NYU Langone Health

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TITLE:
A randomized controlled pilot study of TMS enhancement of associative memory networks in healthy subjects and epilepsy patients.

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List of Abbreviations

EEG – electroencephalography

TMS-Transcranial Magnetic Stimulation

fMRI – functional magnetic resonance imaging

Study Summary

Title	A randomized controlled pilot study of TMS enhancement of associative memory networks in healthy subjects and epilepsy patients.
Protocol Number	s15-00732
Methodology	Randomized, single-blinded, controlled phase 1 trial
Study Duration	2 years
Study Center(s)	NYU Langone Medical Center
Objectives	To explore whether rTMS, guided by fMRI based resting state networks, can be a safe and effective method of enhancing associative memory performance.
Number of Subjects	20 healthy subjects 20 Temporal Lobe epilepsy patients
Diagnosis and Main Inclusion Criteria	Healthy subjects will be 1) 18-40 years, 2) fluent in English, 3) be right-handed, 4) Score at least 26 out of 30 on the Montreal Cognitive Assessment (MOCA), and 5) be able to provide informed consent. Epilepsy subjects will be 1) 18 - 40 yrs, 2) fluent in English, 3) Right-handed, 4) Score at least 26 out of 30 on the Montreal Cognitive Assessment (MOCA). Healthy subjects will be matched to age, handedness, and education compared to epilepsy subjects. 5) Must be able to provide informed consent, 6) Demonstrate evidence of verbal memory dysfunction, 7) Have TLE, and 8) Well controlled epilepsy.
Study Product and Planned Use	MagStim RapidStim2
Reference therapy	No currently available therapy

Statistical Methodology	The primary outcome measure will be improvement in an associated memory task (verbal word pairs). A secondary outcome measure will be increased fMRI-based functional connectivity between the hippocampus and cortical regions. Changes in hippocampal-cortical functional connectivity will be identified using voxel-wise paired T-tests (pre-post TMS).

1 INTRODUCTION

1.1 Background

Memory difficulty, slowed processing, and attention deficits are the most common complaints of epilepsy patients (Dodrill 2004). Current models of cognitive dysfunction rely mostly on patients with mesial temporal lobe epilepsy (TLE) and suggest that deficits are widely distributed. TLE affects not only memory, but also intelligence quotient, executive functions, language, and sensorimotor function (Oyegbile, Dow et al. 2004, Hermann, Lin et al. 2009). Similarly, instead of localized brain changes, functional and structural MRI reveal that these patients display widespread dysfunction and atrophy in the bilateral frontal, temporal, and parietal lobes, as well as the thalamus, basal ganglia, and cerebellum (Dabbs, Jones et al. 2009, Meador and Hermann 2010, Vlooswijk, Jansen et al. 2010). However, it is unclear whether treating more transient variables, such seizure frequency and interictal activity, plays a role in improving cognition (Aldenkamp and Arends 2004, Aldenkamp, Arends et al. 2010).

Our current therapies for these cognitive comorbidities are limited. Currently there are no proactive means of addressing memory dysfunction. Many anti-epileptic medications have undesirable mood and cognitive side effects. Many anti-depressants interact with anti-epileptic medications, have undesirable side effects, take a significant amount of time to reach therapeutic effect, or may themselves lower the seizure threshold. Finding safe, alternative methods of addressing the affective and cognitive aspects of epilepsy is therefore of tremendous clinical significance.

This project seeks to develop a technology with significant therapeutic potential for memory remediation: non-invasive transcranial magnetic stimulation (TMS). A recent study demonstrated that targeted TMS increased functional connectivity among cortical-hippocampal networks in healthy subjects (Wang, Rogers et al. 2014). Moreover, the enhancements of connectivity correlated with improved memory performance. We propose to extend these findings to a clinically-relevant population; specifically, to develop an intervention (repetitive TMS) and approach (resting state fMRI guided) that could be used for memory remediation in epilepsy patients.

This will be a randomized, controlled, and single-blinded cross-over pilot study. The purpose of this study is to demonstrate feasibility and explore the neurophysiologic and clinical effects of repetitive transcranial magnetic stimulation (TMS) interventions in epilepsy patients and healthy controls. The inclusion of a control group will be used to see whether epilepsy patients, who suffer from a higher degree of comorbid memory difficulty presumably from entorhinal-hippocampal dysfunction, can benefit from a TMS intervention can benefit as much as a healthy matched population.

1.2 TMS.

Transcranial Magnetic stimulation (TMS) is a non-invasive method of neurostimulation and modulation, in which an applied magnetic field may induce a secondary electric field in the brain. The field may be of sufficient magnitude and density to depolarize neurons; when TMS is applied in repetitive trains (rTMS), modulation of cortical excitability can occur beyond the duration of the train of stimulation.

