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TITLE: Validation of Presurgical Motor Mapping with Transcranial Magnetic Stimulation (TMS) in patients with Epilepsy

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List of Abbreviations

ADM – abductor digiti minimi

APB – abductor pollicis brevis

DCS – direct cortical stimulation

EEG – electroencephalography

EMG – electroencephalography

MEP – motor evoked potential

nTMS – navigated transcranial magnetic stimulation.

TMS – transcranial magnetic stimulation.

rMT – resting motor threshold

Study Summary

Title	**Validation of Presurgical Motor Mapping with Transcranial Magnetic Stimulation (TMS) in patients with Epilepsy**
Protocol Number	
Methodology	Open label phase 1 trial
Study Duration	2 years
Study Center(s)	NYU Langone Medical Center NYU Comprehensive Epilepsy Center
Objectives	To examine the degree of concordance between presurgical neuronavigation guided TMS (nTMS) and direct cortical stimulation (DCS) in identifying hand motor cortex in adults undergoing epilepsy surgery.
Number of Subjects	14
Diagnosis and Main Inclusion Criteria	Patients ages 12-60 years, with planned neurosurgery involving implantation of intracranial subdural electrodes including over the precentral gyrus.
Study Product and Planned Use	Navigated transcranial magnet stimulation (nTMS), Magstim Rapid^2 and Brainsight Neuronavigation. Magnetic stimulation will be delivered to hand primary motor cortex, with positive and negative functional sites determined through surface electromyography (EMG).
Reference therapy	N/A
Statistical Methodology	The primary outcome measure will be spatial correlation between topographic maps of hand motor representation obtained through nTMS compared to direct, extra-operative cortical stimulation performed as part of routine clinical care. A secondary outcome measure will be safety and tolerability of TMS in the epilepsy patients.

1 Introduction

This document is a protocol for a human research study. This study is to be conducted in accordance with US government research regulations, and applicable international standards of Good Clinical Practice, and institutional research policies and procedures.

1.1 Background

Surgical treatment of focal epilepsy and motor mapping

Over 30% of epilepsy patients experience recurrent seizures despite the advent of new anti-epileptic medications (Kwan & Brodie 2000). Randomized controlled trials reveal that in appropriately selected surgical populations, epilepsy surgery can achieve superior outcome compared to continued medical therapy (Engel et al 2012).

Patients whose seizure foci are close to the motor cortex remain a challenge due to the potential risk of motor deficits after the surgery. Accurate mapping of the epileptogenic zone and surrounding cortical area is used to guide maximal resection of the epileptogenic cortex while avoiding unacceptable damage to eloquent cortex. **Currently intra-operative direct current stimulation (DCS) is the gold standard, and is the clinical standard of care for surgical planning.** if epileptogenic cortex and putative resection site is close to eloquent cortex. A subdural grid is implanted for intracranial EEG monitoring and seizure foci localization. After enough interictal or ictal events are captured, the patient will have functional mapping while in close monitored EMU setting.[1]

However, noninvasive functional mapping of motor cortex, via TMS and other non-invasive modalities such as fMRI or MEG, would optimize presurgical planning and patient counseling. In addition, in some cases, presurgical evaluation could determine whether a surgical resection is feasible, or whether the patient would be a better candidate for another procedure such as responsive neurostimulation (RNS) or vagal nerve stimulation (VNS) which would spare overlapping eloquent cortex. Furthermore in the pediatric epilepsy population, presurgical motor mapping by TMS may determine that motor and other eloquent cortex has completely reorganized (sometimes to the contralateral hemisphere), such that surgical resection of the epileptogenic cortex would be unlikely to cause a functional deficit.

A neurostimulation technique, navigated transcranial magnetic stimulation (nTMS) is a potentially valuable tool for preoperative motor mapping. Previously there have been several studies to test the accuracy of TMS to DCS, and in comparison with other noninvasive modalities, including magnetoencephalography (MEG) and functional MRI (fMRI) (Najib 2011; Romero 2011, Tarapore 2012, Krieg 2012), suggesting that nTMS can have an extremely high degree of functional accuracy, identifying primary motor cortex within 2 mm of accuracy, and with a high positive and negative predictive value (Tarapore 2012).

A similar neuronavigated device, the integrated Nexstim device manufactured by Neurostar, was FDA approved for presurgical motor mapping in 2009 (Please see appendix). We are testing the Magstim Rapid[2] TMS coil and Brainsight Neuronavigation system (instead of the Nextstim) because the dual system allows co-registration to the patient's structural MRI, functional MRI(fMRI) or EEG. Furthermore,

[1] Electrical stimulation of the cerebral cortex will be conducted utilizing a NicoletOne Cortical Stimulator which delivers a constant current output. The stimulus parameters are set to a pulse width of 500 microseconds, pulse frequency of 50 Hertz and maximum train duration of 5 seconds. The stimulus current is manually controlled during the stimulation and ranged from 1 mA to 12 mA. Stimulation is applied to adjoining electrode pairs. Responses are confirmed with repeat stimulation and testing at the initial pair and with adjoining electrodes when necessary. Electrical stimulation is started at 1 mA and gradually increased in increments of 1-4 mA until a maximum of 12 mA was achieved or until after-discharges are seen or a functional response is observed. Positive and negative functional sites will be recorded.

the dual system is a more flexible system for other research use with other stimulation devices (such as transcranial direct current stimulation and simultaneous EEG recording) and robotic devices.

We propose an open-label feasibility study to test the accuracy of nTMS to the gold standard DCS, as well as to fMRI (an adjunctive presurgical planning tool), in determining both positive and negative motor sites, and correlate with clinical outcomes.

