Title: Repeated TMS at Low Frequencies to Reduce Seizure

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Repeated TMS at Low Frequencies to Reduce Seizure Occurrence

I. SUMMARY OF THE RESEARCH

Perform non-invasive neuro-navigated repeated Transcranial Magnetic Stimulation (rTMS) at low frequencies (LF) with the intent to reduce the occurrence of seizures over time. Seizure reduction and improvements in the quality of life in patients with epilepsy will be associated with increased cortical inhibition resulting from the LF-rTMS sessions over time. This procedure using rTMS at low frequencies (LF-rTMS) between 0.5 and 1 Hz is a safe and painless method for noninvasive focal cortical brain stimulation, which will be evaluated in its efficacy at reducing/suppressing seizures. Accordingly, we propose a clinical trial in patients with epilepsy to test whether LF-rTMS can improve seizure suppression. The location of the presumed 3D source in the brain will be stimulated for few minutes (10 to 15mns). With the same rTMS modality, we will also perform motor threshold mapping in conjunction with its fully integrated and compatible electroencephalography (EEG) module.

Despite the progress made in the development of multimodal imaging algorithms, there are still limitations and drawbacks to be overcome in the area of time and space alignments. The simultaneous use (time alignment) of different recording modalities on a same patient (space alignment) would validate a given outcome as long as it is imaged or recorded in more than one imaging/recording modality. As such, brain mapping and 3D source localization are consolidated in a same 3D space and in context to the 3D source where seizures are anticipated to emanate from. The multimodality structure relies in the simultaneous use of TMS, MRI, EEG and Electromyography (EMG), all non-invasive, safe, and FDA approved. The complete procedure will include tasks of motor threshold mapping using non-invasive brain navigated magnetic stimulation, while simultaneously monitoring EEG and EMG. The study is of minimal risk with common risks/discomforts of the test limited to mild and brief discomfort of the skin on the scalp from the Velcro strap or the EEG electrodes. Also, occasional side effects of the test are minor and brief headache from prolonged TMS stimulation.

The significance of this work is related to addressing the effectiveness of long-term use of rTMS for medically refractory patients (failed two or more medications) as a non-invasive alternative to other established techniques (i.e. VNS, RNS, among others). For this purpose, we will unify data from different sources whose analysis and results are strengthened and validated in more than one modality (TMS, MRI, EEG in consortium), which will secondarily provide higher resolution for assessing the dysfunction in both temporal and spatial domains. All of these steps are to ensure the delivery of the most effective rTMS brain stimulation with the intent to reduce/suppress the occurrence of seizures in patients with epilepsy to include both children and adult populations.

II. SCIENTIFIC BACKGROUND & LITERATURE REVIEW

Transcranial Magnetic Stimulation with both single (sTMS) and repetitive simulation (rTMS) capabilities is a non-invasive technology, which serves not only as a powerful tool for mapping the eloquent cortex of the brain, but provides great potential for treatment and eliciting new insights into a variety of brain disorders, especially for patients who do not benefit from drug treatments. The TMS technology was introduced in the 1980s, and since then, it has been used in clinical care for several neurological disorders [1–4]. The initial intent of this technology was to improve the health of patients with depression as exemplified in studies [5–8]. Its application has now been

extended to gauge the merits of magnetic stimulation to other neurological disorders such as epilepsy [9–11], Huntington's disease [12], Parkinson's disease [13], different effects of schizophrenia [14–16], Alzheimer's disease, and effects of aging [17, 18], in patients who have had a stroke [19–21], autism [22, 23], and attention deficit and hyperactivity disorders [23, 24]. These are by no means an exhaustive listing of such noteworthy references, but these are examples of studies that highlight the extensive use of TMS technology. It should be noted that the use of TMS can be performed under two modes of operation, namely, single pulse [25] or repetitive mode of stimulation [26, 27].