The Magstim Rapid^2 used to produce rTMS in this study is considered a nonsignificant risk device because:

- It is non-invasive and does not pose a serious risk of the healthy, safety or welfare of a subject if used under appropriate safety guidelines, delineated below.
- Is not purported for supporting or sustaining human life

- Is not intended to be substantially important in diagnosing, curing, mitigating or treating disease
-

Does not otherwise pose a potential for risk to the health, safety or welfare of a subject (please see detailed evidence below provided under research risks and benefits for common and rare risks).

Safety guidelines have been delineated since 2009 by the Safety of TMS Consensus Group(Rossi, Hallett et al. 2009). Multi-session rTMS at higher intensities, higher frequencies, and longer durations for depression have been tested in thousands of patients without significant adverse events and been approved FDA approved as an option for treating medication-refractory depression, as well as for presurgical motor mapping. The rTMS protocol described in this study complies with these current safety guidelines for TMS. Specific risks to an epilepsy patient population, as well as appropriate safety guidelines, will be discussed below.

*1.3 **Research Risks & Benefits***

1.3.1 Risks

According to the Safety of TMS Consensus Group (2009), the following side effects and risks have been reported.

Common:

- Headache and Neck Pain: The most common side effect of TMS is focal discomfort at the area of stimulation, as well as headache and neck pain of muscular origin. This pain typically lasts up to a few hours after the session and can be relieved with over the counter pain medications.(Daskalakis, Paradiso et al. 2004).
- Tinnitus, Hearing Loss: Tinnitus is occasionally reported after a TMS session. Hearing loss has been reported in one patient whose earplug became dislodged during the session.

Rare:

- Seizures: Low-frequency rTMS, as administered in this study, has been used for inhibition of seizure activity. However, high-frequency rTMS, used for depression treatment, may rarely provoke seizure activity. TMS-induced seizures are almost always self-limited and are not reported to produce permanent sequelae. Seizure risk is related to intensity of stimulation, as well as use of neuroleptics, antidepressants, or other medications which may lower the seizure threshold.(Rossi, Hallett et al. 2009).

- Epilepsy, or a history of recurrent unprovoked seizures, is considered a relative contraindication to most TMS studies given the risk of provoking a seizure. However, a recent meta-analysis of safety of rTMS in epilepsy(Bae, Schrader et al. 2007) indicated a 1.4% crude per subject risk of seizure and no cases of status epilepticus. In another recent safety review, there were no TMS-triggered seizures among 152 patients with epilepsy who underwent weekly rTMS application at <1Hz frequency in trials investigating applications to *reduce* seizure frequency (Theodore, Hunter et al. 2002, Tergau, Neumann et al. 2003, Fregni, Otachi et al. 2006, Cantello, Rossi et al. 2007, Joo, Han et al. 2007, Santiago-Rodriguez, Cardenas-Morales et al. 2008). Furthermore, the use of high frequency/high intensity rTMS was *unsuccessful* at activating epileptogenic foci, with the exception of a subgroup of patients with progressive myoclonic epilepsy (Tassinari, Rubboli et al. 2005). One case series of two patients with epilepsia partialis continua receiving high frequency rTMS (100 Hz, 20 Hz), there were no adverse effects (Rotenberg 2009). In other studies investigating rTMS in patients with a history of higher seizure risk, including chronic stroke, was safe (Fregni and Pascual-Leone 2006). However, rTMS trains which are generally safe for healthy volunteers (20-25 Hz, 110-130% MT) are able to induce peripheral manifestations including spread of cortical excitability, which has led to the recommendation of more rigorous monitoring of patients at higher risk.

    - Changes in memory, attention, cognition, or psychiatric condition: TMS could cause occasional changes in memory, attention and other cognitive functions. However, none of these effects have been reported to be lasting, they are very mild, and they seem to be extremely rare. There have been reports of patients with an underlying depression or mood disorder developing mania after TMS. Hallucinations, delusions, personality changes, anxiety and agitation have been reported. Psychotic symptoms and suicidal ideation have never been described in normal subjects during or after rTMS. In all these cases, these psychiatric side effects induced by TMS did not last and went away by itself or with medication.

    - Dental Pain: Rarely, dental pain has been reported during TMS stimulation. This may indicate that the patient has a cavity, but will not cause lasting pain after stimulation has been stopped.

    - Motor Symptoms: Rare cases of transient worsening in motor task performance or increased tremor have been reported in Parkinson's patients.

    - Syncope, which has been reported as a rare risk.

Given the potential for exacerbation of seizures during rTMS, one of the investigators who has specialty expertise in recognizing and managing seizures- Dr. Liu, Kuzniecky, or Friedman- will be onsite during the TMS sessions for epilepsy patients. Because the risk of seizures is extremely low in healthy controls, sessions will be supervised by Dr. Milton Biagioni. All physicians performing TMS procedures are either trained epileptologists, or have documented training in the first aid for seizure management and attend a quarterly training “TMS Seizure Recognition and First Aid Seizure Management Drill”. In addition, subject will be screened for any adverse effects, such as skin rashes, headache, or tinnitus, and necessary referrals and arrangements will be made. If any other unanticipated adverse events occur, the patient will be withdrawn from further participation in the study.