1.2 Investigation device: TMS basics

Application of magnetic pulse for motor cortex stimulation was developed decades ago (Barker 1985). TMS machine consists of a coil which generates a brief, powerful magnetic field. As the current passes through the coil, it generates a magnet field that can penetrate the scalp and skull and in turn induce an electric current in the brain tissue (Kobayashi & Pascual-Leone 2003). When pyramidal neurons of the primary motor cortex are stimulated by electric current, the resultant motor evoked potential (MEP) triggers small movements in the relevant muscle groups, which can then be detected via electromyography (EMG). (Fig 1 adapted from Kobayashi & Pascual-Leone 2003)

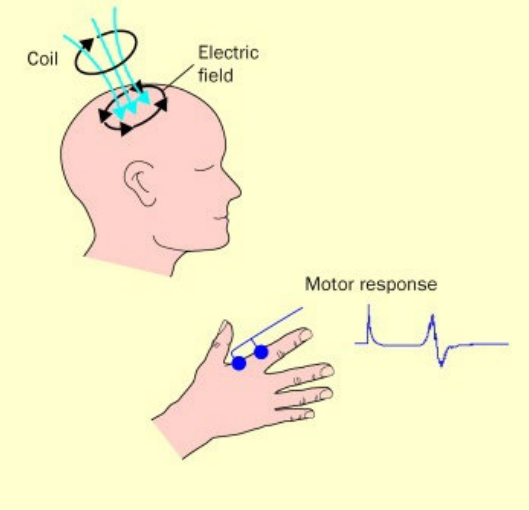

Fig 1 Principle of TMS: The current flowing briefly in the coil generates a changing magnetic field that induces an electric current in the tissue, in the opposite direction. A motor response can be detected on electromyography when motor cortex is stimulated. (Kobayashi & Pascual-Leone 2003)

TMS can also be integrated with a neuronavigation system, allowing for coregistration with an anatomical scan, such as MRI scan. This navigated TMS (nTMS) system allows for more precise position of coils during the brain stimulation and generate motor maps of high resolution. (Gugino et al., 2001; Julkunen et al., 2009; Kring et al., 2001).

Single pulse and repetitive pulse TMS are both used in neurological research studies and clinical practice. Repetitive TMS can induce lasting changes in cortical excitability and it has been approved for treatment of depression. Single pulse TMS will be used in our study for motor cortex mapping.
The practical application of TMS is simple. The TMS stimulation is administered on skull over the motor cortex via the guidance of MRI anatomical scan, surface EMG was applied on individual target muscle (Fig 2, picture adapted from Pitch 2011).

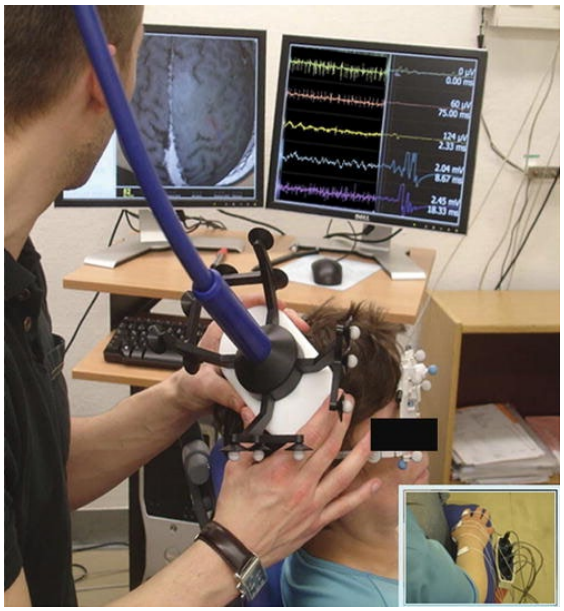

Figure 2. Photograph showing the navigated transcranial magnetic stimulation system in use. The stimulator coil is shown placed against the patient's head. The 3D reconstruction of the patient's brain is shown on the computer screen on the top left; the motor evoked potential output tracings are shown on the computer screen on the top right. The image in the bottom right corner shows the surface electrodes for electromyographic monitoring.
(Picht et al., 2011).

We will be using the Magstim Rapid^2, which is a microprocessor-controlled machine which delivers both single and repetitive transcranial magnetic stimulation (TMS). The proposed device is not currently FDA approved for presurgical motor mapping, but is approved for peripheral nerve stimulation (K051864). However, the Nextstim TMS system is currently FDA approved for presurgical motor mapping (K091457).

Currently, there have been a number of clinical protocols using TMS, which have considered TMS a non-significant risk device.

The TMS device poses a non-significant risk because
1. The device is not an implant with potential for serious risk to health, safety, or welfare of subject.
2. The device is not purported for use supporting or sustaining human life with potential for serious risk to health safety or welfare of subject.
3. The device is not for substantial use in diagnosing, curing, mitigating, or treating disease or otherwise preventing impairment of human health with a potential for serious risk to health safety or welfare of subject.
4. The device does not otherwise present a serious risk to the health safety or welfare of a subject.
We anticipate that this will be a step toward eventual wider application of TMS.

In particular, because TMS will be applied as single pulses to determine motor evoked potentials (MEPs), there will be no modulation of cortical excitability. Single pulse TMS produces monophonic magnetic field pulse of peak amplitude range of 1-2 Tesla is achieved to discharge a capacitor, and is commonly used for research and diagnostic purposes.

In a review by Quintana (2005) of TMS in in persons under the age of 18, there were 35 studies using single pulse TMS involving 980 children; with a single seizure reported, even in children with epilepsy or cerebral palsy (which is associated with an increased risk of seizures). In a more recent meta-analysis of data from 165 pediatric subects from 2009 to 2014, there were no seizures or severe related adverse events were reported with single pulse TMS. For these reasons, IRBs at other peer institutions including Cincinnati Children's Hospital, Kennedy-Krieger Institute, Children's Hospital Boston, and University of Pennsylvania and the NINDS have rendered single pulse TMS studies in children minimal risk.

Magnetic fields attenuate rapidly with distance, so it seems unlikely that the fetus might be directly affected by TMS. There are anecdotal reports of pregnant women who underwent successful rTMS

treatment for depression, and no side effects to the child were reported (Nahas et al., 1999; Klirova et al., 2008; Ross 2007). Nevertheless, the effects of the TMS device on the reproductive system (sperm, eggs) or to the developing fetus are unknown. For this reason, pregnant patients will be excluded from participation in this study.

