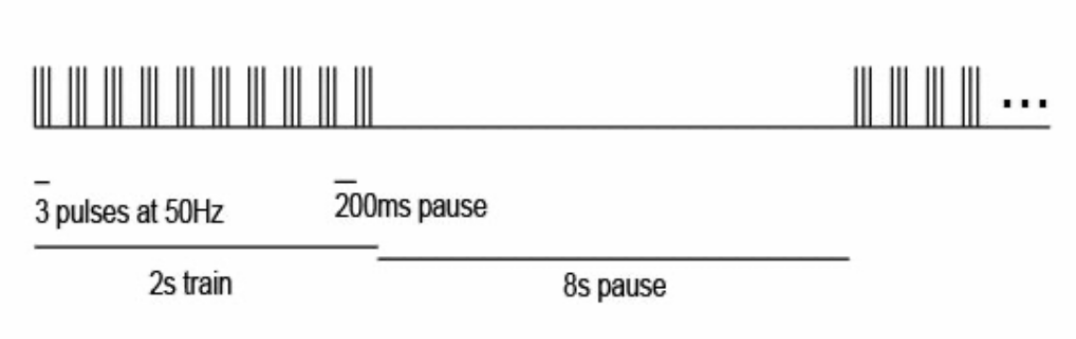


Figure 2. intermittent Theta Burst Stimulation (iTBS).

DOSING AND ADMINISTRATION

Stimulation intensity will set at 120% of that participant's resting motor threshold (RMT). First, motor hotspot for right first dorsal interossei (FDI) will be identified. Then the RMT will be determined using the adaptive threshold hunting procedure(68). RMT assessment will take place at the beginning of each iTBS visit. iTBS using 120% RMT will be delivered to left DLPFC in accordance with iTBS protocol as specified in 6.1.1.

6.2 PREPARATION/HANDLING/STORAGE/ACCOUNTABILITY

Please refer to the package insert.

6.3 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

Our study will use a parallel group design in which subjects are randomized to either active iTBS or sham stimulation with 1:1 ratio. To ensure balance of the treatment groups with respect to the various combinations of the prognostic variables, stratified randomization will be implemented using baseline S-FDMRS (dichotomized into <=14 or >14) as covariate (see Table 1). For each stratum, the treatment (iTBS or sham) will be determined through randomization.

Strata	Baseline S-FMDRS	Randomized order or active (A) or sham (B) assignment
1	<=14	i.e. A-B-B-B-A-B-A-A-B …
2	>14	i.e. B-A-A-B-A-B-B-A-B …

Table 1. Stratified Randomization

All participants will be assigned to de-identified study code according to the order of study enrollment. Randomization code will be kept encrypted by the Human Motor Control section at at NINDS and will not be released until the study is completed. In case of serious adverse events such as seizure, acute psychosis, or any other unexpected serious complications that require hospitalization, study blind will be broken for the patient and the physician who will guide treatment decision. Study blind will be maintained for the clinician who will perform clinical rating scales. Blinding will be not possible for the researcher who will be performing iTBS or sham stimulation as different coils are used for iTBS vs sham. Study participants will not be able to notice the difference between active vs sham coil as the coils look identical and produce the

same operational sound. The clinician performing clinical rating scales will remain blinded until the completion of the study. If unblinding occurs inadvertently for the clinician, another clinician will be assigned for the subsequent outpatient visits.

6.4 Study Intervention Compliance

Administration of study intervention will be done by a researcher at the time of outpatient visit and each step of intervention will be kept in written records.

In the event that circumstances beyond our control preclude the travel of one or more of the study participants to the NIH Clinical Center for their outpatient visit, or otherwise would put their health at greater risk (i.e. epidemic or pandemic), we will endeavor to establish capabilities for remote visits for new subjects and existing subjects. When required, the screening visit, visits 7, 8, and 9 may take place in person or remotely per discretion of the designated study investigator with the agreement of the participant(e.g., at participant's home via MS Teams or other NIH approved remote platforms used in compliance with policy including HRPP Policy 303). Unscheduled visits due to safety, may also be conducted remotely through telehealth. In the event that subjects are unable to come to the clinical Center because of safety issues or travel restrictions, any required in person assessment will be conducted as part of a make-up study visit.

6.5 Concomitant Therapy

For this protocol, a prescription medication is defined as a medication that can be prescribed only by a properly authorized/licensed clinician. Medications to be reported in the Case Report Form (CRF) are concomitant prescription medications, over-the-counter medications and supplements. Study participates will be allowed to continue their medications according to their physicians' guidance. Any medications that may affect mood, such as antidepressant or anxiolytics will be allowed as long as there is no dose change for 6 weeks prior to the study participation. Once the participant is enrolled, we will attempt to maintain the stable dose until the completion of study, however the dose could change if it is medically necessary.