The hypothesis is that low frequency brain stimulation focused on and around the seizure onset zone will reduce the occurrence of seizures over time. We base this hypothesis on clinical trials and reports on the treatment of seizures reported in the literature. It has been shown that high frequency rTMS, although beneficial in the treatment of patients with depression, can actually cause seizures [28], while low-frequency rTMS has the opposite effect in that it can actually inhibit the occurrence of such seizures. Modulating brain activity is shown to depend on the selection of the frequency used during stimulation [29, 30]. Therefore, and on the basis of this knowledge, we will restrict the brain stimulation process to a low frequency range between 0.5 and 1 Hz rTMS in people with focal and generalized epilepsy, while taking into consideration all the safety guidelines, ethical issues, and required precautions from prior research in the use of TMS technology [31, 32, 33].

The significance of this work is to address the efficacy of the long-term use of rTMS in the treatment of refractory epilepsy patients. Additionally, the integration of multimodal imaging where TMS, MRI, and EEG could provide data not available through DCS or fMRI alone, which in turn can only augment our understanding of brain mapping and brain dynamics. This study will employ a carefully planned low frequency rTMS protocol, with therapeutic sessions over a one-year time frame, with a possible extension phase protocol if initial study is successful.

III. RESEARCH OBJECTIVES

1. To reduce/suppress the number of seizures in patients with medically intractable epilepsy (partial and generalized) with the use of long-term LF-rTMS. Stimulation will be applied with determined seizure onset zone by inverse solutions and 3D software algorithms of analysis of electroencephalographic data. This objective is based on promising rTMS studies that reported reductions in seizure frequency. The primary continuous outcome measures for this aim will be seizure frequency, EEG epileptiform discharge frequency, seizure severity scale, and psychometric testing.
2. Statistical analysis will be conducted using ANOVA and secondary outcome measures will analyze the number of patients whose seizure frequency decreases by at least 50% (e.g., the "responder" threshold used in studies of anticonvulsant efficacy).
3. Localize through TMS stimulation motor threshold cortex mapping of the abductor pollicus brevis-evoked response. This is an important step for determining the appropriate patient-specific stimulation threshold.
4. Measure EEG alpha asymmetry before and after rTMS and compare the change in this continuous variable among treatment and sham groups in intractable epilepsy. We

hypothesize, that rTMS will alter the ratio of right to left EEG alpha power (8-13 Hz). Alpha asymmetry is known to be common in patients with epilepsy in contrast to healthy controls where alpha symmetry is seen as more prevalent.

IV. INCLUSION AND EXCLUSION CRITERIA

All individuals between ages 18 to 80 that are medically refractory who have completed informed consent/assent, and able to cooperate with non-sedated navigated TMS testing will be included. Exclusion criteria include the presence of implanted electronic devices (e.g., pacemaker, medication pump, brain or vagus nerve stimulator, cochlear implant), intracranial metal (e.g., aneurysm clip), or inability to cooperate with the rTMS session.
Goal recruitment will be 90 epilepsy patients, based on the following:

- At least 3 seizures in one month
- No status epilepticus for 1 year
- No change in medication for 1 month

V. METHODS AND ACTIVITIES

5.1 Interventions and Interactions of the Research Study

An Informed Consent will be obtained by Baptist Health personnel and the subject will be explained the aims and procedures of the research task that will be performed by FIU personnel.

- Positioning of the subject in the TMS chair along with the registration apparatus (spectacles or head band) and performing a high-resolution (< 2mm) registration of the subject head to the pre-acquired magnetic resonance imaging (MRI) since the TMS machine is MRI-guided.
- Connecting 1-6 EMG surface electrodes on target muscles to evaluate muscle response to TMS stimulation, and
- EEG electrodes will be placed according to the 10-20 system montage.

The systems (EMG and EEG) will continuously record the activity from the subject throughout the procedure. It should be noted that since these acquisition techniques, which are completely non-invasive and used regularly in clinical settings, render little or no discomfort to the test subjects. There will be a neurologist (Dr. Alberto Pinzon) on the premises during all procedures. Sections 5.1-5.3 and 5.4.3-5.4.4 of the “Methods and Activities”, as explained below will be performed completely by FIU personnel (Mercedes Cabrerizo, Ph.D. and Ms. Niovi Rojas). Malek Adjouadi, Ph.D. from FIU will supervise all the protocol outcomes. Dr. Pinzon will refer all epileptic patients that will be included in this study research. Also copies of standard care MRI images (not taken as part of this study) will be provided by Baptist Hospital Radiology Department after enrolled subjects sign a HIPAA agreement to allow it.