As evidence of safety, the Nexstim TMS system, which provides exactly the same type of single TMS described here, is approved for use as a tool to perform mapping of motor cortex in patients with neurological disorders of all ages (December 2009, FDA approval notice K091457), for pre-surgical planning (for example, in epilepsy patients and in brain tumor patients). The Magstim Rapid² is developed and manufactured in accordance with US 21 CFR 820 and is cleared in the USA under 510(k) number K051864 for the stimulation of peripheral nerves. However, unlike the Nexstim system, which is fully integrated with a built in-neuronavigation system, the neuronavigation system (Brainsight) compatible with Magstim permits targeted neuronavigation with MRI layered with fMRI, EEG, or NIRS (near infrared spectroscopy), permitting greater research flexibility and other modalities of validating motor and other eloquent function.

TMS Advantages: In this study, TMS is safe, non-invasive, and offers a potentially useful adjunctive test for presurgical planning. The stimulation coil can be easily placed precisely on interested cortical surface with guidance of anatomical scans. TMS session does not interfere with other treatment or diagnostic tests.

1.3 Clinical Data to Date

Cortical function mapping with TMS has been used and it generates reproducible motor maps in previous research studies. Accurate coil position can be achieved with nTMS and the system achieved an error of less than 3 mm in about 95% of the stimulation (Romero et al., 2011). Evaluation of the physiologic responses, revealed no significant differences between MEP latency, amplitude, and area among sessions in the same subject. In addition, comparing the motor map parameters revealed no significant differences between map area, volume, and amplitude in the 2 mapping sessions (Fig. 3). (Romero et al., 2011; Krieg et al., 2012).

Motor mapping via TMS has been used in planning of surgical resection of brain tumors. Maps of motor system generated with TMS have been demonstrated to correlate well with those generated by MEG and DCS in brain tumor patients (Tarapore et al., 2012; Takahashi 2013). In addition, nMTS mapping studies results in further modification of surgical plans such as leading to more extensive or more restrictive resection in some patients. (Frey et al., 2014; Kreig et al., 2012; Takahashi 2013).
Besides tumor patients, TMS motor cortical mapping can be also used to map motor cortex anatomy in epilepsy patients (Barba et al., 2010; Kamida et al., 2003; Vitikainen et al., 2009 Zsoter 2012), without exacerbating seizure frequency.

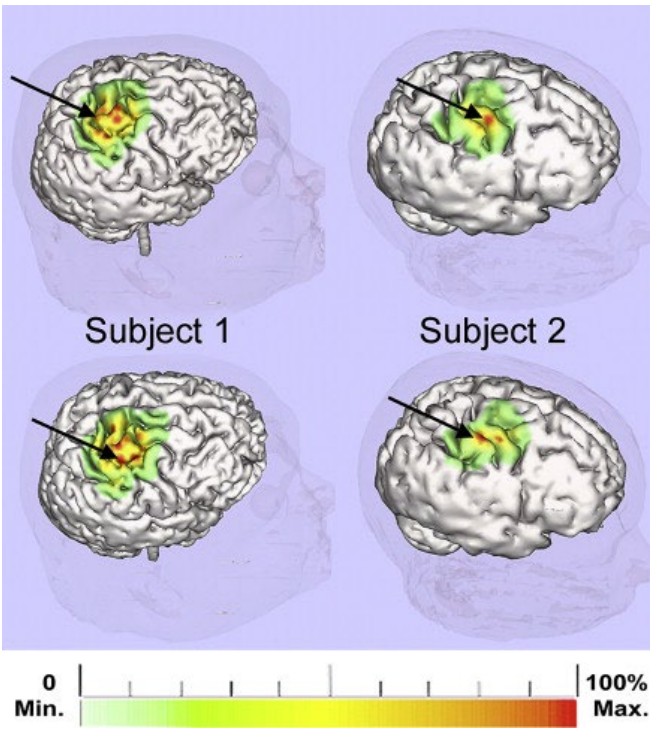

Fig. 3. Example of interpolated cortical maps of the motor representation for the contralateral FDI muscle in 2 separate mapping sessions. The color scale represents the relative peak-to-peak amplitude of the MEP. The arrow points to the location where the largest averaged peak-to-peak amplitude MEP was elicited (ie, hot spot). The 2 subjects shown underwent 2 mapping sessions (initial session top, second session bottom). No significant differences were observed in motor map parameters between the 2 mapping sessions. (Romero et al., 2011)

1.4 Research Risks & Benefits

1.4.1 Risks of Investigational Devices

Generally TMS is safe and well tolerated in both healthy subjects and neurological patients, as long as general safety recommendations are followed (Wasserman 1998). TMS applied as single pulse mode does not carry the risk of significant magnetic field exposure since the total stimulation time is short, and modulation of cortical excitability is highly unlikely. Single-pulse TMS does not cause any detrimental effects on EEG or cognitive and motor test performance (Bridgers and Delaney, 1989; Bridgers, 1991) and can be safely used in children (Eyre et al., 2001). According to a consensus statement on the safety of TMS (Rossi et al 2009), known side effects of TMS include transient headache (which occurs occasionally), syncope (mostly likely an epiphenomenon instead of relate to direct brain effect, which occurs rarely), local pain (rarely), neck pain (rarely), toothache (rarely) paresthesias (rarely); possible transient hearing changes (rarely) and possible malfunction of electric device only if TMS is delivered in close proximity with devices (rarely) (Rossi 2009). The overall incidence of these mild adverse events are thought to be approximately 5%, with headache being reported as the most common (Maizey 2013). , Side effects are transient, and have not been reported to induce permanent neurological changes (Rossi et al 2009, Evans 2007).

The most serious possible side effect of TMS is that of an induced seizure. To date, there have been a total of 16 reports of seizures associated with TMS, of thousands of published studies. Previously the risk of inadvertently induces seizures is estimated to be less than 1 in 1000 rTMS procedures (which is considered a higher risk procedure than single pulse TMS as used in this protocol), a higher risk than most commonly prescribe antidepressants (O'Reardon et al 2005) In a safety review of TMS, Hallet et al (2007) report 3 seizures associated with single-pulse TMS since the 1998 safety guidelines were published for safe stimulation parameters. In first case, Haupt's et al (2004) report a generalized tonic clonic seizure in a patient with multiple sclerosis using single pulse TMS at 66% of TMS output. The authors suggested that the use of olanzapine and the underlying MS likely increased the patient's seizure risk. In the second case, Tharayii et al (2005) reported a generalized seizure in a patient with bipolar

depression taking chlorpromazine and lithium, both medications known to increase seizure risk. To date, there has been a single report of an induced focal motor seizure during single pulse TMS of an epilepsy patient with a known epileptic focus in the left frontal cortex (Classen et al 1995). These few reported seizures were not associated with long term adverse outcome (Schrader et al. 2004).