1. In parallel with recording the primary outcome, we will monitor for increase in seizure severity attributable to rTMS by identifying all instances of generalized tonic clonic seizures after rTMS

treatments. Instances where seizure frequency increased after rTMS will be reported to the IRB within 72 hours of data analysis.

2. If a self-limited, short (<5 min) focal seizure with alteration of consciousness occurs, treatment will stop for that day. Subjects will be monitored clinically by an epilepsy physician (Dr. Liu) during the entire course of treatment and for 30 minutes afterwards, to ensure that the patient returns to baseline clinical status. Subjects will be followed up by phone call 24 hours later.
3. If a secondarily generalized (convulsion starting in one area of body and then spreading to other areas) or 2 focal seizures with alteration of awareness occurs during treatment, the patient will be withdrawn from further participation in the study. . If a seizure occurs and lasts for more than 5 minutes, or if there are 2 seizures occurring within 30 minutes without return to clinical baseline, the patient will be assisted to the NYU emergency room for further monitoring and care. Subjects will be followed up by phone call 24 hours later.
4. In case of, erythema, transient itching or rashes of the skin under the electrodes necessary referrals and arrangements will be made.
5. If any other unanticipated adverse events occur, the patient will be withdrawn from further participation in the study.

1.3.2 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 PO1, P02, 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.

1.3.3 Potential benefits

Given that TMS will be applied based on the subject's fMRI resting state connectivity, there is potential for improvement of verbal associative memory function. However, it is more likely that subjects may not benefit individually from this study, but that knowledge gained from this study will benefit others in the future.

2 STUDY OBJECTIVES

The goal is to use targeted repetitive TMS (rTMS) to: 1) improve associative memory function in 16 healthy subjects and 16 temporal lobe epilepsy (TLE) patients, and 2) enhance hippocampal-neocortical functional connectivity. It is hypothesized that rTMS targeted to a superficial cortical node with high resting state functional connectivity with the hippocampus will enhance functional networks involved in memory consolidation and improve memory performance in both healthy subjects and TLE patients.

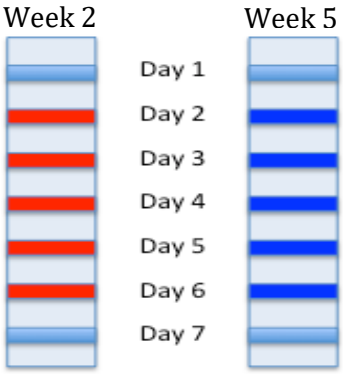

Fig. 1. General Study Design. **Week 1** (not shown): Epilepsy Subjects only will be asked to start a seizure diary. **Week 2** (both healthy and epilepsy subjects). Each subject will receive baseline fMRI, EEG, and cognitive tests (light blue), followed by 5 daily sessions of rTMS to parietal cortex (red), then repeat fMRI, EEG, and cognitive tests. **Week 3-4** two week washout period. **Week 5:** each subject will receive a baseline fMRI, EEG and cognitive tests, followed by 5 daily sessions of rTMS delivered to the motor cortex (dark blue), then follow-up testing. Subjects will be assigned to the stimulus condition in a randomized and counterbalanced manner. They will then have a follow up fMRI, EEG, and cognitive tests. **Week 6** Epilepsy subjects will be asked to continue a seizure diary.

3. STUDY DESIGN

3.1 General Design

The study will last between 4-6 weeks: one week with involve stimulation to the left lateral parietal site (treatment) and one week with stimulation to the motor cortex (control), separated by two weeks of rest (*Fig. 1*). Each stimulation week will include a baseline (day 1) and post-treatment (day 7) measurements, including fMRI, associative memory testing, IQ testing, and a seizure diary. Epilepsy subjects will be asked to maintain a seizure diary for 1 week prior to the first stimulation week, and for 1 week after the second stimulation week.

1. fMRI acquisition. MRI scans will be performed on a Siemens Prisma 3T scanner without contrast. There will be a total of 4 scans performed: 1) Baseline resting state fMRI which will be performed within 7-10 days prior to the first session of TMS for each condition (Visit 2, 9), (2) followup fMRI will be performed after the last session of rTMS for each condition (Visit 8, 15). The resting state fMRI acquisition will consist of 197 contiguous echo planar imaging volumes with the following parameters: TR = 2000 ms, TE = 25 ms, flip angle = 90 degrees, 39 slices, matrix = 64 x 64, field of view = 192 mm, with a resulting voxel size of 3 mm isotropic. Subjects will be instructed to lie still with their eyes trained on a cross-hair displayed on an LED display. A whole brain T1-weighted 1 mm isotropic MRI scan will also be acquired for inter-subject coregistration and display of results.

A *target stimulation site* will be determined for each of the 32 subjects using resting state fMRI performed at the beginning of Weeks 1 and 3. For each subject, a left lateral parietal cortical target will be identified by carrying out a seed-based resting state functional connectivity analysis. The anterior left hippocampus will be used as the seed region. This stimulation location was marked in stereotactic space and then transformed into the original structural MRI space and overlaid on the structural MRI to provide localization during rTMS.