5.2 TMS mapping and recording

The technology used in this research study is based on the so-called Neuro-navigated Brain Stimulation (NBS), a technology developed for mapping the eloquent cortex of the brain as well for therapy as currently used on different neurological disorders in different centers and healthcare

providers. This newly acquired technology by the CATE center is to improve accuracy in the diagnosis and in improving mapping the brain non-invasively. TMS mapping and recording will allow for (1) MRI-guided neuro-navigation with electric-field controlled stimulation to precise 3D targets in the cortex; (2) powerful and highly focal magnetic stimulator and coils with the ability to monitor the point of focality as well depth attenuation; (3) a compatible fully integrated EMG for motor functions; and (4) a compatible 60-channel EEG module for integrating brain electrical activities at rest and under the TMS stimulation process. TMS thus offers a non-invasive alternative to DCS (gold standard). This can be further augmented with the fMRI images in order to validate the location of these eloquent cortical areas.

Since the TMS is FDA approved for motor threshold mapping, the following protocol is used to map the eloquent cortex.

5.2.1 Motor Threshold Mapping Protocol

All the patients will lie down in a comfortable chair in a supine position. The Nexstim system's 6-channel EMG module (SR=1450 Hz, cut-off frequency of 350 Hz for the low pass filter) will automatically calculate the motor evoked potential (MEP) amplitudes and latencies as the motor cortex (cortex area of the thumb) is stimulated. Disposables Ag-AgCL surface electrodes will be used to record the MEP responses displayed in a computer screen in order to assess the validity of the response based on the strength of MEPs, reflecting the ability of that area to develop a muscle contraction.

This protocol will consist of the following two steps:

- Perform TMS in order to determine the motor threshold for each individual patient.
- In order to obtain the motor threshold, the intensity of the TMS is gradually increased in order to elicit responses from the Abductor Pollicis Brevis (APB) muscle near the thumb.
- Once the motor threshold is determined the complete tracking of the motor cortex is carried out at an intensity of 10% greater than the motor threshold.
- The entire process of motor cortex mapping is estimated to take 15-20 minutes.

Prior studies have demonstrated that partial motor threshold can vary in a person from session to session and for this reason, it will be performed every time patients are treated.

5.3 Epilepsy Protocol for rTMS at low frequencies in Epilepsy (long-term protocol)

Repetitive transcranial magnetic stimulation (rTMS) at low frequency range (0.5-1 Hz), LF-rTMS is a safe and painless method for noninvasive focal cortical brain stimulation which is efficacious in suppressing seizures. Accordingly, we propose a clinical trial in patients with epilepsy to test whether LF-rTMS can improve seizure reduction/suppression. The location of the presumed 3D source in the brain and its immediate surroundings will be stimulated for 14 minutes at these low frequencies.

Repeated TMS at Low Frequencies to Reduce Seizure Occurrence

Existing protocols that are related to this work [34-41] are listed in Table 1. These were reviewed in order to bring in synergy the strengths of each for carrying out safe and effective rTMS sessions. Accordingly, we propose a long term trial in patients with focal and generalized epilepsy, to test whether LF-rTMS can reduce/suppress the occurrence of seizures, and determine for how long such outcomes can last for each patient. The proposed protocol that will be followed in this study is described in Table II on the basis of the knowledge gained from these previous studies.

Table 1: Existing Protocols.