7. STUDY INTERVENTION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 Discontinuation of Study Intervention

Discontinuation from iTBS (or sham stimulation) does not mean discontinuation from the study, and remaining study procedures should be completed as indicated by the study protocol. If a clinically significant finding is identified after enrollment (including, but not limited to changes from baseline), the investigator or qualified designee will determine if any change in participant management is needed. Any new clinically relevant finding will be reported as an adverse event (AE).

The data to be collected at the time of study intervention discontinuation will include the following:

S-FMDRS and fMRI (if applicable) will be collected at the time of iTBS (or sham stimulation) discontinuation and S-FMDRS, GCI, SF-36 and HADS will be collected for remaining follow up visits.

Participants are free to withdraw from participation in the study at any time, upon request.

An investigator may discontinue or withdraw a participant from the study for the following reasons:

- Completion of study intervention
- If any clinical adverse event (AE) or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the participant
- Investigator discretion
- Positive pregnancy test
- Participant unable to receive iTBS or sham for 3 days

7.2 Participant Discontinuation/Withdrawal from the Study

Prior to removal from study, effort will be made to have all subjects complete a safety visit approximately 30 days following the last session of iTBS vs. sham.

Participants are free to withdraw from participation in the study at any time upon request.

An investigator may discontinue or withdraw a participant from the study for the following reasons:

- Significant study intervention non-compliance
- If the participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation
- Subject has completed the study follow-up period
- Death
- Screen Failure

The reason for participant discontinuation or withdrawal from the study will be recorded on the Case Report Form (CRF). Subjects who sign the informed consent form and are randomized but do not receive the study intervention may be replaced. Subjects who sign the informed consent form, and are randomized and receive the study intervention, and subsequently withdraw, or are withdrawn or discontinued from the study, will not be replaced.

7.3 Lost to Follow-up

A participant will be considered lost to follow-up if he or she fails to return for three scheduled visits and is unable to be contacted by the study site staff.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site will attempt to contact the participant and reschedule the missed visit one time and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain if the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee will make one effort to regain contact with the participant either by phone or email. Contact attempt should be documented in the participant's medical record or study file.
- Should the participant continue to be unreachable, he or she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

8. STUDY ASSESSMENTS AND PROCEDURES

8.1 SCREENING PROCEDURES

8.1.1 SCREENING ACTIVITIES PERFORMED PRIOR TO OBTAINING INFORMED CONSENT

Minimal risk activities that may be performed before the subject has signed a consent include the following:

- Email, written, in person or telephone communications with prospective subjects.
- Review of existing medical records to include H&P, laboratory studies, etc.
- Review of existing MRI, x-ray, or CT images.
- Review of existing photographs or videos.
- Review of existing pathology specimens/reports from a specimen obtained for diagnostic purposes.
-

The aforementioned screening activities may be conducted under protocol 000865, "Natural History Protocol for Movement Disorders".

8.1.2 SCREENING ACTIVITIES PERFORMED AFTER OBTAINING INFORMED CONSENT

The following activities will be performed only after the subject has signed the study consent form. Assessments performed at outside facilities or on another NIH protocol within the timeframes below may also be used to determine eligibility once a participant has signed the consent.

All screening tests and procedures must be performed within 28 days prior to enrollment, unless a time period is specifically mentioned.

History and Physical Exam, Including, Vital Signs, Height and Weight: A comprehensive clinical assessment will take approximately one hour and will include a detailed history and physical examination. Vital signs with heart rate and blood pressure in addition to height and weight will be measured.

S-FMDRS: Please see section 8.2 for a description of the S-FMDRS procedure. If the screening visit and visit 1 occurs on the same day, this will only be performed once.

8.2 STUDY EVALUATIONS & PROCEDURES

Clinical scales: This includes focused neurological exam to measure S-FMDRS and other clinical scales by medical interview as specified below. S-FMDRS will be used as a primary outcome measure to determine the efficacy of iTBS at 1 month post treatment and as a secondary outcome measure to determine the long-term efficacy of iTBS at 2 and 6 months post treatment. 36-SF, CGI and HADS will be used as secondary outcome measures to support efficacy of iTBS.