Resting state fMRI will also be performed at the end of Weeks 2 (Visit 8) and 5 (Visit 15) to assess for stimulation-induced changes in connectivity.

2. rTMS. Subjects will have rTMS applied using a **Magstim Rapid 2 system**. A 70 mm Figure of 8 coil will be used. A motor threshold will be determined for each subject at the baseline study visit, and defined as the minimum stimulator output required to generate a 50 mV threshold response in the abductor pollicis brevis (APB) for at least 50% of trials. rTMS will be applied for 5 daily sessions at 80%

motor threshold for 20 min of 20 Hz stimulation for 2 sec followed by 28 sec of no stimulation (Wang, Rogers et al. 2014), or a comparable high frequency stimulation protocol. Subjects will be closely monitored for seizure occurrence and side-effects. After a break of two weeks, to allow for washout effects, subjects will receive 5 daily rTMS sessions (same intensity as described above) to the motor cortex (control condition).

3. Cognitive Testing. Two associative memory tasks (a word-face task and a word-pairs task) will be administered before, at treatment mid-point, and after each condition. A standardized neuropsychological battery (WASI IQ Testing, Verbal List Learning) will also be administered to control for non-specific cognitive enhancements with neurostimulation.

The Wang and Voss 2014 study which is the model for our proposed study used a face-word recognition task, which included 20 arbitrarily paired face-word dyads. They then used functional MRI to determine the left lateral parietal cortical node which demonstrated greatest functional connectivity to the left hippocampus for each subject, and delivered a series of high frequency rTMS sessions or sham rTMS sessions to the subjects. Real stimulation to the left lateral parietal node increased accurate recall of face-word pairs, whereas sham rTMS did not. Their findings suggest that stimulation of a Superficial node in a hippocampal-neocortical network can produce a memory enhancing effect.

In the study S15-00732, we are proposing to replicate and extend the Wang and Voss 2014 findings to a healthy population and epilepsy population. We will utilize a similar face-word paradigm as Wang and Voss (20 pairs), as well as an unassociated word-pairs protocol. The face-word pairs task is described in more detail in a supplementary document. During each testing session (baseline, mid-treatment, and post-treatment), different sets of word-face pairs are presented to control for practice effect.

The unrelated word-pairs tasks is a verbal associative paradigm which has also been used in memory consolidation studies (Marshall, Molle et al. 2004, Marshall, Helgadottir et al. 2006, Antonenko, Diekelmann et al. 2013), and a paradigm which we have been testing and refining for the last year for S14-00609 Mechanisms and Enhancement of Memory Consolidation During Sleep. In this task, we present 20 unrelated word pairs to subjects and test for delayed recall and recognition. Patients with epilepsy often demonstrate declarative memory consolidation, or difficulty with explicit encoding and recall of episodic and semantic information. Adding a verbal word-pair associative task would allow us to understand whether enhanced function of a left hippocampal-cortical functional network is domain-specific. We predict that epilepsy patients, who will be screened to demonstrate a baseline level of verbal memory dysfunction (defined as 1 SD below normative values on the Rey Auditory Verbal Learning Task, a verbal list learning task), will demonstrate enhanced verbal associative memory function from rTMS delivered to the left parietal lobe only and not from rTMS delivered to the motor cortex.

Task Piloting: Before enrollment begins, we will pilot the word-pair and word-face tasks to assess for behavioral performance and variance. Pilot subjects will be recruited on www.mturk.com, and will be redirected to the memory tasks hosted on NYUMC's license of Qualtrics.com. All data is encrypted by Qualtrics and stored securely as per HITECH requirements. No identifying information will be collected from pilot subjects, and they will be informed of this before completing the tasks. We will recruit participants to complete a testing block will be comprised of 2-3 tasks, which will take approximately 10 minutes. Participants will be compensated $1 per completed set. Therefore, participants will perform tasks for 20-30 minutes and be paid between $4-5. The task performance data is the only data that will

be collected, and will be identified by a participant number assigned by Qualtrics.com that is not linked to the pilot subjects. Feedback from the pilot tasks will be used to ensure that test blocks are at the appropriate difficulty level.

