Perelman School of Medicine
University of Pennsylvania

A PHASE II RANDOMIZED BLINDED, STUDY OF THE EFFECTS OF TRANSCRANIAL MAGNETIC STIMULATION AND CONSTRAINT INDUCED LANGUAGE THERAPY FOR THE TREATMENT OF CHRONIC APHASIA

Principal Investigator (1)

H Branch Coslett, MD
Department of Neurology
Hospital of the University of Pennsylvania
3400 Spruce Street, Philadelphia, PA 19104
(215) 687-7550
hbc@pennmedicine.upenn.edu

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List of Abbreviations

AE: Adverse event

BAC: Biostatistics Analysis Center

CAT: Computerized Axial Tomography

CILT: Constraint Induced Language Therapy

DSMB: Data and Safety Monitoring Board

fMRI: Functional Magnetic Resonance Imaging

IFG: Inferior Frontal Gyrus

NAVS: Northwestern Assessment of Verbs and Sentences

PNT: Philadelphia Naming Test

PWA: Patients With Aphasia

SAE: Serious Adverse Event

SLT: Speech Language Therapy

TMS: Transcranial Magnetic Stimulation

WAB-(AQ): Western Aphasia Battery - (Aphasia Quotient)

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Study Summary

Title	A Phase II, Randomized, Blinded Study of Transcranial Magnetic Stimulation and Constraint Induced Language Therapy for the Treatment of Chronic Aphasia
Short Title	TMS and CILT for Chronic Aphasia
IRB Number	831532
Phase	Phase 2
Methodology	Randomized, Blinded, Sham-Controlled
Study Duration	5 years
Study Center(s)	University of Pennsylvania
Objectives	Primary: To determine if the combination of TMS and CILT is more effective than sham TMS and CILT as a treatment for chronic aphasia from stroke. Secondary: To identify anatomic and behavioral predictors of response to treatment and the mechanism underlying the beneficial effect of the treatment.
Number of Subjects	75 subjects
Main Inclusion and Exclusion Criteria	Proficent English speakers with a single left hemisphere stroke causing aphasia will be included. Main exclusion criteria are multiple infarcts, history of head trauma, psychiatric illness, and substance abuse and contraindications to TMS.
Investigational Product (drug, biologic, device, etc.) **For Device include the planned use**	TMS will be delivered using a MagVenture MagPro X100. 1200 pulses of 1 Hz repetitive stimulation at 90% motor Threshold at inferior pars triangularis during 10 sessions over 2 consecutive weeks

For Drug, food, cosmetic, etc. include the dose, route of administration and dose regiment	
Duration of administration (if applicable)	10 sessions of 20 minutes 1 Hz stimulation at 90% Motor Threshold
Reference therapy	There is no standard reference therapy for repetitive transcranial magnetic stimulation; this regimen has been used in many similar published studies, including our own work with patients with aphasia
Statistical Methodology	Linear Mixed Models will be used to compare the performance of subjects receiving TMS to subjects receiving sham TMS on change in WAB-AQ scores
Safety Evaluations	Subject reports of adverse events will serve as the primary measure of safety.
Data and Safety Monitoring Plan	A Data and Safety Monitoring Committee consisting of 3 individuals with experience with aphasia and/or non-invasive brain stimulation will serve as the DSMB. The BAC group, under the guidance of the faculty statisticians, will provide safety reports every six months to this monitor and the PI. These reports will be blinded as to treatment assignment, unless unblinding for individual events is requested by the DSMB. All SAEs will also be reported to the IRB.

Sub-Study Summary

Title	A Phase II, Randomized, Blinded Study of Transcranial Magnetic Stimulation and Constraint Induced Language Therapy for the Treatment of Chronic Aphasia – Alzheimer Disease Sub-study
Short Title	Alzheimer Disease Sub-study

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IRB Number	831532
Phase	Phase 2
Methodology	Randomized, Blinded, Sham-Controlled
Study Duration	2 years
Study Center(s)	University of Pennsylvania
Objectives	Primary: To determine if the combination of TMS and CILT is more effective than sham TMS and CILT as a therapy for impaired verbal communication in Alzheimer Disease. Secondary: To identify anatomic and behavioral predictors of response to treatment and the mechanism underlying the beneficial effect of the treatment.
Number of Subjects	30 subjects
Main Inclusion and Exclusion Criteria	Proficent English speakers with mild-moderate Alzheimer Disease. Main exclusion criteria are history of stroke, seizure, or other significant neurologic disease, significant depression, and substance abuse and contraindications to TMS.
Investigational Product (drug, biologic, device, etc.) **For Device include the planned use** **For Drug, food, cosmetic, etc. include the dose, route of administration and dose regiment**	TMS will be delivered using a MagVenture MagPro X100. 30 two-second trains of 10 Hz TMS every 30 seconds at left inferior parts triangularis and at left posterior superior temporal gyrus at 100% motor threshold during 10 sessions over 2 consecutive weeks

Duration of administration (if applicable)	10 sessions of 2 minutes overall of 10 Hz stimulation at 100% Motor Threshold
Reference therapy	There is no standard reference therapy for repetitive transcranial magnetic stimulation; this regimen has been used in many similar published studies.
Statistical Methodology	Linear Mixed Models will be used to compare the performance of subjects receiving TMS to subjects receiving sham TMS on change in WAB-AQ scores
Safety Evaluations	Subject reports of adverse events will serve as the primary measure of safety.
Data and Safety Monitoring Plan	A Data and Safety Monitoring Committee consisting of 3 individuals with experience with aphasia and/or non-invasive brain stimulation will serve as the DSMB. The BAC group, under the guidance of the faculty statisticians, will provide safety reports every six months to this monitor and the PI. These reports will be blinded as to treatment assignment, unless unblinding for individual events is requested by the DSMB. All SAEs will also be reported to the IRB.

BACKGROUND AND STUDY RATIONALE

This document is a protocol for a clinical research study. This study will be conducted in full accordance with all applicable University of Pennsylvania Research Policies and Procedures and all applicable Federal and state laws and regulations including US and international standards of Good Clinical Practice.