- S-FMDRS: S-FMDRS measures abnormal movements in each body region in FMD patients. Symptom severity in each body region is rated from 0 to 3 (0 = none, 1 = mild, 2 = moderate, 3 = severe). Then the duration score is assigned to each body region from 0

to 3 (0 = none; 1 = symptomatic movement spotted at least once or only a few times; 2 = symptom is intermittent but frequent, so that there are periods during which it is absent or does not affect purposeful movement; 3 = the symptom is evident continuously). Gait and speech are also rated according to severity and duration.

- 36-SF: 36-SF is an indicator of health-related quality of life using 36 questions. It has eight domains; the scores are weighted sums of the questions in each section. Scores range from 0 – 100 in each domain (lower scores = more disability, higher scores = less disability).
- CGI: CGI can assess both clinician's and patient's view of the patient's global functioning prior to and after initiating a study medication.
- HADS: HADS measures anxiety and depression in a general medical population of patients

Functional MRI: fMRI results will be used as tertiary/exploratory outcome

MR will be conducted using a 3T scanner in the NMR Research Center. If the subject does not have a clinical brain scan performed within 12 months, one will be collected during or before the MRI research procedure and will be submitted to the Diagnostic Radiology Department of the Clinical Center for interpretation. MRIs are accomplished by having the subject lie down on a bed that slides into the "bore" of a magnet (in our case, 3.0 T). The "bore" is a hollow cylinder. During the scan, the subject will hear a thumping or buzzing sound. Earplugs or MRI-compatible headphones will be provided to all individuals. Earplugs will be inserted by trained NIH staff. We may also record blood pressure, skin conductance, skin temperature, and respiratory rate during the experiment with devices and systems that are compatible with the MRI environment and approved by the NMR center safety committee.

During the scan, we will first collect structural data. Subsequently, we will collect resting state functional MRI (rs-fMRI). Participants will be asked to keep their eyes closed and not think of anything. Resting state FC data will be acquired during 2 blocks of 6 minutes each. Finally, subjects will perform a task, called the 'Valenced Faces' task, during which they will watch images of fearful, happy and neutral facial expressions obtained from a standardized series (Karolinska Directed Emotional Faces set (69), and 50% male and 50% female faces will be presented. Subjects will be asked to perform a gender identification task during the stimuli presentation using a button response box, to ensure that they are alert during the task.

The stimuli will be projected onto a screen via a projector. Subjects will be able to view the images via a mirror placed above their head in the scanner. Participants will remain in contact with the experimenters at all times via an intercom system built into the scanner.

BIOSPECIMEN EVALUATIONS

Not Applicable

CORRELATIVE STUDIES FOR RESEARCH/PHARMACOKINETIC STUDIES

Not Applicable

SAMPLES FOR GENETIC/GENOMIC ANALYSIS

Not Applicable

8.3 Safety and Other Assessments

- **Vital signs**: daily during iTBS sessions
- **Pregnancy test:** At visit 1~6
- **Assessment of adverse events:** Subjects will be constantly observed throughout all the experimental procedures at NIH. Experimental sessions will be conducted on an outpatient basis and experiments will be performed in a laboratory with appropriate access to medical and nursing assistance. A credentialed health care provider will supervise the MRI and TMS/iTBS procedures and will be responsible for monitoring study participants. During the stimulation procedure, subjects will be monitored for complaints of pain, headache, or changes in hearing as well as for potential seizure activity. The stimulation will be stopped immediately if any of these occurs, and the side effects will be investigated by the supervising NIH credentialed health care provider.

8.4 Adverse Events and Serious Adverse Events

Definition of Adverse Event

Adverse event (AE) means any untoward medical occurrence associated with the use of an intervention in humans, whether or not considered intervention-related (21 CFR 312.32 (a)). AE is defined as any change from participants' baseline symptoms or disease and temporally associated with participation in the protocol.

Definition of Serious Adverse Events (SAE)

An adverse event (AE) or suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes: death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

Classification of an Adverse Event

Severity of Event

For adverse events (AEs) not included in the protocol defined grading system, the following guidelines will be used to describe severity.

- **Mild** – Events require minimal or no treatment and do not interfere with the participant's daily activities.
- **Moderate** – Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.

- **Severe** – Events interrupt a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating. Of note, the term "severe" does not necessarily equate to "serious".

RELATIONSHIP TO STUDY INTERVENTION

All adverse events (AEs) must have their relationship to study intervention assessed by the investigator who examines and evaluates the participant based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below. In a clinical trial, the study product must always be suspect.

- **Related** – The AE is known to occur with the study intervention, there is a reasonable possibility that the study intervention caused the AE, or there is a temporal relationship between the study intervention and event. Reasonable possibility means that there is evidence to suggest a causal relationship between the study intervention and the AE.
- **Not Related** – There is not a reasonable possibility that the administration of the study intervention caused the event, there is no temporal relationship between the study intervention and event onset, or an alternate etiology has been established.