In the event of a concurrent seizure during stimulation, one or more co-investigators with specialty training in epilepsy will be present to monitor for adverse effects and monitor for exacerbation of seizure type and frequency. If there is immediate cause for concern the PI and Co-PI will make necessary medical arrangements, including direction to the emergency room if needed. If any other unanticipated adverse events occur which are thought to be related to study intervention, the patient will be withdrawn from further participation in the study. Though our clinical trial will include a safety-monitoring plan, there are no known severe or lasting adverse effects with TMS using proper set-up.

1. Though minimal, due to the concern of potential increased seizures with TMS, we will monitor increase in seizure severity attributable to TMS by identifying all instances of generalized tonic clonic seizures after TMS treatments (defined as occurring within 20 minutes of stimulation). In addition, subjects will be asked to keep a seizure diary for the 7 days prior to stimulation, and the 7 days after stimulation. Instances where seizure frequency increased after TMS will be reported to the IRB within 1 week.
2. If a self-limited, short (<5 min) complex partial seizure or evolution into generalized tonic clonic seizures occur during the procedure, TMS mapping will stop for that day.
3. In case of, pain, transient hearing impairment, the patient's primary epileptologist will be notified and appropriate medical followup will be arranged.
4. If any other unanticipated adverse events occur, the patient will be withdrawn from further participation in the study.

1.4.2 Other Risks of Study Participation

There is the potential for loss of confidentiality for subjects participating in this study. However, every effort will be made to protect the confidentiality of subjects. After enrollment, patient identifiers will be linked to sequential numerical codes (Subject #1, #2, etc.). The detailed results of the research will be kept in a separate research file maintained by and accessible to only the investigators in a locked cabinet in Dr. Liu's office. The numerical code key will also be maintained in a locked cabinet in Dr. Liu's office and accessible only to investigators. If the patient is consented, and then withdraws from the study, their PHI will be discarded.

Furthermore, there is minimal risk of the electromyography (EMG) procedure). EMG is a noninvasive procedure which measures the compound muscle action potential (CMAP), experienced by the patient as a muscle twitch over the abductor pollicis brevis over the base of the thumb. EMG in this case will be measured by a surface electrode, which will be applied via an electrolyte gel and reinforced by tape. The patient may have a local allergic reaction to the gel and/or tape, which will be evaluated by the physician.

1.4.3 Potential Benefits

TMS is able to provide functional anatomy that can be used during surgical interventions and help in presurgical planning, potentially reducing the need for a more prolonged intraoperative mapping procedure. nTMS may be a useful adjunctive presurgical planning tool, in addition to other non-invasive

modalities including magnetoencephalography or functional MRI (fMRI). In addition, presurgical TMS mapping is also useful in planning the operative approaches and brain retraction and operative corridor (Najib 2011).

Because this is a feasibility study, results of nTMS motor mapping will not be presented as clinical information to surgeons in our study, therefore subjects may not benefit individually from this study. The ongoing practice during this study will be the use of DCS as standard of care. However knowledge gained from this study will benefit others in the future.

In particular, because TMS for motor mapping will likely result in generalizable knowledge which will benefit children and adolescents for future surgical planning (see page 2, Background section), we would like to include subjects from the ages of 12-17 years to establish validity in this population. Children and adolescents may benefit most from TMS mapping because their primary motor cortex is likely to have reorganized as a result of early brain injury and/or ongoing seizure activity (in some cases completely to the contralateral hemisphere), and who are less likely to tolerate other presurgical modalities such as functional MRI (fMRI) or magnetoencephalography (MEG).

The current study presents experiences which would be reasonably commensurate (or even less risk) with those expected in their actual medical evaluation for epilepsy surgery, most notably direct cortical stimulation for determination of functional cortex. The procedures would present no more than a minor increase over minimal risk, including the low possibility of an induced seizure (discussed on pages 4-5, under risks of investigational device), loss of confidentiality, and skin irritation from the EMG electrodes. There have never been reported any incidents of extreme pain, discomfort, stress or harm associated with single pulse TMS as described in our protocol. Any potential harm associated with TMS will be transient and reversible. To mitigate these minor risks, either Dr. Liu and Dr. Friedman, who regularly see children and adolescent on the outpatient and inpatient services (the latter while on call on the weekend) and who have specialty training in epilepsy, will be physically present during stimulation. However, to ensure maximum comfort and safety for children, the first 3 subjects run on this protocol will be adults (over 18 years old). Furthermore, to fully communicate the nature of these risks, adequate provisions are made for soliciting the assent of children and permission of their parents or legal guardians.

2 Study Objectives

2.1 Primary Objective

We propose a phase 1 clinical trial to examine the degree of concordance between neuronavigation guided TMS (nTMS) and direct cortical stimulation (DCS) in identifying hand motor cortex in adults and children undergoing epilepsy surgery.

2.2 Secondary Objective(s)

This trial is also designed to detect safety and tolerability of nTMS in epilepsy patients.

3 Study Design

3.1 General Design and Study Protocol

This study will be an open-label feasability study which applies nTMS to subjects with incoming epilepsy surgery and pre-surgical motor mapping. No study-related medication changes are expected -- participants will remain compliant with their regular anticonvulsant regimen throughout each study phase. All patients will have undergone a complete history and neurological exam as part of their routine clinical care at the NYU Comprehensive Epilepsy Center.