Cited Literature	Frequency	Threshold	Stimuli	Schedule	Coil	Outcome-seizures	Position	Daily Stimulation time
Cantello, et al. 2007 [34]	0.3 Hz	100%MT 65%MSO	500/train	2 trains/day For 5 days	0	No change	vertex	28 min.
Fregni, et al. 2006 [35]	1Hz	70%MSO	1200/train	1 train/day For 5 days	8	Decreasing	3D source vertex	20 min.
Theodore, et al. 2002 [36]	1 Hz	120% MT	900/train	2 trains/day For 1 week	8	Decreasing	3D source	15 min.
Tergau, et al. 2003 [37]	0.33, 1 Hz	Below MT	1000/Train	1 train/day For 5 days	0	Decreased 0.33 Hz	vertex	55 min. 17 min.
Brasil-Neto, et al. 2004 [38]	0.5 Hz	90% MT	100/train	Biweekly / 4 weeks	8	Decreased	3D source vertex	3 min.
Misawa, et al. 2005 [39]	0.5 Hz	90%MT	100	Single session repeated at 3 months	8	Decreased for 2 months	3D source	3 min.
Menkes, et al. 2000 [40]	0.5 Hz	95%MT	20/train	5 trains/day Biweekly for 3 months	0	decreased	3D source	0.6 min.
Rossi, et al. 2004 [41]	1 Hz	90% rMT	900	Single session	8	decreased	3D source	15 min.

MT: Motor threshold, MSO: Maximum stimulator output

Table 2: Suggested Long-Term Protocol for this Study: Treatment vs. Placebo Groups (Stimulation time: 14 minutes)

Frequency	Threshold	Stimuli	Schedule	Coil	Position	Study

						Design
1Hz	120%MT	800	5 days/week for 2 weeks 1/week for 1 month 1/month for 11 months	8	3D Source Localization, vertex, and bipolar frontal	double-blinded, sham-controlled
1Hz	120%MT	800	5 days/week for 2 weeks 1/week for 1 month 1/month for 11 months	8	coil will be placed with an angle of 45 degrees with respect to the scalp without direct contact	double-blinded, sham-controlled

Using a single-blinded, sham-controlled design, we will screen patient's age 2 to 80 years with focal and generalized retractable epilepsy. Baseline data will include a detailed seizure diary over 4 weeks, psychometric testing/neuropsychology evaluation, and 20-minute EEG recordings. Each patient will then begin treatment with 14 minute sessions of 1 Hz rTMS or sham rTMS, 120%MT, and 800 stimuli on the position of the calculated 3D source using EEG, MRI, and digitized electrode locations. The protocol will be divided in 3 groups (Groups 1, 2 and 3) as follows:

- Groups 1, 2, and 3: LF-rTMS for 2 weeks (5 days per week for total of 10 days).
- Group 1: protocol total duration: 1 year: LF-rTMS 1 session/week for 1 month (4 days), and LF-rTMS 1 session/month for 11 months
- Group 2: protocol total duration: 1 year: LF-rTMS 1session/month for 12 months
- Group 3 (placebo protocol, total duration: 1 year): LF-rTMS 1session/week for 1 month (4 days); and LF-rTMS 1session/month.

During each session EEG will be recorded. Also, we would update number of events and frequency data from ongoing seizure diary. Psychometric testing will be performed at the beginning of study, 3 months, and at the end of the study. Thus, each patient will have rTMS testing, psychometrics, and EEG recordings.

Goal recruitment will be 90 medically refractory participants, with 30 participants for each of the three groups, based on the following:

- At least 3 seizures in one month
- No status epilepticus for 1 year
- No change in medication for 1 month

In retrospect, promising rTMS studies have reported reductions in seizure occurrence [35, 42-54]. Several studies [45-48] included children, and reported improvement in seizure occurrence in the majority of these children, due to a modulation in cortical excitability, induced by low frequency rTMS. Other studies measured EEG alpha asymmetry [49] before and after rTMS to assess the change in this continuous variable among treatment and sham groups in intractable epilepsy. In these studies, it is hypothesized that rTMS could alter the ratio of right to left EEG alpha power

(8-13 Hz). Alpha asymmetry is known to be present in patients with epilepsy in contrast to healthy controls. The major objective in all of these studies is to seek seizure reduction associated with increased cortical inhibition resulting from the LF-rTMS sessions [34, 50-53]. TMS (single or repetitive pulse) thus offers a noninvasive option that could serve as a therapeutic tool that will reduce the occurrence of seizures.