EXPECTEDNESS

Principal Investigator will be responsible for determining whether an adverse event (AE) is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study intervention.

TIME PERIOD AND FREQUENCY FOR EVENT ASSESSMENT AND FOLLOW-UP

The occurrence of an adverse event (AE) or serious adverse event (SAE) may come to the attention of study personnel during study visits and interviews of a study participant presenting for medical care, or upon review by a study monitor.

All AEs including local and systemic reactions not meeting the criteria for SAEs will be captured on the appropriate case report form (CRF). Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All AEs occurring while on study must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode.

Study investigators will record all reportable events with start dates occurring any time after informed consent is obtained until 7 (for non-serious AEs) or 30 days (for SAEs) after the last day of study participation. At each study visit, the investigator will inquire about the occurrence

of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

ADVERSE EVENT REPORTING

Adverse event reporting will be in accordance to Policy 801.

SERIOUS ADVERSE EVENT REPORTING

In consultation with the PI, a trained member of the study team will be responsible for conducting an evaluation of all adverse events and shall report the results of such evaluation to the NIH Institutional Review Board (IRB) as per Policy 801.

NIH INTRAMURAL IRB REPORTING OF IND SAFETY REPORTS

Only IND Safety Reports that meet the definition of an unanticipated problem or is new information that might affect the willingness of subjects on the NIH study to enroll or remain in the study will need to be reported to the NIH Intramural IRB.

EVENTS OF SPECIAL INTEREST

Not applicable

REPORTING OF PREGNANCY

If pregnancy was to occur during the study, it will be reported to the principal investigator. Participants will be discontinued from the study intervention, while safety follow-up will be continued.

8.5 UNANTICIPATED PROBLEMS

DEFINITION OF UNANTICIPATED PROBLEMS (UP)

Any incident, experience, or outcome that meets **all** of the following criteria:

- Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the Institutional Review Board (IRB)-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied; and
- Related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- Suggests that the research places participants or others (which many include research staff, family members or other individuals not directly participating in the research) at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or expected.

UNANTICIPATED PROBLEM REPORTING

The investigator will report unanticipated problems (UPs) to the NIH Institutional Review Board (IRB) as per Policy 801.

9. STATISTICAL CONSIDERATIONS

9.1 STATISTICAL HYPOTHESIS

- Primary Endpoint(s): The relative change of S-FMDRS from the baseline to 1 month post treatment in the iTBS group is greater than that in the sham group.

- Secondary Endpoint(s):
    1. There will be long term benefit of DLPFC iTBS in FMD patients – S-FMDRS will remain lower at 2 month and 6 month follow up visits compared to baseline in active iTBS group compared to sham stimulation group.
    2. DLPFC iTBS will improve overall health related quality. GCI will be lower and 36-SF will be higher in iTBS group at 1 month, 2 month and 6 month follow up visits compared to sham stimulation group.
    3. DLPFC iTBS will improve mood in FMD patients – HADS will be lower in iTBS group at 1 month, 2 month and 6 month follow up visits compared to sham stimulation group.

9.2 SAMPLE SIZE DETERMINATION

The primary outcome, relative change in S-FMDRS from the baseline to one -month post-treatment, was used to perform power analysis. Our pilot study data from 17-N-0160 was not enough to estimate the standard deviation (only 6 patients). Therefore, we used Taib et al. study to estimate our sample size. They tested the effect of 5 daily sessions of rTMS vs sham on M1 for 18 functional tremor patients(39). Their patient cohort and intervention is deemed comparable to ours. Their primary outcome measure was Psychogenic Movement Disorder Rating Scale (PMDRS). Although our study will use S-FMDRS as core symptom measurement, we expect to see similar degree of relative change in either PDMRS or S-FMDRS with similar intervention (64). Both measures display good sensitivity to change but S-FMDRS is preferred for its ease of use (70). PMDRS collected from Taib et al. study (Table 2 and Table 3) was used to estimate the standard deviation, of which the upper limit of 80% confidence interval (std=25) is used for power analysis. According to this study, we assume that 1) the relative change in PMDRS follows normal distribution, and 2) the variances of the two groups are equal. Additionally, 30% difference in relative change between rTMS and Sham group is considered as clinically important. Power analysis using two-sample test indicated that a total of 24 subjects, 12 per group, will be needed to achieve a power of 80% to detect the difference of 30% in relative change between the two groups at significant level of 0.05 (Table 4.). By anticipating dropout rate of 20%, a total of 30- subjects (15 per group) will be recruited.