The phases described in detail below are as follows:

Phase	Description	Duration
Baseline	Informed Consent and baseline neurological visit, instructions for maintaining a seizure diary	30 min-1 hours
1	nTMS mapping	2 hours
2.	Follow-up clinical visit after the surgery	30 minutes

3.1.1 Baseline clinical visit and seizure diary

We will enroll 14 patients who will undergo epilepsy surgery with expected subdural grid coverage over primary motor cortex. Potential subjects will be identified at the weekly multi-disciplinary epilepsy conference. Subjects must have a recent (<2 years) MRI scan, and registration of the TMS coil to the MRI scan via the Brainsight neuronavigation system will be utilized to guide TMS coil placement (Gugino et al 2001). When a presurgical fMRI is available which demonstrates the patient's hand knob, the fMRI will be used with the Brainsight neuronavigation system. Subjects will be recruited and consented during a presurgical clinical visit where the patient's primary epileptologist will introduce members of the research team.

Patients will be asked to keep a 7 day seizure diary prior to the TMS session.

3.1.2 nTMS mapping

Patients will receive a session of single-pulse TMS mapping of the motor area, at the outpatient TMS clinic at NYU Neurology Ambulatory Care Center, at 240 E 38th St 20th Floor prior their epilepsy surgery, according to the following procedures:

a. Determination of the motor threshold by (1) finding the most excitable region in the hand knob which elicits the strongest compound muscle action potential (CMAP) in the APB muscle; (2) finding the motor threshold by determining output stimulation intensity which generates peak to peak CMAP response above 50 mV in 5/10 stimulation cycles (Rossini et al., 1994).

b. Concurrent EMG will be measured with electrodes placed at APB, abductor digiti minimi, flexor carpi radialis muscles. Reference electrode will be placed at the ipsilateral elbow above the brachial biceps muscle.

c. Mapping of the upper extremity. After determination of the MT, mapping of the UE will be performed at 110% of the rMT. All positive and negative stimulation sites will be recorded and saved.

Patients will be closely monitored during TMS stimulation. Each subject will have a complete neurological examined by a neurologist before and immediately after nTMS. Patients will also be provided a side effects questionnaire after TMS mapping. Patients will then be asked to keep a 7 day seizure diary after the nTMS session

3.1.3 Follow-up clinical visit after the surgery

After epilepsy surgery patients will receive the standard care for post-operative patients which including close monitoring in ICU overnight. Patients will be transferred to the floor for further clinical evaluation before discharge. Clinical outcome will be evaluated in the post-operative clinic visit within 1 month after discharge. The value of a clinical follow up is to evaluate for any discrepancy between nTMS and DCS, to determine which modality better predicts functional outcome. Any seizure recurrence or neurological deficit will be recorded at the follow-up clinical visit.

3.2 Primary Study Endpoints

The trial is designed to detect strength of spatial correlation between topographic maps of hand motor representation obtained through noninvasive nTMS compared to direct, extra-operative cortical stimulation obtained as part of usual clinical evaluation during epilepsy surgery, as measured by (a) average distance between positive motor mapping sites of DCS compared to nTMS and (b) degree of concordance between positive and negative motor mapping sites between DCS and nTMS, to generate positive and negative predictive values, and (c) average distance between positive motor functional sites of fMRI compared to nTMS.

3.3 Secondary Study Endpoints

In addition, this study is designed to detect safety and tolerability of TMS in the epilepsy patient, as measured by 7 day seizure diaries before and after the nTMS sessions.

4 Subject Selection and Withdrawal

We will recruit 14 patients, aged 12-60 years, who will have motor mapping and epilepsy surgery. Because nTMS is expected to most benefit pediatric patients, we plan to enroll at least 4 subjects under the age of 17, to establish validity in this population. There will be no restrictions on race or ethnicity.

Safety and tolerability in healthy volunteers is established for TMS in previous studies, and therefore healthy controls will not be necessary. However side effect questionnaire will be provided after TMS mapping.

4.1 Inclusion Criteria

1. 12-60 years of age
2. Planned neurosurgery involving implantation of intracranial subdural electrodes over the precentral gyrus

4.2 Exclusion Criteria

1. Inability to sign informed consent .
2. Hemiparesis worse than 4-/5 on the side contra lateral to the planned implant
3. Inability to get an MRI, or MRI older than 2 years
4. Frequent (>1 per day) motor seizures
5. Prior neurosurgery
6. Metal in the head, including shrapnel
7. Implanted stimulation devices, including DBS, RNS, VNS, PPM
8. Pregnancy
9. Use of a medication known to increase the risk of seizures, including certain antipychotics (clozapine), bronchodilators (aminophylline, theophylline), immunomodulatory agents (cyclosporine), and antibiotics (penicillins, cephalosporins, amphotericin, imipenem).

4.3 Subject Recruitment and Screening

We will announce the opening of the trial with a group email sent to the NYU Comprehensive Epilepsy Center. We will identify potential subjects at surgical conference, during which all epileptologists participate in the decision-making regarding the patients' surgical planning, and maintaining regular communication with attendings about potentially eligible subjects (see recruitment email).

For potentially eligible outpatients, a research team member will discuss a subject's eligibility with their treating epileptologist. If the patient is deemed an appropriate subject, the treating epileptologist will first introduce the study to their patients and get permission from the patient for a study team member to contact them in person or by telephone using the IRB approved telephone script. The study team member will then discuss study details with the patients. The treating physician will not be asked to provide any details of the proposed study. When possible, i.e., when potential subjects are identified, he or she will meet with Drs. Liu, Friedman, or Chen in person to review the study and TMS technology and study design.

Patients (or their parents/guardians) contacted by phone (or who call in) will be pre-screened over the telephone using the IRB approved telephone script, which reviews study rationale, activities, and includes a brief questionnaire to assess eligibility criteria. We will obtain a waiver of documentation of consent for the minimal risk phone pre-screening since we will obtain verbal consent. Furthermore, for patients who do not continue to sign the written consent (either because they are deemed ineligible or do not want to participate in the study), we will immediately destroy all information we collected from them. We will give these patients (or parents/guardians) a copy of the study information sheet, either in person or via mail.

4.4 Early Withdrawal of Subjects

4.4.1 When and How to Withdraw Subjects

This study is expected to end after all participants have completed all visits, and all information has been collected. Under the following circumstances the subject's participation will be terminated by the investigator without regard to the participant's consent:

- The subject not able to attend the study visits required by the study.
- The subject fails to follow the study requirements.