5.3.1 Epilepsy Protocol for rTMS at low frequencies in Epilepsy (short-term protocol)

Epilepsia partialis continua (EPC) can be considered the status epilepticus (SE) equivalent of focal onset seizure with retention of awareness. EPC may occur as a single episode, repetitive episodes, and it may be chronic progressive or non-progressive. The significance of this work is to address the efficacy of the short-term use of rTMS in the treatment of EPC patients. This study will employ a carefully planned low frequency rTMS protocol, with therapeutic sessions over a short period of time (3 to 5 days), with a possible extension phase protocol if initial study is successful.

Existing protocols that are related to this work [1-7] are listed in Table 3. These were reviewed in order to bring in synergy the strengths of each for carrying out safe and effective rTMS sessions. Accordingly, we propose a short term trial in patients with EPC, to test whether LF-rTMS can reduce/suppress the status epilepticus, and determine for how long such outcomes can last for each patient. The proposed protocol that will be followed in this study is described in Table 4 on the basis of the knowledge gained from these previous studies.

During each session EEG will be recorded. Goal recruitment will be 10 acute phase medically refractory participants, based on the following:

- At least 2 medications failed
- At least 24 hours of acute phase
- Family consent or available proxy (legal representative)

Equipment:

The MagVita TMS is CE approved for “treatment of Major Depressive Disorder. MagVenture’s rTMS system is effective and it is an alternative to medications.

Table 3: Existing Protocols.

Cited Literature	Frequency	Threshold	Stimuli	Schedule	Coil	Outcome-seizures	Position	Stimulation time
Gersner, et al. 2016 (1)	20Hz	80%MO	500/train	10 trains of 3s with 30s intertrain One time	8	Reduced epileptic spike frequency decreased seizures during stimulation	vertex	Single 5 min.

Liu A, et al. 2015 (3)	1Hz	70%MO		1 train	8	Reduced epileptic spike frequency and seizures	3D source	20 min.
Rotenberg, 2009 (4)	1Hz:1800 sec.	100%MT	3 trains	3 trains		Seizures stopped	3D source	1800 sec
Graff Guerrero. 2004(5)	20Hz	50%MO	15 trains	15 trains of 2 sec		Seizures stopped	3D source	
Graff Guerrero. 2004(5)	20Hz	128%MT	15 trains	15 trains of 2 sec		Improved EEG	3D source	
Schrader LMKL, 2005 (6)	0.5 Hz	100%MT	16 trains of 900 sec	2 trains per session, biweekly, for 4 weeks)		decreased seizures	3D source	
Misawa S, 2005 , (7)	0.5 Hz	90%MT	1 train of 200 sec	1 train		Seizures stopped	3D source	

MT: Motor threshold, MSO: Maximum stimulator output

Table 4: Suggested short-Term Protocol for this Study: (Stimulation time: minutes)

Frequency	Threshold	Stimuli	Schedule	Coil	Position	Study Design
1Hz	100%MO		Up to 5 days/	8	3D Source Localization or vertex	Open-label

5.3.2 Limitations and Alternative Approaches

While TMS is a safe, painless, technically easy procedure, because the orientation of the magnetic field of stimulation needs to be perpendicular to the electrical field of stimulation, TMS may not always generate a response. In such a case, the benefit of the stimulation technique may be limited. The abductor pollicis brevis (APB) is a low voluntary recruitment threshold motor unit, easily activated in most individuals using TMS. However, should this fail to activate with maximal stimulation, another muscle of similar threshold can be substituted: either the first dorsal interosseous or the abductor digiti minimi. These muscles are all in the palm of the hand.