Table 2. Data from Taib et al. study

ID	group	Baseline	M1	Relative change in PMDRS (%)
P01	rTMS	65	47	27.69
P02	rTMS	40	20	50.00
P03	rTMS	35	30	14.29

P04	rTMS	30	15	50.00
P05	rTMS	20	13	35.00
P06	rTMS	20	7	65.00
P07	rTMS	18	9	50.00
P08	rTMS	9	2	77.78
C01	Sham	64	49	23.44
C02	Sham	39	38	2.56
C03	Sham	36	32	11.11
C04	Sham	30	23	23.33
C05	Sham	22	22	0.00
C06	Sham	18	17	5.56
C07	Sham	16	16	0.00
C08	Sham	16	8	50.00
C09	Sham	12	8	33.33

Table 3. Estimation of Standard deviation

group	Method	Mean	Std Dev	**80% CL Std Dev**	
Sham		16.59	17.28	13.37	26.16
rTMS		46.22	20.29	15.48	31.89
Difference	Pooled	**29.63**	18.74	15.37	**24.83**

Test for Equality of Variances

Method	Num DF	Den DF	F Value	Pr > F
Folded F	7	8	1.38	0.6589

Table 4. Power analysis using two-Sample t test for mean difference

Distribution	Normal
Number of Sides	2
Alpha	0.05
Mean Difference	30
Standard Deviation	25
Nominal Power	0.8
Null Difference	0
N Total	24

9.3 Populations for Analyses

Per-Protocol Analysis Dataset will be used to test the primary hypothesis .Participants who took at least three sessions of iTBS or sham and have at least one follow-up outcome data will be included in testing the secondary hypotheses and exploratory analysis.

Evaluable for Toxicity

All participants will be evaluable for toxicity from the time of their first treatment with iTBS

Evaluable for Objective Response

Only those participants who have measurable disease present at baseline, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for response. These participants will have their response classified according to the definitions in section **8.2.1.** (Note: Participants who exhibit objective disease progression prior to the end of cycle 1 will also be considered evaluable.)

Evaluable Non-Target Disease Response

Not Applicable

9.4 Statistical Analyses

General Approach

For descriptive statistics, categorical data will be presented in percentages and continuous data will be presented in means, median, standard deviations and range. Age, sex and baseline measurements will be considered as covariates. Repeated measures ANCOVA will be applied to assess the effect of iTBS for the outcome variables with normal distribution. Box-Cox transformation or Friedman's test will be applied to the outcome variables with non-normal distribution. Normality of residuals will be tested using Shapiro-Wilk method. A significance level of 0.05 will be used in the primary hypothesis test and exploring analysis.

Analysis of the Primary Endpoints

The primary endpoint in this study is Primary Endpoint: the relative change in Functional movement disorder rating scale (S-FMDRS) from the baseline to one month post-treatment (after iTBS or sham): 100 *(S-FMDRS at one-month – S-FMDRS at baseline)/ S-FMDRS at baseline.S-FMDRS is measured as a numerical scale ranging from 0 to 54, higher number being more severe motor symptoms. To evaluate iTBS effect on reducing motor symptoms by comparing with sham, two-sample t-test will be performed as a primary analysis, and ANCOVA with covariates of sex and age as a sensitivity analysis.

Analysis of the Secondary Endpoint(s)

Modified Intention-to-Treat Analysis Dataset will be used for the secondary endpoints. Participants who took at least one session of iTBS or sham and have at least one follow-up outcome data will be included for the analysis. Secondary outcome measures include as below.

- S-FMDRS will be measured repeatedly immediately after completion of 5 sessions of iTBS vs sham, then at 2 months and 6 months after iTBS vs sham. This is a continuous numeric scale ranging from 0 to 54.
- Hospital Anxiety and Depression Scale (HADS) is a continuous numeric scale in depression and anxiety(depression 0-21 and anxiety 0-21) and the questions ask about the feeling in the past week. This will be repeatedly measured at baseline, then at 1 month, 2 months and 6 months after iTBS vs sham and will be compared between iTBS vs sham group.
- DLPFC-Amygdala functional connectivity is a continuous numeric scale (Z score) obtained from resting fMRI analysis
- Amygdala activity (β value) is a continuous numeric scale obtained from task fMRI analysis.