Introduction

Aphasia is an acquired disorder of language that occurs in approximately 30% of individuals with stroke and impacts approximately 1 million Americans (see NINDS.NIH.gov). Persons with aphasia (PWA) suffer greater disability and utilize more health care resources than individuals with stroke without aphasia (33); Boehme et al (16), for example, estimated that aphasia adds $2.16 billion annually to the cost of acute stroke care. The economic burden of aphasia can persist for years, not only due to direct costs of care, but also because of lost wages and productivity. Furthermore, the social isolation felt by PWA leads to enormous personal and psychological costs. Current treatments for aphasia are only modestly beneficial (17, 59). Many individuals with moderate or severe aphasia after stroke continue to suffer significant impairment despite therapy. The fundamental objective of this proposal is to demonstrate that Transcranial Magnetic Stimulation (TMS) paired with language stimulation will improve chronic aphasia. More specifically, we seek to demonstrate that TMS combined with speech-language therapy (SLT) will improve language performance more than SLT alone. Additionally, we will employ modern techniques for network analyses of neuroimaging data collected before and after TMS and SLT to determine the mechanism(s) by which this is achieved. Finally, we seek to identify the predictors of response to TMS,, making use of genetic testing. To achieve these goals, we propose the first double-blind, placebo-controlled investigation of TMS combined with SLT that is sufficiently powered to assess the efficacy of the therapy. If the treatment proves successful, our work will set the stage for a Phase 3 trial of the efficacy of TMS with SLT in the treatment of chronic aphasia.

AD Sub-study Introduction

Alzheimer Disease (AD) afflicts more than 5 million people in the USA at present; this number is expected to rise to 13.5 million by 2050 because of the aging of the population and increases in life expectancy. Impaired verbal communication is a hallmark of AD and represents a major cause of distress and disability (162, 165). This impairment reflects, at least in part, deficits in core language faculties (e.g. phonology, lexical representations and semantic memory (154, 175). There is a paucity of treatments for these impairments. In light of the emerging literature demonstrating that TMS improves general cognition in subjects with AD, we propose to extend our ongoing study of the effectiveness of TMS and speech therapy for treatment of post-stroke aphasia to the issue of impaired verbal communication in subjects with AD. This sub-study will be a double blind, randomized study of subjects with mild-moderate AD to explore the effectiveness of TMS as a therapy for impaired verbal communication. Except when indicated below, the intervention for subjects with AD is identical to the main study,

1.1 Background and Relevant Literature

In the first series of studies of TMS as a treatment of aphasia, Naeser and colleagues delivered inhibitory TMS to the right hemisphere. This decision was motivated by the hypothesis that residual language is supported by the left hemisphere but that the residual left hemisphere structures are inhibited by the intact right hemisphere (70, 86; see also 51, 133, Figure 1A). Predicated on the same assumption, many investigators have attempted to treat chronic aphasia with inhibitory (1 Hz) TMS to the right IFG.

A large body of small studies and several meta-analyses provides proof of concept that TMS can be of substantial beneficial in treating chronic post-stroke aphasia. The studies are small, however, and have differed with respect to a number of parameters (e.g., stimulation site, duration of therapy, presence or absence of concurrent speech therapy) so the benefit of TMS for chronic aphasia has not been established. We propose a well-powered randomized, controlled, treatment experiment that will test for the first time whether inhibitory TMS of the right pars triangularis, when coupled with CILT, yields greater language improvement 3 and 6 months later, relative to sham TMS and CILT.

TMS is a technique by which a brief electrical current is induced in brain tissue causing a brief suppression of the excitability of the underlying tissue; the technique, which was introduced in the 1980s and has been extensively used around the world, has been shown to transiently improve or disrupt specific cognitive operations. To achieve this end, a coil is positioned against the subject's head. The delivery of a single pulse begins with the discharge of current from a capacitor into a circular or figure-of-eight coil; this electrical current generates a brief magnetic field of up to 2.2 Tesla. As the pulse of electricity has a rise time of 0.2 ms. and a duration of 1 ms., the magnetic field changes in intensity quite rapidly. Because the magnetic field passes freely through the scalp, skull, and meninges, the flux in the magnetic field induces a small electric field in the brain that transiently alters neural activity.

TMS may be delivered in a variety of ways. In this study we propose to use 1 Hz TMS; that is, TMS pulses will be delivered at a frequency of 1/second. This style of TMS is assumed to be inhibitory in that it transiently suppresses the function of the cortex under the coil. Using the figure-of-eight coil to be employed here, TMS is thought to reduce activity in approximately 1 cubic cm. of cortex. Many investigators have employed TMS with a frequency of 1 Hz for periods of 20 minutes and longer; mild behavioral deficits are often present for several minutes in these studies.

1.1.1 Clinical Data to Date

TMS has also been used to treat a variety of conditions such as hemiparesis and depression. More relevant to the current application, more than 20 studies (see 25 and starred items in reference list) involving approximately 250 subjects have investigated whether TMS can improve language performance in Persons with Aphasia (PWA). Positive results have been reported in most of these studies and confirmed in several published meta-analyses (66, 91, 103, 118). Our group has also reported positive results from a randomized cross-over study of 10 subjects treated with 1 Hz TMS to the right inferior frontal gyrus (IFG). We found a significant improvement in picture naming after real but not sham TMS that was maximal at 6 months after the completion of therapy (76; see also 47, 49). The Standard Difference of Means (SMD; a measure of effect size) between the real and sham treated groups in our study, to which the current proposal is similar, was approximately 1.1 (119). As will be discussed at length below, there have been no adverse effects from TMS in any of the previous 20+ studies of TMS to treat aphasia.

1.2.2.1 Time course of TMS Benefits

Evidence suggests that the benefit from TMS to the right IFG increases over time in the absence of ongoing therapy (10, 84, 86). We reported a similar finding in a subject followed for 10 months after TMS (47). As most studies assess treatment efficacy 2 months or less after treatment, there is reason to think that many studies reported to date (e.g., 1, 116, 127) have underestimated the benefit from TMS. Our proposed study will measure treatment-related outcomes at 3 and 6 months, with the expectation that the advantage for the TMS-treated group will be maximal at 6 months.