5.3.3 Emergency Response and Treatment Protocol in case of Seizure

A neurologist (Dr. Alberto Pinzon) will be on the premises at all times during the rTMS treatment. In the immediate vicinity of the TMS machine where the patient is laying down on a comfortable chair similar to the ergonomic dental chair, no harmful objects will be present. In case a patient suffers the occurrence of a seizure during an rTMS session, the following steps are undertaken:

- Code rescue will be initiated for the management of acute seizure for patient safety according to hospital's protocols and as below.
- Diastat AcuDial (diazepam rectal gel) will be kept at the chair side in case any seizures are provoked. DIASTAT is a gel formulation of diazepam intended for rectal administration in the management of selected, refractory patients with epilepsy, on stable regimens of AEDs, who require intermittent use of diazepam to control bouts of increased seizure activity for patients 2 years and older.
- If a seizure occurs, testing (TMS) will be postponed at least 1 hour, or until baseline function returns.
- Patient will be placed on their left side in the recovery position to promote airway and prevent aspiration.
- Harmful objects will be moved out of the way, head will be protected.
- Patient will not be restrained. Objects will not be placed in the mouth. Adequate ventilation will be ensured.
- Respiratory changes such as skin color increase/decrease in respiratory rate and noisy or congested breathing will be monitored. If the patient is not breathing, rescue breathing will be started immediate medical attention will be followed. Suction apparatus, clean gloves and pillows will be available for immediate use.

http://www.epilepsy.com/get-help/staying-safe and http://www.epilepsy.com/get-help/managing-your-epilepsy

http://www.emergencycareforyou.org/EmergencyManual/WhatToDoInMedicalEmergency/Default.aspx?id=268

http://www.webmd.com/epilepsy/epilepsy-seizure-what-to-do-in-an-emergency

5.4 Multimodal Imaging

This TMS based protocol for epilepsy relies on multimodal imaging to benefit from (1) structural MRI for MRI-guided TMS motor threshold mapping and for situating in context the 3D source of seizure onsets; and (2) EEG for determining the 3D source exploiting the presence, positioning and singular nature of the interictal spike waveforms.

5.4.1 Magnetic Resonance Imaging -MRI

All patients that will undergo TMS brain stimulation would have had both magnetic resonance imaging (MRI) recording done at any of our collaborating hospitals (Miami Children's Hospital, Baptist Hospital or other) as it concerns this study. Since TMS is an MRI-guided machine, its use in conjunction with an MRI of a patient, it becomes possible to perform pinpointed navigated mapping of the language and motor areas of the brain. And when a 3D source is determined using interictal spikes of the EEG, such a source is also rendered in the context of the 3D brain of the patient.

5.4.3 Electroencephalography recordings - EEG

EEG recordings will be performed using the XLTEK EEG (Electroencephalograph) system. EEG signals will also be collected before and after some selected rTMS sessions, so that more comprehensive subject-specific connectivity maps could be obtained [54-57]. This is performed in order to assess the connectivity maps as a function of the determined position of the 3D source.

This system will be used to record the brain's spontaneous electrical activity and evoked responses non-invasively from the scalp. XLTEK EEG is a robust whole-head EEG system that can be used to record EEG activity so as to determine the 3D source of seizures on the basis of interictal spikes, or subsequent to this first step. Some of the research themes that will be investigated include (1) EEG activity analysis on the basis of the cortical and sub-cortical stimulation using repetitive pulse TMS (rTMS); (2) Study the functional connectivity between areas and the changes that occur in the brain before and after stimulating motor and language areas, respectively; (3) assess TMS-induced modulation of brain rhythms with respect to rest state.

Also EEG recordings in some cases may be performed using the Nexstim eXimia EEG system, designed specifically to be fully compatibility with the TMS machine, and is another major component that can be purchased alongside the TMS machine, which we did. *It is important to note that with the new TMS technology, an EEG module is fully integrated, and unlike the inherent noise in the integration of EEG and fMRI, both EEG and TMS signals are fully compatible as the TMS does not affect the EEG signal.* Consequently, EEG signals will also be collected during brain mapping, so that more comprehensive subject-specific connectivity maps could be obtained [54-57]. This is performed in order to assess the connectivity maps as a function of the determined position of the 3D source.