All secondary and exploratory outcome variables will be treated as continuous (Table 5). For each outcome variable, the measurement score at each timpoint after treatment will be used as dependent variable and age, sex and the score at baseline are considered as covariates. For S-FMDRS, HADS, SF-36, and GCI, repeated measures ANCOVA will be performed to evaluate the treatment effect. The linear mixed model includes the treatment factor, which is a between - subject factor with two levels (iTBS vs. sham), visit factor, which is within-subject factor with 3 levels (visit at 1-month, 2-month, and 6-month post), interaction between treatment and visit, and the covariates. Covariance structure will be specified to model the within-subject correlation. If

the interaction is significant the multiple comparison will be performed to compare sham with iTBS for each visit separately. For DLPFC-Amygdala functional connectivity and Amygdala activity, ANCOVA will be performed. The assumption of normality will be tested using Shapiro-wilk method. If an outcome variable violates the assumption, either data transformation or non-parametric analysis will be applied.

Table 5. Outcome measures

		Baseline	**1 week**	**1 month post**	**2 month post**	**6 month post**
Primary outcome	S-FMDRS	x		x		
Secondary outcome	S-FMDRS	x	x	x	x	x
	HADS	x		x	x	x
	DLPFC-Amygdala functional connectivity	x	x			
	Amygdala activity	x	x			
Tertiary/exploratory outcome	SF-36	x		x	x	x
	GCI	x		x	x	x

SAFETY ANALYSES

Adverse events will be coded according to Medical Dictionary for Regulatory Activities (MedDRA). Information regarding start date, stop date, severity, relationship, expectedness, outcome, and duration of AEs will be reported. Adverse events leading to premature discontinuation from the study intervention and serious treatment-emergent AEs will be presented either in a table or a listing.

BASELINE DESCRIPTIVE STATISTICS

Intervention groups will be compared on baseline characteristics, including demographic, disease duration and severity using descriptive statistics. Phenomenology of FMD will be described in category (ie. tremor, dystonia, myoclonus or others). Mean and standard deviation will be presented for continuous variables (ie. age, disease duration and disease severity) and percent will be presented for categorical variables (ie. sex, phenomenology)

PLANNED INTERIM ANALYSES

Since a pilot study was done for feasibility study, no interim analysis is planned.

SUB-GROUP ANALYSES

Sub-Group analyses are not warranted since there is no expectation that iTBS or sham will have a different effect depending on demographic characteristics.

TABULATION OF INDIVIDUAL PARTICIPANT DATA

Individual participant data will be listed by measure and time point.

EXPLORATORY ANALYSES

Paticipants will have their resting connectivity tested during Visit #1 and the data obtained will be used to identify the voxels in the left DLPFC ROI showing the highest correlation with the amygdala. Based on our preliminary analysis of rsFC data of thirty-five subjects with FMD, we expect the correlation value to be ≥0.1. The individual MNI coordinates of the source of this network will be used to locate the TMS target within DLPFC. Correlation maps will be converted to Fisher's Z-scores. For changes in functional connectivity after iTBS vs sham, individual baseline functional connectivity maps will be subtracted from the respective maps after iTBS vs sham for each subject. For each patient, we will process rsFC data and obtain the z-scores relative to fronto-amygdala connectivity at two timepoints (baseline and post-iTBS vs sham). The percent change in the z-scores from baseline- to post-iTBS vs sham will be tested using the one-sample t-test.

10. REGULATORY AND OPERATIONAL CONSIDERATIONS

10.1 INFORMED CONSENT PROCESS

CONSENT/ASSENT PROCEDURES AND DOCUMENTATION

Consent will be conducted either in person or by telemedicine visit using video/audio communication. Televisits will be conducted in accordance with MAS policy M20-1 and Policy 303. When a document that is in electronic format is used for the documentation of consent, this study will use the iMedConsent™platform, which is 21 CFR, Part 11 compliant, to obtain the required signatures. When the consent is obtained via telemedicine, participants and investigators will view individual copies of the approved consent document on screens in their respective locations. When the consent is obtained in person, participants and investigators will view the same approved consent document simultaneously. Both the investigator and the participant will sign the document with a hand signature using a finger, stylus, or mouse.

All participants will receive a verbal explanation of the purposes, procedures and potential risks of the study and of their rights as research participants in terms appropriate for their level of comprehension. Participants will have the opportunity to carefully review the written consent form and ask questions regarding this study prior to signing. Potential participant will be provided the opportunity to consult with others (family, friend, private physician) prior to providing consent.

Consent will be obtained by designated qualified investigators.

If the investigator feels the individual's capacity to give informed consent is questionable, they will not participate in the study.

The consent form contains all required elements. The original signed consent form will be placed in the medical record and a copy will be given to the subject. The following consent documents will be submitted with this protocol: FMD patient .