1.2.2.2 Coupling of TMS with SLT

There is strong evidence from studies of motor rehabilitation that TMS and behavioral treatments produce synergistic effects in subjects with brain lesions, presumably by enhancing use-dependent plasticity (122). For example, Avenanti et al. (6) demonstrated that subjects with chronic hemiparesis exhibited significantly greater benefit from occupational or physical therapy paired with real as compared to sham 1 Hz TMS over the intact hemisphere. In a number of studies, the improvement with TMS was greater when TMS was delivered before, as compared to after, physical or occupational therapy (see 7, 56, 65 for similar results). In light of these data, the proposed study will couple TMS with SLT in a manner designed to maximize use-dependent plasticity.

1.2 AD Sub-Study Background

TMS has been used to enhance cognition, including language, in normal subjects () as well as subjects with focal brain injury (46, 76). In recent years, TMS has also been demonstrated to enhance cognition in subjects with AD (27, 148, 149, 150, 160, 163, 170, 171) and Mild Cognitive Impairment (155). The majority of studies have assessed the impact of TMS on "general cognition," usually as assessed by broad measures of cognition such as the Alzheimer Disease Assessment Scale – Cognitive subscale (ADAS-Cog;106*);* Koch et al. (163), however, demonstrated significant benefit on memory from repetitive TMS to the precuneus and Wu et al. (179) demonstrated that TMS improved psychiatric symptomatology in AD. Only one study reported data regarding the impact of TMS on language; in a study that explored the effects of TMS on general cognition and memory, Cotelli et al. (27) reported limited data from language tasks. They found that TMS improved performance on a sentence comprehension task.

Two recent reviews and meta-analyses also point to the utility of TMS as a treatment in AD. Cheng et al. (52) reported a meta-analysis of 8 randomized, controlled trials including 194 participants (107 with active treatment and 87 with sham) demonstrating a moderate effect of TMS (SMD-0.48, 95% CI, 0.12-0.84). Vacas et al. (176) reported a meta-analysis of the effects of TMS on behavioral and psychological symptoms from 4 randomized, controlled trials involving non-invasive brain stimulation; they found a significant benefit in studies involving TMS but not tDCS.

It is important to note that TMS was well tolerated in all studies. Several investigators reported minor headache and "non-specific minor discomfort" (see 152 for a review). We are unaware of major adverse events in any study and there is no report of a subject withdrawing from a study because of adverse events.

1.3 Dose Rationale (if applicable)

We propose to administer 1200 pulses of TMS at 90% motor threshold on 10 occasions (Monday-Friday on consecutive weeks). This schedule was selected because it was employed in most of the studies, including our work (47), that demonstrated a beneficial effect from TMS on language function.

1.3.1 AD Sub-Study Dose Rationale

We propose to administer 1200 pulses of TMS at 100% motor threshold on 10 occasions (Monday-Friday on consecutive weeks). This schedule was selected because it was employed in most of the studies, including our work (47), that demonstrated a beneficial effect from TMS on language function. We propose to employ "rapid" rTMS because Ahmed et al (148) demonstrated that rapid rTMS produced benefit in the ADAS-Cog in patients with AD whereas 1 Hz rTMS did not. The decision to stimulate at 10 Hz is motivated by the fact that several studies demonstrating benefit on the ADAS-Cog in subjects with AD employed this frequency (149, 150, 164, 170, 171). Most studies to date have delivered 1200 pulses per session. We note that the stimulation parameters that we propose are within guidelines set forth by Rosse et al (106).

1.3.2 Clinical Studies in Children

We propose to include subjects >18 years of age. We do not have access to children with stroke and there is relatively little experience with TMS in children. Furthermore, as studies to date demonstrating benefit from TMS for aphasia were performed in adults, there is no evidence of efficacy of the treatment in aphasic children.

2 Study Objectives

2.1 Primary Objective

- To demonstrate that TMS combined with Constraint Induced Language Therapy (SLT) will improve language performance more than sham TMS and CILT.

2.2 Secondary Objectives (if applicable)

- To determine the mechanism(s) by which TMS improves language function using modern techniques for network analyses of neuroimaging data collected before and after TMS and CILT.
- To identify the predictors of response to TMS, including using genetic analysis.

3 Investigational Plan

3.1 General Design

The overall timeline for each subject's participation is indicated in Figure 1. Briefly, after randomization to treatment with TMS+CILT or sham TMS+CILT, all subjects will undergo baseline behavioral testing, neuroimaging, and genetic testing before receiving 10 treatment sessions over 2 weeks. Immediate post-treatment effects will be assessed within 4 days of the completion of therapy by repeating the baseline probes of treated and untreated stimulus sets from CILT. At 3 and 6 months after the completion of TMS, subjects will return for follow-up assessments during which the same tasks administered in Visits 1 and 2 will be repeated. Subjects who are able to undergo MRI scanning will have anatomic and fMRI scans at T5 and T22. Subjects who are not able or willing to undergo MRI will undergo CAT scan of the head.

Figure 1: Timeline for each subject

Screening Visit	Baseline 1	Baseline 2	Baseline 3	Baseline 4	Treatment 1-10	Follow-up 1	Follow-up 2 & 3	Follow-up 4, 5, 6
Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6-16	Visit 17	Visit 18-19	Visit 20-22
-Informed Consent -Inclusion/Exclusion Criteria -Demographics History -Medical History -Medical Intake -Geriatric Depression Scale	-WAB -PNT -Pyramids and Palm Trees -Communication Confidence Scale -CILT baseline	-WAB -Ruff Figural Fluency Test -Word and non-word repetition -Cinderella Story -CILT baseline	-Leftover Testing -Baseline will continue into 4th and 5th visits if necessary	-MRI/CAT scan	Real or Sham TMS (20 min, 1hz at 90% MT) + CILT	-CILT probe	3-months: -same as Baseline 1 & 2	6-months: -same as Baseline 1 & 2 -MRI scan
120 minutes	120-180 minutes	120-180 minutes	60-180 minutes	120 minutes	90-120 minutes	60 minutes	120-180 minutes	120-180 minutes

3.1.1 Baseline Phase

The baseline phase will consist of 3 sessions, each lasting 1-2 hours depending on the stamina of the subject. The point of the baseline testing is to characterize the subject's language function. To that end, a number of standard language and neuropsychological tasks will be

administered. These include the Western Aphasia Battery (121), Pyramids and Palm Trees test (52), Figural Fluency Test (108), word and non-word repetition tasks, the Nicholas and Brookshire Narratives (88), CILT stimulus naming, and Northwestern Assessment of Verbs and Sentences (see below for details), as well as a measure of grip strength and finger flexibility. Additionally, during the baseline, subjects will undergo MRI of the brain or, if they have a contraindication to MRI, a CAT scan of the head. No contrast will be used. If they consent to DNA sampling, participants will also have a saliva sample taken for the purpose of genotyping.