5.5. Risks Associated with the Recording Modalities

5.5.1 Risks of TMS

TMS often causes minor short-term side effects. These side effects are generally mild and typically improve after the first week or two of treatment. They can include:

- Headache.
- Scalp discomfort at the site of stimulation.
- Tingling, spasms or twitching of facial muscles.
- Lightheadedness.
- Discomfort from noise during treatment
- Mild and brief discomfort of the skin on the scalp from the Velcro strap or the EEG electrodes.

Uncommon side effects include:

- Mild and brief headaches or neck aches from the TMS stimulation. Serious side effects are rare. They can include:
- Seizure occurring during TMS stimulation at high frequencies. This has only been known to happen in 1% of children and adults with epilepsy, and in less than 1% of children and adults without epilepsy.

- Mania, particularly in people with bipolar disorder.
- Hearing loss due to inadequate ear protection during treatment.

5.5.3 Risks of EEG recording

There are no known risks for this standard noninvasive scalp EEG recordings, except for slight discomfort due to the placement of some of the electrodes that may be too tight on the scalp.

5.5. 3 Minimizing Risks, Harms, and/or Discomforts

In order to reduce discomfort due to use of EEG electrodes, 'comfort rings' are used. As for rTMS stimulation, a mechanical arm with several degrees of freedom is designed to hold the TMS coil to eliminate any potential for pressure on the head of the subject, something that could happen if the coil were handheld by the clinician.

Previous studies have demonstrated that motor threshold mapping in normal subjects is not associated with provoking seizures [58].

VI. DATA TO BE COLLECTED AND DATA ANALYSIS PROCEDURES

Patients will be given a questionnaire to fill out their demographic and health information. Original medical records may be requested and stored by primary neurologist.

For each patient, the following types of data will be collected:

- A 3D MRI volume: This high resolution volumetric imaging data will be collected so that the final results could be displayed in concordance with the regions that were found to be active according to the task applied (motor or speech).
- Scalp EEG s in order to extract time and frequency domain parameters to assess the reaction of the brain to magnetic stimulation using different intensities and frequencies. The lateralization index will be calculated to define the dominant cerebral hemisphere for the language task.
- DICOM stimulation maps for motor threshold mapping.
- EMG data obtained from 1-6 EMG electrodes used for monitoring different muscle groups.

The data will be collected and stored for each patient undergoing the study. All the data will be de-identified by converting into alphanumeric values. The encoded values will be stored in password-protected servers accessible only to research personnel (FIU/Baptist) with authorization throughout data collection and analysis.

All identifiers will be removed from the data once they are transferred off the TMS computer and gathered into a pooling database, where each case will have a unique consecutive identification number. This information will be annotated in a separated document kept in the office of the PI (Dr. Pinzon).

Statistical analysis will be conducted using SPSS 14.0 software. The baseline seizure frequency and seizure frequency change after treatment will be computed from average weekly seizure frequencies before and after rTMS treatment for each patient. A patient data will be categorized into two treatment groups: rTMS treated and placebo groups.

VII. DESCRIPTION OF WRITTEN CHILD/ADULT CONSENT PROCESS

At a potential subject's visit to the physician's office or hospital, the investigator(s) will provide a comprehensive explanation of the purpose, procedures, possible risks/benefits of the study, and participant responsibilities, and discuss the fact that his/her participation is voluntary, that he/she may withdraw from the study at any time, and that the decision not to participate or to withdraw will not affect his/her regular medical care. Potential participants or their surrogates will be given ample opportunity to ask questions and to consider their decision. If the subject or the surrogate agree to participate, then a signed and dated written informed consent will be obtained.

A copy of the consent form will be given to the participant or the surrogate, and another copy will be placed in the subject's medical record. The informed consent form will be obtained by the investigators listed to perform informed consent procedures.

VIII. EXTENSION PHASE

If the results from this study demonstrate significant medical improvement, patients will be offered an extension phase where they could continue receiving the same parameters of stimulation for one to two additional years at no expense

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