- If a subject becomes pregnant.
- If a subject decides not to continue participation in the study (by choice)

5 Study Device

5.1 Description

Preoperative mapping was performed with ***Magstim Rapid²*** (Magstim) brain stimulation system. It delivers a biphasic TMS pulse from a figure-of-eight coil with an outer diameter of 70 mm. The system calculates the strength, location, and direction of the stimulating electric field in cortical tissue and takes the subject's head size and shape into account. The estimates of the induced electric field are based on a dynamic spherical model adjusted in real time and the physical parameters of stimulation.

Brainsight Navigation,(Rogue Resolutions) will provide the hardware and software environment to guide TMS application in a manner which is co-registered to the patient's MRI Brain. With combined use of the Magstim Rapid2 and Brainsight, the TMS coil can be navigated and positioned over a specified target location based upon the MRI Brain, thereby directing the stimulation in a spatially precise manner.

Neither the Magstim Rapid2 or Brainsight are FDA approved. However, the combination of ***Magstim Rapid²*** and ***Brainsight NeuroNavigation*** system is comparable to the Nextstim TMS system, which was FDA approved in 2009 for use in presurgical motor mapping (see attachment).Brainsight NeuroNavigation system is a non-significant risk device, as there it represents an imaging tool complementary to the TMS machines, and does not make contact with the patient.

5.2 Treatment Regimen

TMS with brief single pulse sequence and 3-4 seconds interval between pulses will be used in motor mapping in our study. The hand knob will be determined by free point to point stimulation as the location eliciting the largest MEP Reponses form the muscle interested, The resting motor threshold (rMT) was determined at the hand hotspot. rMT is defined as minimal stimulation intensity capable of generating an MEP in 50% of cases. Muscle representation areas relevant for clinical decisions were mapped with an intensity of 110% of rMT. Cortical muscle presentation areas were stimulated by an induced electric field orientated perpendicular to the central sulcus. The stimulation coil was hold tangential to the scalp. The tilt will be monitored on-line and adjusted so as to produce the strongest field strength in the cortex.

5.3 Method for Assigning Subjects to Treatment Groups

All subjects will be receive nTMS mapping in this open-label, phase 1 study , as well as standard procedures involved in the patient's clinical care involved in epilepsy surgery, including a preoperative MRI, functional mapping using DCS, and clinical followup.

5.4 Implantation of Study Device

TMS is a non-invasive form of neurostimulation. No surgical intervention or medication administration is needed before a TMS session.

5.5 Prior and Concomitant Therapy.

Epilepsy patients enrolled in this study will continue to receive standard of care for their management of epilepsy, and their medications will remain unchanged during phase 1 of participation (nTMS). However, patients will likely have their medications reduced while undergoing invasive monitoring for epilepsy surgery, according to standard clinical practice.

5.6 Receiving, Storage, Dispensing and Return

5.6.1 Receipt and storage of Study Device

The device has been obtained from 240 E38th St 20th Floor at the NYU Langone Medical center. NY 10016. The room is locked at the end of the day and can be open only by authorized personnel who have access to the door key. The TMS will be operated by qualified research staff personnel.

5.6.2 Dispensing and Return

The device will not be dispensed to subjects.

6. Study procedures

6.1 Baseline Visit: Informed Consent and baseline neurological visit (30 min)

This visit may happen in conjunction with a planned clinical visit. Patients will be educated on study design and eligibility requirements. If they are eligible and agree to study participation, they will be sign the informed consent. They will then be asked to maintain a 7 day seizure diary prior to the first study visit.

6.2 Visit 2: nTMS session (2 hours)

For this session, the patient will visit the Ambulatory Care Center, 240 East 38th Street, 20th Floor, TMS room 20-01. One of the study investigators board certified in clinical neurophysiology, and an epilepsy specialist (either Dr. Liu or Friedman) will be present during the stimulation. A questionnaire regarding side effects will be given to patients. Detailed description of TMS session can be found in section 3.1.1. Patients will then be asked to keep a 7 day seizure diary after the study visit.

6.3 Visit 3: Post-operative clinic visit (30 min)

Patients will also be followed approximately 1 months after epilepsy surgery, in conjunction with their regularly scheduled clinical visits. A complete neurological exam will be performed and a questionnaire (Michigan Hand Outcomes Questionnaire) will be administered to detect any changes in motor strength and function after surgery.

7. Statistical Plan

7.1 Sample Size Determination

We estimate 10 subjects total necessary to detect a 50% difference between nTMS and DCS mapping, assuming alpha 0.05 and power 0.8. However, given the possibility of subject dropout, and the unknown nTMS side-effect profile and seizures we propose to add ~1/3 to total patient enrollment, and thus will enroll 14 patients. We plan to enroll at least 4 children ages 12-17 years, to assess for the validity of nTMS in a pediatric population, which is expected to benefit the most from this procedure.

7.2 Statistical Methods

Maps of stimulation locations corresponding to hand and arm muscle groups will be formed. The distance between the averaged positive nTMS stimulation sites for each type of motor response (APB, ADM, etc) and the corresponding averaged DCS site will be calculated, according to co-registered 3D coordinates in MRI anatomical space. For DCS, the center of the electrode eliciting motor response with the lowest current will be defined; when stimulation of several electrodes elicited motor response with the same minimum current, the average ECS site of these electrode centers will be used instead. The weighted mean of the DCS map will also be calculated.

The distance between the averages of nTMS and DCS maps, between the site eliciting a motor response with a minimum current and between the average of the nTMS map and the weighted average of the ECS map will be calculated.

The localizations will be also compared in relation to the patients' gyral anatomy. If the nTMS localization and the electrodes eliciting positive motor response in ECS activated the same gyrus, the localizations will be defined as anatomically concordant.

7.3 Subject Population(s) for Analysis

All subjects who complete the nTMS motor mapping session and later undergo direct cortical stimulation for functional mapping will be included in the analysis.