CONSENT FOR MINORS WHEN THEY REACH THE AGE OF MAJORITY

Not Applicable

CONSIDERATIONS FOR CONSENT OF NIH STAFF, OR FAMILY MEMBERS OF STUDY TEAM MEMBERS

Consent for NIH staff will be obtained as detailed above with following additional protections: Consent from staff members will be obtained by an individual independent of the staff member's team whenever possible. Otherwise, the consent procedure will be independently monitored by the CC Department of Bioethics Consultation Service in order to minimize the risk of undue pressure on the staff member.

CONSENT OF SUBJECTS WHO ARE, OR BECOME, DECISIONALLY IMPAIRED

Adults unable to provide consent are excluded from enrolling in the protocol. However, it is possible that subjects enrolled in the protocol may permanently lose the capacity to consent for themselves during the course of this study. In the event this occurs, the subjects will be withdrawn from the study.

10.2 STUDY DISCONTINUATION AND CLOSURE

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to study participants and investigators. If the study is prematurely terminated or suspended, the Principal Investigator (PI) will promptly inform study participants, the Institutional Review Board (IRB), and sponsor and will provide the reason(s) for the termination or suspension. Study participants will be contacted, as applicable, and be informed of changes to study visit schedule.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Demonstration of efficacy that would warrant stopping
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination that the primary endpoint has been met
- Determination of futility

Study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the sponsor, IRB and, as applicable, the Food and Drug Administration (FDA).

10.3 CONFIDENTIALITY AND PRIVACY

Participant confidentiality and privacy is strictly held in trust by the participating investigators, their staff, and the sponsor(s). Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

All research activities will be conducted in as private a setting as possible.

The study monitor, other authorized representatives of the sponsor, representatives of the Institutional Review Board (IRB), and/or regulatory agencies may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical

records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB, Institutional policies, or sponsor requirements.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored at the NINDS. This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by clinical sites and by NINDS research staff will be secured and password protected. At the end of the study, all study databases will be de-identified and archived at the NINDS.

To further protect the privacy of study participants, a Certificate of Confidentiality has been issued by the National Institutes of Health (NIH). This certificate protects identifiable research information from forced disclosure. It allows the investigator and others who have access to research records to refuse to disclose identifying information on research participation in any civil, criminal, administrative, legislative, or other proceeding, whether at the federal, state, or local level. By protecting researchers and institutions from being compelled to disclose information that would identify research participants, Certificates of Confidentiality help achieve the research objectives and promote participation in studies by helping assure confidentiality and privacy to participants.

10.4 Future use of Stored Specimens and Data

Specimens are not collected or stored in this protocol.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored on password-protected computers or backed up on media stored in locked cabinets within locked HMCS offices. Keys to participant identity will be stored in lab notebooks, available only to study investigators. All data will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. Research Data will be retained at least 2 years, or until it is determined that data are no longer needed for scientific reference as per the NIH Intramural Records Retention Schedule.

Digital record such as images or video recordings will be maintained in the secured NINDS server.

Subjects will be consented for future use their data.

10.5 Safety Oversight

Safety oversight will be under the direction of the Principal Investigator and an Independent safety monitor (ISM). The Independent safety monitor will be Dr. Wassermann or an independent assessor with experience and expertise in functional movement disorders and/or TMS. The independent safety monitor will review any adverse events, unanticipated problems, and significant adverse events to determine if any of the events requires suspension of

enrollment. The review will occur semiannually, or more frequently if needed. The independent safety monitor will be consulted if there is any concern about safety events.

The clinical research team will meet on a regular basis (approximately weekly) when subjects are being actively enrolled/evaluated on the study to discuss each subject.

All data will be collected in a timely manner and reviewed by the principal investigator. Events meeting requirements for expedited reporting as described in HRPP Policy 801 will be submitted within the required timelines.

The principal investigator will review all data on each subject to ensure safety and data accuracy. The principal investigator will personally conduct or supervise the investigation and provide appropriate delegation of responsibilities to other members of the research staff.

10.6 Clinical Monitoring

Not Applicable

10.7 Quality Assurance and Quality Control

The NINDS Quality Assurance (QA) Audit Committee will periodically monitor the protocol.

This protocol will undergo review (audit) by the NINDS Quality Assurance and Data Management Office, on behalf of the Sponsor, as outlined in the NINDS QA Standard Operating Procedure. The Sponsor and the PI will be responsible for providing oversight of the investigation to ensure protection of the rights, welfare, and safety of human subjects and the quality and integrity of the resulting data. This will be evaluated by assessing study compliance with applicable regulatory requirements, good clinical practice guidelines, NINDS/NIH policies. The QA audit will also provide recommendations for improving the management of clinical research data, as needed. This protocol is classified as an "NSR device study" and thus will undergo a Site Initiation Visit prior to commencing participant enrollment and will be targeted to undergo an audit during the first year following first participant enrollment. Frequency of interim monitoring visits will be determined by the Sponsor and study team, and will be outlined in the QA Monitoring Plan. Monitoring visits will continue until the protocol has undergone a close-out visit, unless otherwise indicated by the Sponsor.