Dr. Anli Liu will be overseeing the psychometric assessments for the current study S15-00732. Dr. Liu has completed post-doctoral training in cognitive and behavioral neurology at Harvard Medical School (2011-2012), where she completed PhD level coursework in Cognitive Neuroscience and gained significant clinical experience in the evaluation of patients with cognitive disorders (including memory, attentional, language complaints). In addition, she has completed a Masters Degree in Cognition and Education at UC Berkeley. During medical school at UCSF, she spent two years as a research assistant under the supervision of Dr. Bruce Miller at the Memory and Aging Center, where she conducted prospective research on visual processing in Alzheimer's and Frontotemporal Lobar Dementia patients. Her clinical practice at NYU currently specializes in the management of the cognitive co-morbidities of patients with epilepsy. Moreover, for the last 3 years at NYU, she has been lead investigator on two prospective studies involving noninvasive neurostimulation and memory function in healthy subjects and patients with epilepsy (including S12-03395 Efficacy of TDCS for Treatment of Working Memory Dysfunction in Patients with Temporal Lobe Epilepsy and S14-00609 Mechanisms and Enhancement of Memory Consolidation During Sleep). Through her clinical practice and research experience, she is extremely familiar with psychometric assessments of attention, working memory, associative memory consolidation, and visual memory. She will either directly administer or supervise the administration of psychometric testing for this study.

4. <u>EEG.</u> Subjects will have a 20 minute routine EEG performed before and after the stimulation sessions, at visits 3, 7, 10 and 14.

5. <u>Seizure and Clinical Diary.</u> Epilepsy subjects will be asked to maintain a daily seizure diary for 1 week prior to the first stimulation, through the 4 weeks of the study, and 1 week after the last stimulation session.

	Week 1	**Week 2**							**Week 3**	**Week 4**	**Week 5**							**Week 6**
	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8			Visit 9	Visit 10	Visit 11	Visit 12	Visit 13	Visit 14	Visit 15	
Screening & Informed Consent	X																	
fMRI		X						X			X						X	
TMS Stimulation			X	X	X	X	X					X	X	X	X	X		
Cognitive Testing			X		X			X				X		X			X	
EEG			X				X					X				X		
Seizure Diary (Epilepsy Only)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Hours	**0.5**	**2**	**2.5**	**1**	**2**	**1**	**2**	**3**	**0**	**0**	**2**	**2.5**	**1**	**2**	**1**	**2**	**3**	**0**

Table 1. Study Schedule

3.2 Primary Study Endpoint.
The primary study endpoint will be improvement in a face-object pair association task post stimulation compared to pre-stimulation baseline in both epilepsy subjects and healthy controls.

3.3 Secondary Study Endpoints.
The secondary study endpoint will be improvement in a word-pair association task post stimulation compared to pre-stimulation baseline in both epilepsy subjects and healthy controls. We will also examine changes in hippocampal-cortical functional connectivity between baseline assessment and resting state fMRI assessment following TMS.

4. SUBJECT SELECTION AND WITHDRAWAL
We will recruit 40 subjects, including 20 epilepsy patients and 20 healthy controls. Patients will be maintained on constant anticonvulsant doses for the duration of the trial, unless there is a strong medical need to change them. This study will include both inpatients and outpatients. Patients will

HEALTHY SUBJECTS. Twenty (20) healthy controls will be recruited. It is expected that 20% of recruited subjects will not meet I/E criteria or will not finish all study related tasks, which will result in 16 subjects per study group completing all study related tasks.

Inclusion Criteria:

1) 18 - 40 yrs,
2) fluent in English,
3) Right-handed
4) score at least 26 out of 30 on the Montreal Cognitive Assessment (MOCA). Healthy subjects will be matched to age, handedness, and education compared to epilepsy subjects.
5) Must be able to provide informed consent.

Exclusion Criteria:

1) Any history of a neurological or psychological/psychiatric disorder
2) Chronic or progressive medical condition
3) Any history of severe traumatic brain injury or skull defect
4) Metal or devices in the head, including neurostimulators of metal foreign bodies
5) Any other implanted metal device, including pacemaker, spinal cord stimulator, VNS.
6) Any other ferromagnetic substance in the body (including tattoos, dental prosthetics, etc).
7) Taking a medication which may lower the seizure threshold within the 4 weeks prior to the start of the study, including use of neuroleptic (esp. clozapine), antibiotic (penicillin, cephalosporins), and bronchodilating medications.
8) Pregnancy
9) Previous Transcranial Magnetic Stimulation
10) An inability to refrain from psychoactive drug use during the study visits and the 48 hours prior

EPILEPSY SUBJECTS Twenty *patients with* well-controlled temporal lobe epilepsy (TLE) will be recruited. In addition to the above inclusion and exclusion criteria, epilepsy subjects must additionally be screened for the following criteria. Again, it is expected that 20% of recruited subjects will not meet I/E criteria or will not finish all study related tasks, which will result in 16 epilepsy subjects completing all study related tasks.

Only epilepsy patients with capacity for informed consent will be considered for inclusion. The capacity of the patient will primarily be determined via consultation with the patient's primary epileptologist. If the primary epileptologist is a member of the study team, then another clinician who is knowledgeable of the patient's clinical condition (a neuropsychiatrist, neuropsychologist, nurse practitioner, or adult epileptologist) will be consulted for an independent assessment regarding the decision making capacity of the individual, reflecting an appropriate level of understanding of the risks and benefits of any given medical procedure.
Generally speaking, a patient who is deemed to have capacity to make their own medical decisions will be deemed to have capacity to consent for this study. In addition, the PI will call the patient after the initial informed consent and before each week of study involvement (Weeks 2 and 4) for repetitive teaching and confirmation of patient understanding of study activities. If there is a question of changed capacity during the course of the study, the patient's epileptologist and/or a will be consulted for an independent assessment. Because only patients deemed to have capacity will be included, a surrogate decision maker will not be consulted, however, any family members involved in the clinical care of the patient will be allowed to participate in the consenting process. If the subjects are deemed to lose capacity during the course of the study, they will be withdrawn.