All assessments listed are not mandatory. If the participant wishes to discontinue testing or refuses to perform a certain test due to frustration or fatigue, their request will be granted and not considered a deviation. Instead we will make note of any refused tests in our case report form (i.e. visit checklist).

3.1.2 Study Intervention Phase

In the treatment phase, there will be 10 TMS sessions over 2 consecutive weeks in which 20 minutes (1200 pulses) of 1 Hz TMS at 90% MT will be delivered to the inferior pars triangularis. Each TMS treatment session will be immediately followed by a 60-90 minute session of CILT.

3.1.3 *Follow Up Phase*

There will be two 3-month post-treatment visits and two 6-month post-treatment visits in which the full battery of language and cognitive assessments will be repeated. Subjects who are able to undergo MRI scanning will have anatomic and fMRI scans at or after the 6-month post-treatment visit.

All assessments listed are not mandatory. If the participant wishes to discontinue testing or refuses to perform a certain test due to frustration or fatigue, their request will be granted and not considered a deviation. Instead we will make note of any refused tests in our case report form (i.e. visit checklist).

3.1.4 Allocation to Interventional Group

Participants will be randomized to either TMS or sham TMS in a 2:1 allocation ratio using permuted blocks of variable size. Further, as it has been suggested that aphasia severity influences response to TMS treatment for aphasia, randomization will be stratified by WAB AQ score to ensure an approximately equal allocation of treatments among PWA with WAB AQ <50 and WAB AQ => 50 (see 60). The unblinded study coordinator will be responsible for generating the random numbers used to conduct the randomization.

3.2 General Design AD Sub-Study

Briefly, after randomization to treatment with TMS+CILT or sham TMS+CILT, all subjects will undergo baseline behavioral testing, neuroimaging, and genetic testing before receiving 10 treatment sessions over 2 weeks. Immediate post-treatment effects will be assessed within 4 days of the completion of therapy by repeating the baseline probes of treated and untreated stimulus sets from CILT. At 6 and 12 weeks after the completion of TMS, subjects will return for follow-up assessments during which the same tasks administered in Visits 1 and 2 will be

repeated. Subjects who are able to undergo MRI scanning will have anatomic and fMRI scans at T3 and T17. Subjects who are not able or willing to undergo MRI will undergo CAT scan of the head.

3.2.1 Baseline Phase

The baseline phase will consist of 3 sessions, each lasting 1-2 hours depending on the stamina of the subject. The point of the baseline testing is to characterize the subject's language function. To that end, a number of standard language and neuropsychological tasks will be administered. These include the Western Aphasia Battery (121), Pyramids and Palm Trees test (52), Figural Fluency Test (108), word and non-word repetition tasks, the Nicholas and Brookshire Narratives (88), CILT stimulus naming, and Northwestern Assessment of Verbs and Sentences (see below for details), and the *Repeatable Battery for the Assessment of Neuropsychological Status* (147). Additionally, during the baseline, subjects will undergo an MRI of the brain or, if they have a contraindication to MRI, a CAT scan of the head. No contrast will be used. If they consent to DNA sampling, participants will also have a saliva sample taken for the purpose of genotyping.

All assessments listed are not mandatory. If the participant wishes to discontinue testing or refuses to perform a certain test due to frustration or fatigue, their request will be granted and not considered a deviation. Instead we will make note of any refused tests in our case report form (i.e. visit checklist).

3.2.2 Study Intervention Phase

In the treatment phase, there will be 10 TMS sessions over 2 consecutive weeks. We will employ repetitive TMS (rTMS) in which 30 two second trains of 10 Hz TMS will be delivered every 30 seconds to the left inferior pars triangularis and to the left posterior superior temporal gyrus, both at 100% MT. There will be a total of 600 pulses (30 trains x 2 seconds at 10 Hz) to each site in each session for a total of 1200 pulses/session. Each rTMS treatment session will be immediately followed by a 60-minute session of SLT.

3.2.3 *Follow Up Phase*

There will be two 6-week post-treatment visits and two 12-week post-treatment visits in which the full battery of language and cognitive assessments will be repeated. Subjects who are able to undergo MRI scanning will have anatomic and fMRI scans at or after the 12-week post-treatment visit.

All assessments listed are not mandatory. If the participant wishes to discontinue testing or refuses to perform a certain test due to frustration or fatigue, their request will be granted and not considered a deviation. Instead we will make note of any refused tests in our case report form (i.e. visit checklist).

3.2.4 Allocation to Interventional Group

Participants will be randomized to either TMS or sham TMS in a 2:1 allocation ratio using permuted blocks of variable size. The unblinded study coordinator will be responsible for generating the random numbers used to conduct the randomization.

3.3 Study Endpoints

3.3.1 Primary Study Endpoints

The primary endpoint will be overall change in WAB-AQ between the first baseline visit and the 6 month follow-up visit

3.3.2 Secondary Study Endpoints

Change in naming accuracy on the PNT will serve as a secondary outcome measure

3.3.3 Primary Safety Endpoints

The risks from the behavioral tasks and imaging are minor. Data on adverse events occurring during the 2 weeks in which TMS is being administered will be collected by asking subjects at the beginning and end of every TMS session if they have noted any adverse effects or new symptoms since their most recent. Reports of adverse effects from TMS and other aspects of the study (brain imaging, behavioral tasks and CILT) will serve as the primary safety endpoint.

4 Study Population and Duration of Participation

4.1 Inclusion Criteria

Study subjects must meet all of the following inclusion criteria:

- Clinical evidence and MRI or CT verification of a single left hemisphere cerebral infarct, either ischemic and hemorrhagic, with moderate to severe aphasia as operationally defined by WAB-AQ scores between 85 and 20, inclusive. Patients will not be excluded on the basis of small (less than 1.5cm) lacunar strokes as these are extremely common in the population under study and for which the therapy is ultimately intended.
- Suffered their infarction at least 6 months prior to their testing.
- Be between the ages of 18 and 80.
- Must be able to understand the nature of the study, and give informed consent.