8. Safety and Adverse Events

8.1 Definitions

Unanticipated Problems Involving Risk to Subjects or Others
Any incident, experience, or outcome that meets all of the following criteria:

- Unexpected in nature, severity, or frequency (i.e. not described in study-related documents such as the IRB-approved protocol or consent form, the investigators brochure, etc)
- Related or possibly related to participation in the research (i.e. 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)
- Suggests that the research places subjects or others at greater risk of harm (including physical, psychological, economic, or social harm).

Unanticipated Adverse Device Effect
An Unanticipated Device Effect is any serious adverse effect on health or safety, or any life-threatening problem or death caused by, or associated with a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

Serious injury
Any injury or illness that is any one of the following:

- life-threatening
- results in permanent impairment of a body function or permanent damage to body structure
- necessitates medical or surgical intervention to preclude permanent impairment of a body function or permanent damage to a body structure

Adverse Event
(a) In parallel with recording the primary outcome, we will monitor for increase in seizure severity attributable to TMS by identifying all instances of generalized tonic clonic seizures after TMS treatments. Instances where seizure frequency increased after TMS will be reported to the IRB within 72 hours.

(b) If a self-limited, short (<5 min) partial seizure or evolution into generalized tonic clonic seizure occur, TMS mapping will stop for that day.

(c) If a secondarily generalized (convulsion starting in one area of body and then spreading to other areas) or 2 partial seizures occur during treatment, the patient will be withdrawn from further participation in the study.

(d) If any other unanticipated adverse events occur, the patient will be withdrawn from further participation in the study.

8.2 Recording of Adverse Device Effects

At each contact with the subject, the investigator will record information on adverse device effects by specific questioning and, as appropriate, by examination. Information on all adverse device effects should be recorded immediately in the source document, and also in the appropriate adverse effect module of the case report form (CRF). All clearly related signs, symptoms, and abnormal diagnostic procedures results should recorded in the source document, though should be grouped under one diagnosis.

All adverse device effects occurring during the study period will be recorded. The clinical course of each event should be followed until resolution, stabilization, or until it has been determined that the study treatment or participation is not the cause. Serious adverse device effects that are still ongoing at the end of the study period must be followed up to determine the final outcome. Any serious adverse device effects that occur after the study period will be recorded and reported promptly (see section 8.3 below) to the IRB, the device manufacturer (Magstim), and the FDA.

The minimum initial information to be captured in the subject's source document concerning the adverse device effect includes:

- Study identifier
- Study Center
- Subject number
- Device model and serial number
- A description of the event
- Date of onset
- Investigator assessment of the association between the event and study treatment
- Current status
- Whether study treatment was discontinued
- Whether the event is serious and reason for classification as serious

8.3 *Reporting of Adverse Device Effects and Unanticipated Problems*

8.3.1 Investigator reporting: *Notifying the IRB*

Federal regulations require timely reporting by investigators to their local IRB of unanticipated problems posing risks to subjects or others. The following describes the NYULMC IRB reporting requirements, though Investigators at participating sites are responsible for meeting the specific requirements of their IRB of record.

Report Promptly, but no later than 5 working days:
Researchers are required to submit reports of the following problems promptly but no later than10 working days from the time the investigator becomes aware of the event:

- ***Unanticipated problems including adverse events*** **that are unexpected and related**
  - *Unexpected: An event is "unexpected" when its specificity and severity are not accurately reflected in the protocol-related documents, such as the IRB-approved research protocol, any applicable investigator brochure, and the current IRB-approved informed consent document and other relevant sources of information, such as product labeling and package inserts.*
  - *Related to the research procedures: An event is related to the research procedures if in the opinion of the principal investigator, the event was more likely than not to be caused by the research procedures.*
  - *Harmful: either caused harm to subjects or others, or placed them at increased risk*

- ***Unanticipated adverse device effect***: Any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application, or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

Other Reportable events:
The following events also require prompt reporting to the IRB, though no later than10 working days:

- ***Complaint of a research subject*** when the complaint indicates unexpected risks or the complaint cannot be resolved by the research team.
- ***Protocol deviations or violations*** (includes intentional and accidental/unintentional deviations from the IRB approved protocol) for any of the following situations:
  - *one or more participants were placed at increased risk of harm*
  - *the event has the potential to occur again*
  - *the deviation was necessary to protect a subject from immediate harm*
- ***Breach of confidentiality***
- ***Incarceration of a participant*** when the research was not previously approved under Subpart C and the investigator believes it is in the best interest of the subject to remain on the study.
- ***New Information indicating a change to the risks or potential benefits*** of the research, in terms of severity or frequency. (e.g. analysis indicates lower-than-expected response rate or a more severe or frequent side effect; Other research finds arm of study has no therapeutic value; FDA labeling change or withdrawal from market)

Reporting Process
The reportable events noted above will be reported to the IRB using the Reportable New Information submission (including a description of the event with information regarding its fulfillment of the above criteria, follow-up/resolution and need for revision to consent form and/or other study documentation).

Copies of each report and documentation of IRB notification and receipt will be kept in the Clinical Investigator's study file.

8.4 Stopping Rules

Should a safety concern arise, the study will be voluntarily paused until further review. Specific events that may prompt a study pause are: exacerbation of seizure intensity or frequency, syncope, and/or exacerbation of underlying neurologic symptoms.

8.5 Medical Monitoring

It is the responsibility of the Principal Investigator to oversee the safety of the study at his/her site. This safety monitoring will include careful assessment and appropriate reporting of adverse events as noted above, as well as the construction and implementation of a site data and safety-monitoring plan (see section 9 Auditing, Monitoring and Inspecting). Medical monitoring will include a regular assessment of the number and type of adverse device events.