Inclusion Criteria:

1) 18 - 40 yrs,
2) fluent in English,
3) Right-handed
4) Score at least 26 out of 30 on the Montreal Cognitive Assessment (MOCA). Healthy subjects will be matched to age, handedness, and education compared to epilepsy subjects.
5) Must be able to provide informed consent.
6) Demonstrate evidence of verbal memory dysfunction, which is defined as performance 1 SD below normative values in the Rey Auditory Verbal Learning Task (RAVLT)] or comparable task (such as the RBANS test), or evidence of left mesial temporal dysfunction on the WADA test (defined as ≤8/12 on the memory task with a right hemispheric injection).
7) Have TLE. A diagnosis of TLE will be made if the patient has at least 2 of the following features: a) characteristic semiology b) characteristic interictal or ictal pattern seen on EEG and/or c) concordant MRI brain or PET scan abnormality.
8) Well-controlled epilepsy will be defined by stable seizure frequency in the 2 months prior to study participation. Stable seizure frequency will be defined as ≤1 non-disabling seizure (auras or SPS only) per month and no generalized-tonic clonic seizures for >1 year.

Exclusion criteria:

1) Any history of severe traumatic brain injury or skull defect
2) Metal or devices in the head, including neurostimulators of metal foreign bodies
3) Any other implanted metal device, including pacemaker, spinal cord stimulator, VNS.
4) Any other ferromagnetic substance in the body (including tattoos, dental prosthetics, etc).
5) Taking a medication which may lower the seizure threshold within the 4 weeks prior to the start of the study, including use of neuroleptic (esp. clozapine), antibiotic (penicillin, cephalosporins), and bronchodilating medications.
6) Subjects must NOT have an epileptogenic focus near the proposed stimulation site [ie. left lateral parietal region (P3)
7) Pregnancy
8) Previous Transcranial Magnetic Stimulation
9) An inability to refrain from psychoactive drug use during the study

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, as well as maintain regular communication with epilepsy attending physicians about potentially eligible subjects. For potentially eligible epilepsy patients under the care of one of the investigators, a research team member will approach potential subjects during their clinic visit and provide Dr. Liu's contact information, and advise that if the patient agrees, Dr. Liu will contact him/her. If the patient is under the care of a physician who is not an investigator, then the treating physician will be asked to introduce the study and obtain the patient's permission to be contacted by a study team member for further information.

We will recruit healthy controls through a combination of flyers and web-announcements.

All potential subjects will be pre-screened for eligibility either over the telephone, through an online OpenRedcap form, or in person. The telephone recruitment script and OpenRedcap form are included as supporting documents. When possible, i.e., when potential subjects are identified, he or she will meet with Dr. Liu or a study team member in person to review the study and further screen the participant, including special considerations regarding fMRI and TMS. We will seek a waiver of documentation of consent for this prescreening process, as it is minimal risk. The PI or one of the co-investigators will conduct pre-screening for eligibility for the study. Information collected about the patient will be immediately discarded if the patient is ineligible for the study or the person chooses not to participate in the study. If the patient is deemed eligible for the study, the information will be kept in a subject binder in a locked filing cabinet or protected in the Redcap database. After consent, subjects will complete a screening form about drug and medication use in order to determine eligibility. Subjects will also complete a demographics questionnaire. These forms are included as supporting documents.

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 study is cancelled by the principal investigator
- The subject experiences an increase in seizure frequency at 50% above seizure frequency baseline, or a GTC during stimulation week.
- The subject not able to attend the study visits required by the study.
- The subject fails to follow the study requirements.
- The subject needs a treatment or medication that may not be taken while on the study or the Principal Investigator feels it is in the best interest of you/your child to be taken of this study.
- If a subject becomes pregnant. Participants will be asked to take a pregnancy test before receiving stimulation to ensure they are not pregnant.
- If a subject decides not to continue participation in the study (by choice)

4.4.2 Data Collection and Follow up for Withdrawn Subjects.

The PI will call all withdrawn subjects at 1 week after withdrawal, to ensure that there are no ongoing clinical or safety issues related to study participation.

5.STUDY DEVICE

5.1 Description

The **Magstim Rapid 2** is a machine which provides repetitive magnetic stimulation, which induces a secondary electrical currents in tissue using a non-invasive stimulating coil at frequencies up to 36 Hz. The stimulating coil is placed near the intended site of stimulation to trigger pulses and initiate brief magnetic pulses. The stimulation produces biphasic pulses from 1 Hz to 60 Hz at varying stimulation intensities, to produce a peak magnetic field from 0.5-2 Tesla at 100% of machine output. The Magstim Rapid2 is currently FDA approved for the treatment of major depression and peripheral nerve stimulation, however is not currently approved for treating memory dysfunction.