10.8 Data Handling and Record Keeping

Data Collection and Management Responsibilities

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site investigator. The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data.

Hardcopies of the study visit worksheets will be provided for use as source document worksheets for recording data for each participant enrolled in the study. Data recorded in the electronic case report form (eCRF) derived from source documents should be consistent with the data recorded on the source documents.

Clinical data (including adverse events (AEs), concomitant medications, and expected adverse reactions data) and clinical laboratory data will be entered into Clinical Informatics System for Trials and Research (CiSTAR), a 21 CFR Part 11-compliant data capture system provided by the NINDS.The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Clinical data will be entered directly from the source documents.

STUDY RECORDS RETENTION

Study documents will be retained as per the NIH Intramural Records Retention Schedule.

10.9 PROTOCOL DEVIATIONS AND NON-COMPLIANCE

It is the responsibility of the investigator to use continuous vigilance to identify and report deviations and/or non-compliance to the NIH Institutional Review Board as per Policy 801. All deviations must be addressed in study source documents, reported to NINDS Program Official and Section Chief. The investigator is responsible for knowing and adhering to the reviewing IRB requirements.

NIH DEFINITION OF PROTOCOL DEVIATION

A protocol deviation is any changed, divergence, or departure from the IRB-approved research protocol.

- Major deviations: Deviations from the IRB approved protocol that have, or may have the potential to, negatively impact the rights, welfare or safety of the subject, or to substantially negatively impact the scientific integrity or validity of the study.
- Minor deviations: Deviations that do not have the potential to negatively impact the rights, safety or welfare of subjects or others, or the scientific integrity or validity of the study.

10.10 PUBLICATION AND DATA SHARING POLICY

HUMAN DATA SHARING PLAN

This study will be conducted in accordance with the following publication and data sharing policies and regulations:

National Institutes of Health (NIH) Public Access Policy, which ensures that the public has access to the published results of NIH funded research. It requires scientists to submit final peer-reviewed journal manuscripts that arise from NIH funds to the digital archive PubMed Central upon acceptance for publication.

This study will comply with the NIH Data Sharing Policy and Policy on the Dissemination of NIH-Funded Clinical Trial Information and the Clinical Trials Registration and Results Information Submission rule. As such, this trial will be registered at ClinicalTrials.gov, and results information from this trial will be submitted to ClinicalTrials.gov. In addition, every attempt will be made to publish results in peer-reviewed journals. Data from this study may be requested by other researchers 1 year after the completion of the primary endpoint by contacting NINDS study PI and will be available on clinicaltrials.gov as well as in NINDS public repository: data.ninds.nih.gov.

GENOMIC DATA SHARING COMPLIANCE

Not Applicable

10.11 CONFLICT OF INTEREST POLICY

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this trial. The study leadership in conjunction with the NINDS has established policies and procedures for all study group members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest.

11. ABBREVIATIONS

ACC	Anterior cingulate cortex
AE	Adverse Event
ANCOVA	Analysis of Covariance
CFR	Code of Federal Regulations
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case Report Form
DLPFC	Dorsolateral prefrontal cortex
eCRF	Electronic Case Report Forms
EEG	Electroencephalography
EMG	Electromyography
FDA	Food and Drug Administration
FMD	Functional movement disorders
GCP	Good Clinical Practice
IB	Investigator's Brochure
ICH	International Conference on Harmonisation
IDE	Investigational Device Exemption
IND	Investigational New Drug Application
IRB	Institutional Review Board
ISM	Independent Safety Monitor
ISO	International Organization for Standardization
iTBS	Intermittent theta burst stimulation
M1	Primary motor cortex
MEP	Motor evoked potential
MNB	Medical neurology branch
NIH	National Institutes of Health
NIH IC	NIH Institute or Center
OHRP	Office for Human Research Protections
PI	Principal Investigator
QA	Quality Assurance
QC	Quality Control
RMT	Resting motor threshold
S50	Intensity that elicits 50% of maximal MEP response
SMA	Supplementary motor area
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SMC	Safety Monitoring Committee
SOA	Schedule of Activities
SOP	Standard Operating Procedure
TMS	Transcranial magnetic stimulation
UP	Unanticipated Problem
US	United States

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