4.2 Exclusion Criteria

Study subjects must not meet any of the following exclusion criteria

- Multiple infarcts as defined by brain imaging
- History of serious and/or ongoing issues with substance abuse.
- Previous head trauma with loss of consciousness for more than 5 minutes
- Psychiatric illness (We note that subjects will be assessed with the 15-item Geriatric Depression scale. Because depression is very difficult to evaluate in aphasic subjects, potential subjects will not be excluded on the basis of the depression score, but this measure will serve as a covariate in subsequent analyses.)
- Chronic exposure to medications that might be expected to have lasting consequences for the central nervous system (e.g. haloperidol, dopaminergics).
- History of or neuropsychological findings suggestive of dementia

Additional contraindications related to TMS include:

- Uncontrolled seizures, as operationally defined by a history of seizure while taking their current medical regimen during the last 6 months.
- Previous brain surgery (excludes procedures where bone is removed to release pressure, such as a craniotomy, so long as the bone is replaced and allowed to fuse back together).
- Other medical or neurologic conditions, aside from stroke, in which the likelihood of developing a seizure is known to be increased.
- Other medical or neurologic conditions, in which a seizure would be particularly harmful (e.g., increased intracranial pressure)
- Presence of metallic hardware near coil; examples include cardiac pacemakers, intracardiac lines, intracranial stents, implantable defibrillators, medical pumps, ventriculo-peritoneal shunts, deep brain stimulators, and vagus nerve stimulators.
- History of tinnitus
- Pregnancy – there are no known problems in delivering TMS during pregnancy, but the issue has not been thoroughly addressed; all female participants must have a negative urine pregnancy test at the time of testing to participate

4.3 AD Sub-Study Inclusion Criteria

Study subjects must meet all of the following inclusion criteria:

- A diagnosis of mild-moderate AD as defined by the National Institute of Aging – Alzheimer's Disease and Related Disorders Association criteria
- Mild-moderate cognitive impairment, indicated by Mini-Mental Status Exam (MMSE) scores between 23 and 15 inclusive.
- Between the ages of 50 and 85
- Must be right handed as defined by the Edinburgh Handedness Inventory
- Must be proficient in English
- Must be able to understand the nature of the study, and give informed consent

4.4 AD Sub-Study Exclusion Criteria

Study subjects must not meet any of the following exclusion criteria:

- History of stroke
- History of seizure
- History of any other significant neurologic disease (e.g., ALS)
- Significant depression as defined by the Geriatric Depression Scale; subjects with scores suggesting significant depression will not be included and Dr. Dawn Mechanic-Hamilton, Co-I and Neuropsychologist at the Penn Memory Center, will be available to address concerns regarding safety and provide a referral, if needed.
- Any significant medical disorder that, in the view of the investigators, could threaten the subject's ability to complete the study (e.g., cancer, significant cardiac disease)
- Any contraindications to TMS as specified in section 4.2 above

Additional contraindications related to MRI include the presence of any of the following devices:

1. Cardiac pacemaker
2. Other programmable implanted devices, e.g., for the carotid sinus, insulin pumps and nerve stimulators, lead wires or similar wires
3. Optic implant

4. Implanted cardiac defibrillator
5. Aneurysm clip
6. Any electronically, magnetically, and mechanically activated implant
7. Ferromagnetic implant: coils, filters, and stents; metal sutures or staples
8. Claustrophobia
9. Metal in eye or orbit
10. Tattooed eyeliner

4.5 Subject Recruitment

Subjects will be recruited from several sources. The first source is from personal contacts within the University of Pennsylvania Health system, including neurologists, psychologists, neurosurgeons, and rehabilitation therapists. The study coordinator will receive referrals from members of UPHS who have previously agreed to identify potential individuals who meet the criteria of the database. The PI or study coordinator will then reach out to the subject or family member via in-person (i.e. at bedside), telephone, email, or letter to determine whether they wish to consent into the protocol. A second source is from the Penn Institute of Rehabilitation Medicine (PIRM). The study coordinator will have access to the medical charts of inpatients at PIRM and will prospectively and retrospectively review charts to determine if patients match the inclusion criteria of the protocol. Another source will be the Penn Data Store, where the study coordinator will review patient charts using the Cohort Explorer and Pennseek tools offered by the Penn Data Analytics team. Cohort Explorer will be used to identify patients that meet our inclusion/exclusion criteria. We will also use Pennseek to search free text within their chart for clinical impairments germane to currently recruiting studies (e.g. “aphasia”, “stroke”). The study coordinator will send our query to the Penn Data Store, and work with the Penn Data Analytics team to refine our request. The study coordinator will request the names, telephone numbers, and addresses of patients. This data request will be automatically generated on a monthly basis. Another source is from subjects already enrolled in the Center for Cognitive Neuroscience (CCN) Focal Lesion Database (FoLD) or already listed in the FoLD Recruiting Database (covered by Protocol #824122). Whenever a researcher requests a subject enrolled into the FoLD Database under Protocol #824122, the Patient Coordinator will invite that patient to continue their participation in the database under the current protocol.

PWA will also be recruited from the Moss Rehab Research Institute (MRRI); Dr. Erica Middleton is a co-investigator at MMRI, and along with Adelyn Brecher CCC-SLP will recruit approximately 8-9 subjects with chronic aphasia annually.

Finally, Dr. Nadine Martin, a consultant to the project, will refer potential participants from the Saffran Aphasia Center at Temple University. These potential subjects will then be contacted by study personnel.

Flyers will be posted at the clinics and rehabilitation centers noted above. All flyers will be submitted to the IRB for approval before use. Radio advertisements will be broadcasted either over conventional radio or via podcasts. All radio/podcast copy will be submitted to the IRB for approval before use.

Flyers will also be posted on social media (Facebook, Twitter, etc.). These will be one-way ads. No communication with potential subjects will be conducted on social media. All social media postings that include information or language besides the already approved flyers will be submitted to the IRB for approval before use.