5.2 Treatment Regimen

Repetitive TMS (rTMS) will be applied to the stimulation location (determined by fMRI based connectivity to a hippocampal seed region, as described In the protocol section) using a **Magstim Rapidstim 2 device.** A 70 mm figure of 8 coil will be used. Motor threshold was determined for each subject during the baseline visit of each study week, defined as the minimum stimulator output value required to generate contraction of the abductor pollicis brevis (APB) for at least 5 of 10 consecutive pulses (measured via Emg using a contraction threshold of 50 mV). For the stimulation condition, high frequency rTMS will be applied at 80% motor threshold (MT) to the stimulation location for 20 minutes of consecutive blocks of 20 Hz pulses for 2 seconds followed by 28 seconds of no stimulation, or a comparable high frequency protocol (between 5-20 Hz). This protocol is similar to a previously published protocol Wang and Voss 2014), except that the stimulation intensity will be reduced to 80% to reduce the risk of seizure exacerbation.

For the control stimulation, rTMS will be applied to another superficial cortical location determined to have low functional connectivity to the hippocampus. Subjects will be blinded to stimulation condition (which stimulation site is expected to result in a behavioral effect), and will not be aware of the different hypothesis regarding the effects of stimulation of the different locations.

5.3 Method for Assigning Subjects to Treatment Groups

All subjects will undergo both treatment and control stimulation arms, but will be assigned in a randomized and counterbalanced manner at the beginning of the study. Randomization assignments will be maintained by Dr. Daniel Friedman, and will be communicated to Dr. Liu or other co-investigators directly involved in the administration of TMS to the subject. However, co-investigators involved in neuropsychological testing and fMRI analysis (Dr. Pardoe), and study subjects will remain blinded to their randomization assignment.

5.4 Prior and Concomitant Therapy. Epilepsy patients enrolled in this study will continue to receive standard of care for their management of their partial onset epilepsy, and their medications will remain unchanged during participation.

5.5 Receiving, Storage, Dispensing and Return

The Transcranial Magnetic Stimulation (TMS) machine is stored at 240 East 38th Street, 20th Floor, NY 10016. The room is locked at the end of the day and open only by authorized personnel who have access to the door key. The TMS device will only be operated by qualified research staff personnel. Training will be supervised by Dr. Milton Biagioni, Assistant Professor in the Department of Neurology, Division of Movement Disorders, who has extensive experience in using TMS for both clinical and research indications. Dr. Biagioni will be responsible for ensuring that members of the research team

demonstrate competency in performing TMS before enrolling subjects. In addition, Dr. Liu (PI) has completed a fellowship in cognitive neurology at Beth Israel Deaconess-Harvard Medical School, where she trained in the research lab of Dr. Alvaro Pascual Leone, an international leader in noninvasive brain stimulation. Dr. Liu has significant scientific and practical experience in methods of noninvasive brain stimulation, including transcranial electrical stimulation (TES) and transcranial magnetic stimulation (TMS). She is the principal investigator on four other IRB-approved studies utilizing non-invasive stimulation techniques at NYU School of Medicine. One of them will be present for the first five enrolled research subjects.

6. Statistical Plan

6.1 Sample Size Determination

Sample size is based on the assumption that the memory performance change, defined as the difference in recall performance on a word-pair associates task after the assigned condition minus the recall performance before assigned condition, will be higher in each treatment condition (parietal rTMS), than in the control condition (motor cortex rTMS). Assuming an improvement of 30% above baseline memory performance in the treatment arm, and no change in performance in the control arm (which is a large effect size, with F=1.3), with a standard error of 10%, confidence level of 95%, and power of 0.80, each condition will have a sample size of 16 (Wang, Rogers et al. 2014). Assuming a 20% drop out rate, we will need 20 study subjects per study arm. Therefore, we expect to recruit a total of 40 subjects for this study.

6.2 Statistical Methods

All data will be checked for completeness, out-of-range values, and distributional form. Analyses to measure relationships between TMS conditions (parietal vs motor cortex) and outcome measures (memory performance and fMRI based functional connectivity) will include a repeated measures ANCOVA with condition (parietal vs motor cortex) as the main within-subject variable, and order of stimulation as the main between-subject variable. Linear regression will be used to test relationships between memory performance change, degree of change in functional connectivity, and EEG variables. For group-wise comparisons we will also use t-test comparisons with diagnosis (healthy or epilepsy) as the independent variables and change in memory performance and functional connectivity as dependent variables.

6.3 Subject Population(s) for Analysis

All patients will be analyzed according to an intention-to-treat analysis.