8.5.1 Data Monitoring Committee

The primary responsibility of data safety monitoring will lie with Dr. Liu, although all members of her research team will have responsibility for DSMP. DSMP committee will meet in person or have telephone conversations every 2 months, and informally meet on an as needed basis. The DSMP will review patient safety, data quality, protocol compliance, and subject enrollment numbers. A summary DSMP report will be submitted to the IRB as part of the yearly continuation process. Reportable events will be reported in an expedited fashion, as described above in section 8.3.1. All team members have extensive experience in clinical neurophysiology as well as design and implementation of clinical trials, will participate:

NYU PI: Anli Liu MD MA
Assistant Professor of Neurology
NYU School of Medicine
Comprehensive Epilepsy Center

223 East 34th Street
New York, NY 10016

NYU Co- Principle Investigator: Daniel Friedman MD
Assistant Professor of Neurology
NYU School of Medicine
Comprehensive Epilepsy Center
223 East 34th Street
New York, NY 10016

9. Data Handling and Record Keeping

All collected information will be secured in a locked office on a computer with password protection. No individual who is not part of this protocol will be given access to this information.

9.1 Confidentiality

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why. Only site PIs and study team members will have access to PHI. Outside collaborators will only have access to patient's de-identified data.
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI.

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e. that the subject is alive) at the end of their scheduled study period.

Data will be coded in an anonymous fashion, according to enrollment order (eg P001, P002, etc).

9.2 Source Documents

Source data is all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents. Examples of these original documents, and data records include: hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial.

9.3 Case Report Forms

The study case report form (CRF) is the primary data collection instrument for the study. All data requested on the CRF must be recorded. All missing data must be explained. If a space on the CRF is left blank because the procedure was not done or the question was not asked, write "N/D". If the item is not applicable to the individual case, write "N/A". All entries should be printed legibly in black ink. If any entry error has been made, to correct such an error, draw a single straight line through the incorrect entry and enter the correct data above it. All such changes must be initialed and dated. DO NOT ERASE OR WHITE OUT ERRORS. For clarification of illegible or uncertain entries, print the clarification above the item, then initial and date it.

9.4 Records Retention

Dr. Liu will retain study essential documents for at least 2 years after the last approval of a marketing application in their country and until there are no pending or contemplated marketing applications in their country or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product.

10 Study Monitoring, Auditing, and Inspecting

10.1 Study Monitoring Plan

Because of the potential risk of adverse side effects, patients will be monitored closely during the study period through detailed medication history, physical examinations, and close follow-up, as described in the protocol. Study participants will be able to contact one of the study members at any time with questions or concerns, as indicated in the consent form. All adverse events will be recorded, scored for severity and for relationship to the study, as described. All serious and unexpected adverse events will be reported to the IRB and the DMC within 72 hours. All regulatory authorities will be able to inspect the collected data. Should a safety concern arise, the study will be voluntarily paused until further review. Specific events that may prompt a study pause are: seizure, syncope, exacerbation of underlying neurologic symptoms.

10.2 Auditing and Inspecting

The investigator will permit study-related monitoring, audits, and inspections by the IRB, government regulatory bodies, and University compliance and quality assurance groups of all study related documents (e.g. source documents, regulatory documents, data collection instruments, study data etc.). The investigator will ensure the capability for inspections of applicable study-related facilities (e.g. pharmacy, diagnostic laboratory, etc.).

Participation as an investigator in this study implies acceptance of potential inspection by government regulatory authorities and applicable University compliance and quality assurance offices.

11 Ethical Considerations

This study is to be conducted according to US and international standards of Good Clinical Practice (FDA Title 21 part 312 and International Conference on Harmonization guidelines), applicable government regulations and Institutional research policies and procedures.

This protocol and any amendments will be submitted to a properly constituted independent Ethics Committee (EC) or Institutional Review Board (IRB), in agreement with local legal prescriptions, for formal approval of the study conduct. The decision of the EC/IRB concerning the conduct of the study will be made in writing to the investigator before commencement of this study.

All adult subjects (or parents/guardians for minors) for this study will be provided a consent form describing this study and providing sufficient information for subjects to make an informed decision about their participation in this study. Dr. Liu and Dr. Friedman will be allowed to consent patients. All have significant experience with patient oriented clinical research, and are specialists in epilepsy and clinical neurophysiology, and have significant clinical experience with both adults and children. Only subjects, their family members, and study team members will be present during the consent process to protect patient privacy. For potential subjects ages 12-17, a separate assent form for subjects aged 12-14 (see attached) and aged 15-17 (see attached) will be used to obtain assent. Furthermore, the permission of both parents will be obtained, unless (1) one parent is deceased, unknown, incompetent, or not reasonably available, or (2) only one parent has legal responsibility for the care and custody of the child.

See Attachment 1 for a copy of the Subject Informed Consent Form. This consent form will be submitted with the protocol for review and approval by the EC/IRB for the study. The formal consent of a subject, using the EC/IRB-approved consent form, must be obtained before that subject undergoes any study procedure. The consent form must be signed by the subject or parent/guardian for minors, and the

investigator-designated research professional obtaining the consent. . If patients meet eligibility criteria and provide informed consent, they will be given a copy of their consent. We will keep a copy of the informed consent in patient data binders, which will be kept in a secure, locked location, with other collected study data.

12 Study Finances

12.1 Funding Source

Department of Neurology.

12.1.1 Subject compensation. Patients will be compensated $50 an hour for their participation in this study, or an expected total of $200. The investigators believe this is reasonable given that participation in the study constitutes 3 separate visits.

12.1.2 Study related costs. The cost of the initial neurological consultation (visit 1) prior to surgery, as well as the routine follow up within 6 months after the surgery is considered part of routine clinical care, and will be billed to the patient's insurance company. Furthermore the cost of epilepsy surgery, including subcortical grid implantation, and functional mapping, is considered part of routine clinical care. There will be no cost of participation to the patient.

12.2 Conflict of Interest

Any investigator who has a conflict of interest with this study (patent ownership, royalties, or financial gain greater than the minimum allowable by their institution, etc.) must have the conflict reviewed by a properly constituted Conflict of Interest Committee with a Committee-sanctioned conflict management plan that has been reviewed and approved prior to participation in this study. All NYU investigators will follow the applicable University conflict of interest policy(ies).

13 Publication Plan

Neither the complete nor any part of the results of the study carried out under this protocol, nor any of the information provided for the purposes of performing the study, will be published or passed on to any third party without the consent of the principal investigator. Any investigator involved with this study is obligated to provide the principal investigator with complete test results and all data derived from the study.

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