4.6 AD Sub-Study Recruitment

Subjects will be recruited from the large, well-characterized research cohort of the Penn Memory Center, the clinical arm of the NIA-supported Penn Alzheimer Disease Research Center (ADRC). Drs. Wolk, Director of the Clinical Core of the Penn ADRC, and Mechanic-Hamilton, Director of Neuropsychology in the Penn ADRC, are Co-Is on the project.

4.7 Duration of Study Participation

The duration of the study as outlined above is approximately 7-8 months.

4.8 Total Number of Subjects and Sites

We intend to enroll up to 83 subjects to achieve an evaluable sample size of 75. This attrition estimate is based on past experience.

4.9 AD Sub-Study Total Number of Subjects

We intend to enroll up to 30 subjects. Given our historical attrition rate, we expect attrition of approximately 15%

4.10 Vulnerable Populations:

Children, fetuses, neonates, or prisoners are not included in this protocol.

Although there is no known risk of TMS to the fetus, the issue has not been fully addressed; consequently, pregnant women will be excluded. All women of childbearing age (that is, not postmenopausal) will be asked to undergo a pregnancy test at the beginning of study visits. Prisoners will not be recruited. As the technique has not been studied in children, only subjects 18 and older will be permitted to participate.

5 Study Intervention (Study drug, device, biologic, vaccine, food etc.)

5.1 Description

We will use a MagVenture MagPro X100 with a C-B60 Butterfly Coil or Cool-B65 A/P Butterfly Coil. A sham MagVenture TMS coil (Cool-B65 A/P Butterfly Coil) that looks and sounds like the active coil but does not generate a magnetic field will be used for the sham TMS. Current stimulation surface electrodes are placed on the skin at the site of the coil which provide a small amount of current stimulation to simulate TMS.

We will use the MagVenture MagPro X100 with subjects in the AD sub-study. We will also make use of the Magstim Standard Rapid Package with an air-cooled figure-of-eight coil.

5.2 Intervention Regimen

Pertinent parameters for consideration in any TMS study include the location, frequency, intensity, and duration of brain stimulation.

5.2.1 Stimulation Location

TMS will be delivered to the right inferior pars triangularis of the contralesional, right hemisphere (part of the inferior frontal gyrus). The stimulation site will be targeted using the Localite Frameless stereotactic system for image-guided TMS research (Localite GmbH, Bonn, Germany). This system uses infrared reflectors attached to the patient's head and brain. The stimulating coil is similarly co-registered via infrared reflectors to the patient's head and to the imaging data allowing precise control of the stimulation site.

5.2.2 AD Sub-Study Stimulation Location
TMS will be delivered to the left inferior pars triangularis and to the left posterior superior temporal gyrus. The stimulation site will be targeted using the Brainsight frameless stereotactic system for image-guided TMS research (Rogue Research, Montreal, Canada). This system uses infrared reflectors attached to the patient's head and brain. The stimulating coil is similarly co-registered via infrared reflectors to the patient's head and to the imaging data allowing precise control of the stimulation site.

5.2.3 Stimulation Parameters

Our protocol involves repetitive TMS at a frequency of 1 Hz. According to established guidelines, the maximum safe duration of single trains of rTMS at 1 Hz using an intensity of 110% of MT is ">1800" (that is >30 minutes) (Wassermann, 1998). Working well within these guidelines, we will administer 1200 pulses in one session at 1 Hz (20 minutes) at 90% of MT. We note that recent evidence suggests that stimulation intensities as high as 120% of MT are safe in stroke patients, even when applied directly to the lesioned hemisphere (61) for a period of 10 days. Our protocol calls for stimulation at a relatively lower intensity (90% MT), applied to the undamaged hemisphere of the brain, which we feel increases the safety of the study. We also note that the stimulation parameters we propose were employed in our previous clinical trial employing rTMS (protocol #805362) in which we had no adverse events.

Prior to administering experimental TMS, we will determine the motor threshold (MT) of each patient by stimulating the motor cortex in the unaffected hemisphere. MT will be defined as the minimum percentage of machine output required to produce MEPs of at least 50 microVolts on at least 5 of 10 consecutive trials at the same location. MT will be determined by single-pulse stimulation of the motor cortex subserving the contralesional hand at a suprathreshold level and subsequently reducing the percentage of the machine output until MEPs are not identified. The coil will be placed with the handle pointing to the patient's back at about 45° from the vertical position. Following determination of MT, patients will undergo 1 Hz rTMS.

The sham TMS group will be treated in the same manner as the experimental group except that MT will not be determined for the sham group. Thus, subjects in this group will never receive TMS. Sham treatment will employ a sham coil that produces the same sound as the real coil. Additionally, surface electrodes will be placed on the scalp, which will simulate the sensation of TMS. The sham and real coils will be numbered and the coil used and the MT will be recorded for each session.

5.2.4 AD Sub-Study stimulation parameters

This protocol involves repetitive TMS at a frequency of 10 Hz. According to establish guidelines, the maximum safe duration of single trains of rTMS at 10 Hz using an intensity of 110% of MT is >5 seconds (106). Working well within these guidelines, we will be administering 2 second trains at 100% of MT. There will be 30 trains delivered to each of the two stimulation locations, with a 30s inter-train interval.

Prior to administering experimental TMS, we will determine the motor threshold (MT) of each patient by stimulating the motor cortex in the unaffected hemisphere. MT will be defined as the minimum percentage of machine output required to produce MEPs of at least 50 microVolts on at least 5 of 10 consecutive trials at the same location. MT will be determined by single-pulse

stimulation of the motor cortex subserving the contralesional hand at a suprathreshold level and subsequently reducing the percentage of the machine output until MEPs are not identified. The coil will be placed with the handle pointing to the patient's back at about 45° from the vertical position. Following determination of MT, patients will undergo 10 Hz rTMS.

The sham TMS group will be treated in the same manner as the experimental group except that MT will not be determined for the sham group. Thus, subjects in this group will never receive TMS. Sham treatment will employ a sham coil that produces the same sound as the real coil. Additionally, surface electrodes will be placed on the scalp, which will simulate the sensation of TMS. The sham and real coils will be numbered and the coil used and the MT will be recorded for each session.