7. Safety and Adverse Events

7.1Definitions

Unanticipated Problems Involving Risk to Subjects or Others

Any incident, experience, or outcome that meets <u>all</u> of the following criteria:

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

(b) If a self-limited, short (<5 min) partial seizure or evolution into generalized tonic clonic seizure occur, treatment 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.

7.2 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 should be recorded and reported promptly (see section 8.3 below).

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

7.3 Reporting of Adverse Device Effects and Unanticipated Problems

7.3.1 Investigator reporting: *Notifying the study sponsor*

The following describes events that must be reported to the study sponsor in an expedited fashion.

Reportable events:

- **<u>Unanticipated adverse device effect,</u> regardless of seriousness or severity**
- **<u>Unanticipated problems</u> related to study participation**

- **Deviations from the study protocol**
  Deviations from the protocol must receive both Sponsor and the investigator's IRB approval <u>before</u> they are initiated. Any protocol deviations initiated without Sponsor and the investigator's IRB approval that may affect the scientific soundness of the study, or affect the rights, safety, or welfare of study subjects, must be reported to the Sponsor and to the investigator's IRB as soon as a possible, but ***no later than 5 working days*** of the protocol deviation.
- ***Withdrawal of IRB approval***
  An investigator shall report to the sponsor a withdrawal of approval by the investigator's reviewing IRB as soon as a possible, but ***no later than 5 working days*** of the IRB notification of withdrawal of approval.

7.3.2 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**
  - *<u>Unexpected</u>**:** 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.*
  - *<u>Related to the research procedures</u>**:** An event is related to the research procedures if in the opinion of the principal investigator or sponsor, the event was more likely than not to be caused by the research procedures.*
  - *<u>Harmful</u>: 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 form: "Reportable Event Form" or as a written report of the event (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.

7.4 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/follow-up 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 Data Monitoring Committee below).

7.5. Data Monitoring Plan and Committee

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.

(a) If a self-limited, short (<5 min) partial seizure or evolution into generalized tonic clonic seizure occur,

treatment will stop for that day for that subject.

(b) 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.

(C) If >50% of epilepsy patients have a >=50% increase in seizure frequency above baseline, then the study will stop.

The primary responsibility of data safety monitoring will lie with Dr. Liu, although all co-investigators of her research team will comprise a Data Monitoring Committee and have responsibility for carrying out the DSMP. Data Monitoring Committee will meet in person or have telephone conversations every 2 months, and informally meet on an as needed basis. All Committee 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-PI: Heath Pardoe PhD
Assistant Professor of Neurology
NYU School of Medicine
Comprehensive Epilepsy Center
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NYU Co-Investigator:
Ruben Kuzniecky MD
Professor of Neurology
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Comprehensive Epilepsy Center
223 East 34th Street
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NYU Co-Investigator: Daniel Friedman MD
Assistant Professor of Neurology
NYU School of Medicine
Comprehensive Epilepsy Center
223 East 34th Street
New York, NY 10016

NYU Co-Investigator:
Orrin Devinsky MD
Professor of Neurology

7. 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.

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).

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.

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 will 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. For clarification of illegible or uncertain entries, print the clarification above the item, then initial and date it.

4. Records Retention

It is the investigator's responsibility to 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. These documents should be retained for a longer period if required by an agreement with the sponsor. In such an instance, it is the responsibility of the

sponsor to inform the investigator/institution as to when these documents no longer need to be retained.

8. Study Monitoring, Auditing, and Inspecting

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.

2. Auditing and Inspecting

The investigator will permit study-related monitoring, audits, and inspections by the EC/IRB, the sponsor, 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.

9. 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 and a copy of this decision will be provided to the sponsor before commencement of this study. The investigator should provide a list of EC/IRB members and their affiliate to the sponsor.

All subjects 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, Dr. Friedman, and Dr. Kuzniecky will be allowed to consent patients. All have significant experience with patient oriented clinical research, and are specialists in epilepsy and clinical neurophysiology. Only subjects, their family members, and study team members will be present during the consent process to protect patient privacy. Informed consent will be documented by obtaining a signed and witnessed copy of the informed consent.

10. Study Finances

1. Funding Source

Finding a Cure for Epilepsy and Seizures (FACES) will support all research related costs.

10.1.1 **Subject compensation**. Patients will be compensated $15 per hour of participation in this study plus an additional $25 for completing all visits. The study requires approximately 27.5 participation hours over 15 visits for a total of approximately $437.50. Subjects will be paid at the end of study participation, for whichever portion of the study they completed (even if subjects decided to withdraw during the study), via a mailed check.

10.1.2 **Study related costs.** The costs of all study visits will be billed to the research team. There will be no cost of participation to the patient. The cost of subject compensation, fMRI studies, and EEG will be supported by research funds.

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 by the study sponsor prior to participation in this study. All NYU investigators will follow the applicable University conflict of interest policy(ies).

11. 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 by the sponsor for the purposes of performing the study, will be published or passed on to any third party without the consent of the study sponsor. Any investigator involved with this study is obligated to provide the sponsor with complete test results and all data derived from the study.

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