5.2.5 Constraint Induced Language Therapy (CILT)

CILT is a commonly used form of speech therapy. CILT will be delivered immediately after TMS to take advantage of the "state-dependent" effects of TMS. In our version of CILT, a Speech Pathologist (or research personnel trained under the supervision of our Speech Pathologist) will function as both conversational partner and therapist-coach. In each session, the patient and SLP will start with identical decks of treatment card. Seated across a 30-cm. barrier, each will array their cards 6 at a time. Choosing a card from his/her array, the participant will call for its match using a verbal description (e.g., at the HFA level: "throw the ball"). If the description is incorrect or insufficiently precise to specify the target, the SLP will view the participant's card and supply cues to its description, using the Boston Naming Test cueing hierarchy: semantic, followed by phonologic, followed, after ~5 seconds, by repetition of the target word or phrase. Non-verbal expressions of the target, though not prohibited, will not be accepted as a substitute for the verbal response. The SLP will then take a turn, and request a card from the subject. Once all 6 cards are gone, the next 6 cards will be set up and the protocol repeated. On each trial, the SLP will score accuracy and type/amount of cuing needed to generate the response.

Each session will last 60-90 minutes, depending on the pace of participants' responses. If a person finishes a particular stimulus set in less than 45 minutes of therapy, the SLP will repeat the same stimulus subset from the easiest category.

Stimuli for the CILT protocol will include 2 different sets of 48 cards. Each set will contain 12 exemplars of 4 categories: High Frequency nouns (HFO); Action/Function verbs associated with the HFO (HFA); Low Frequency nouns (LFO); Action/Function verbs associated with the LFO (LFA). To avoid biasing performance on the primary outcome measure (WAB), there will be no overlap between the CILT stimuli and the stimuli of the WAB. We will also minimize overlap with items on the PNT.

The two 48-item sets will be used to select treated and untreated items, as follows. Each set will be presented twice in the baseline sessions (see Fig. 1), with participants scored on their ability to name the image and use the name in a sentence. Phonemic, semantic, self-correction, and no response errors will be coded from audio transcripts. If accuracy on one or more categories varies substantially between the sets (i.e. greater than 20% difference) the sets will be redistributed to match accuracy and, to the degree possible, error type. One set will be used for the treatment phase of the study; the other will be untreated and will provide a measure of generalization.

Scores on the pre-treatment baselines will be used to set the starting point for CILT treatment, using an 80% criterion. For example, if the participant's baseline performance is > 80% accurate for HFO production but < 80% for HFA, then treatment will begin at the level of HFA and will remain at this level of difficulty until the 80% is met in two successive sessions.

5.3 Blinding

Participants will not be informed of their assignment to active or sham status. Sham TMS will be administered with a sham TMS coil that looks and sounds like the active coil but does not generate a magnetic field. Surface electrodes applied to the scalp during sham stimulation will simulate the sensation of TMS, therefore allowing subjects with prior experience with TMS to be blind to condition as well.

The unblinded study coordinator will keep the master file of subject assignments. This individual will administer TMS, but all other individuals in contact with the subject or their data will be unaware of group assignment. In particular, the speech-language pathologist (SLP) and the individuals administering and scoring the language measures will not be present for the administration of TMS and will be blinded with respect to subject assignment. In the case of an adverse event, the blind may be broken if the PI deems it necessary.

5.4 Administration and Accountability

All stimulation sessions will be logged in a TMS log that will be kept in a secure location in the lab space. This log will include the date of stimulation, the individual administering TMS, and the MT of the patient as percentage of machine output.

5.5 Subject Compliance Monitoring

Noncompliance with regard to the randomized intervention could occur if participants miss therapy sessions or if the wrong coil is used to administer TMS. To minimize noncompliance due to missed therapy sessions, participants who miss up to 3 sessions will be allowed to make up missed sessions the following week. To avoid error in coil selection, sham and active TMS coils will be labeled numerically, and TMS technicians will be asked to record the number of the coil used in each administration of TMS in the TMS log.

6 Study Procedures

6.1 Screening

The screening visit will consist of:

- Informed Consent
- Review of the Inclusion/Exclusion Criteria
- Review of Demographics/Medical History
- Medical Intake (performed by the study PI or Dr. Hamilton, both of whom are neurologists).
- In cases where the baseline visits will be conducted via tele-assessment, the Ruff Figural Fluency test may be administered at this visit.

The anticipated time of this visit is 30 minutes; depending on the subject's interest and responses to the screening tests, this visit could be combined with Visit 1 below.

An initial remote screening visit may be conducted via Bluejeans. Before screening and the medical intake, remote consent will be obtained, with e-signatures collected via RedCAP (explained in detail below). An in-person Medical Intake screening may occur after the remote consent and screening.

At the time of screening, or sometime afterwards, the Aphasia Depression Rating Scale (ADRS) will be completed by the patient's caregiver. The caregiver rates the subject on 9 different items. The ADRS has high reliability, sensitivity and specificity and is specifically designed for evaluation of aphasic patients (147). The ADRS will be given to the patient's caregiver to complete at the

time of screening, or will be mailed to the caregiver or close relative before the baseline screening. The ADRS will serve as a covariate in statistical analysis.

6.2 AD Sub-Study Screening

The screening visit will consist of:

- Informed Consent
- Review of the Inclusion/Exclusion Criteria
- Review of Demographics/Medical History
- Medical Intake (performed by the study PI or Dr. Hamilton, both of whom are neurologists).
- 15 item Geriatric Depression Scale (GDS): This test requires the subject to answer "yes" or "no" to convey symptom presence/absence over the past week. The GDS has good reliability, sensitivity, and specificity for older persons.
- The Mini-Mental State Exam (MMSE)
- In cases where the baseline visits will be conducted via tele-assessment, the Ruff Figural Fluency test may be administered at this visit.
-

The anticipated time of this visit is 30 minutes; depending on the subject's interest and responses to the screening tests, this visit could be combined with Visit 1 below.

An initial remote screening visit may be conducted via Bluejeans. Before screening and the medical intake, remote consent will be obtained, with e-signatures collected via RedCAP (explained in detail below). An in-person screening visit for in-person Medical Intake, GDS, and MMSE may take place after the remote consent and screening.

6.3 Study Intervention Phase

6.3.1 Visit 1 (Baseline 1)

- Western Aphasia Battery
- Philadelphia Naming Test
- Pyramids & Palm Trees
- Communication Confidence Rating Scale for Aphasia
- CILT Baseline Assessment
- Genetic testing: A saliva sample will be collected to determine the gene polymorphism for brain derived neurotrophic factor (BDNF)

The anticipated time of this visit is 120-180 minutes. Testing that is not finished in this visit will be continued in the second Baseline visit.

Baseline visits might be conducted via tele-assessment, using Bluejeans, or a HIPAA compliant alternative. In such cases, testing materials may be mailed to participants beforehand, and instructions provided during the tele-assessment. Other test materials will be displayed over the video software. Video and audio of the tele-assessment will be recorded. The genetic sample will not then be collected during virtual assessment.

6.3.2 Visit 1 (Baseline 1) for AD Sub-Study

- Western Aphasia Battery
- Philadelphia Naming Test
- Pyramids & Palm Trees

- Communication Confidence Rating Scale for Aphasia
- CILT Baseline Assessment
- Semantic fluency
- Genetic testing: A saliva sample will be collected to determine the gene polymorphism for brain derived neurotrophic factor (BDNF)

The anticipated time of this visit is 120-180 minutes. Testing that is not finished in this visit will be continued in the second Baseline visit

Baseline visits might be conducted via tele-assessment, using Bluejeans, or a HIPAA compliant alternative. In such cases, testing materials may be mailed to participants beforehand, and instructions provided during the tele-assessment. Other test materials will be displayed over the video software. Video and audio of the tele-assessment will be recorded. The genetic sample will not then be collected during virtual assessment.

6.3.3 Visit 2 (Baseline 2)

- Western Aphasia Battery
- Figural Fluency
- Word and Non-word repetition
- Cinderella Story
- CILT baseline

The anticipated time of this visit is 120-180 minutes. Testing that is not finished in this visit will be continued in the third Baseline visit.

Baseline visits might be conducted via tele-assessment, using Bluejeans, or a HIPAA compliant alternative. In such cases, testing materials may be mailed to participants beforehand, and instructions provided during the tele-assessment. Other test materials will be displayed over the video software. Video and audio of the tele-assessment will be recorded. The genetic sample will not then be collected during virtual assessment.

6.3.4 Visit 2 (Baseline 2) for AD Sub-Study

- Western Aphasia Battery
- Figural Fluency
- Word and Non-word repetition
- Cinderella Story
- Repeatable Battery for the assessment of Neuropsychological Status (RBANS)
- CILT baseline

The anticipated time of this visit is 120-180 minutes. Testing that is not finished in this visit will be continued in the third Baseline visit.

Baseline visits might be conducted via tele-assessment, using Bluejeans, or a HIPAA compliant alternative. In such cases, testing materials may be mailed to participants beforehand, and instructions provided during the tele-assessment. Other test materials will be displayed over the video software. Video and audio of the tele-assessment will be recorded. The genetic sample will not then be collected during virtual assessment.

6.3.5 Visit 3 (Baseline 3)

Baseline testing that is not finished in the previous visit will be continued in this visit. There is the possibility that a third day will not suffice, therefore, patients may return for a 4th and 5th baseline visit.

The anticipated time of this visit is 60-180 minutes.

6.3.6 Visit 4

- MRI scan/CT scan: those subjects who are able to undergo an MRI scan will be scanned on a 3T or 1.5T Siemens unit; if subjects are unable to undergo MRI they will have a CT scan of the head. If the subject is concerned about the potential for metal fragments in the head or body, we will offer an x-ray scan to check for foreign objects in the body. No contrast will be administered.
- In cases where the baseline visits will be conducted via tele-assessment, the Ruff Figural Fluency test may be administered at this visit.

The anticipated time of this visit is 120 minutes.

If genetic sampling was not able to be collected at baseline visits, it will be collected during Visit 4.

6.4 Phase 2 of the Study (Visits 5-14)

In the treatment phase, there will be 10 TMS sessions over 2 consecutive weeks in which 20 minutes (1200 pulses) of 1 Hz TMS at 90% MT will be delivered to the inferior pars triangularis. Each TMS treatment session will be immediately followed by a 60-90 minute session of CILT. On the first day of treatment, we will take the grip strength and finger flexibility motor measurements, as well as the 5th and 10th day. The total anticipated time of these visits will be 90-120 minutes.

6.4.1 AD Sub-Study Phase 2 (Visits 5-14)

In the treatment phase, there will be 10 TMS sessions over 2 consecutive weeks in which 30 two second trains of 10 Hz TMS will be delivered every 30 seconds at 100% MT to the left inferior pars triangularis and to the left posterior superior temporal gyrus. There will be a total of 600 pulses (30 trains x 2 seconds at 10 Hz) to each site in each session for a total of 1200 pulses per session. Each TMS treatment session will be immediately followed by a 60-90 minute session of CILT. The total anticipated time of these visits will be 90-120 minutes.

6.5 Follow Up Phase of the Study

6.4.1 Visit 15

- CILT Probe: this will assess the immediate effect of TMS + CILT on the treated words from CILT.

The anticipated time of this visit is 60 minutes.

The follow-up visit may be conducted via tele-assessment.

6.4.2 Visit 16 & 17 (3-month follow-up)

The same battery of tasks administered in visits 1 and 2 will be administered in these visits which will occur at 3 months after the end of TMS. The anticipated time of these visits is 120-180 minutes.

The 3-month follow-up visits may be conducted via tele-assessment.

6.4.3 AD Sub-Study Visit 16 & 17 (6-week follow-up)

The same battery of tasks administered in visits 1 and 2 will be administered in these visits, which will occur at 6 weeks after the end of TMS. The anticipated time of these visits is 120-180 minutes.

The 6-week follow-up visits may be conducted via tele-assessment.

6.4.4 Visit 18, 19 & 20 (6-month follow-up)

The same battery of tasks administered in visits 1 and 2 will be administered in these visits which will occur at 3 months after the end of TMS. The anticipated time of these visits is 120-180 minutes. Additionally, for those subjects who had an MRI at the beginning of the study, a repeat MRI scan will be performed using the same acquisition parameters described below. The ADRS will also be collected again at the 6-month follow-up timepoint. The ADRS is completed by the participant's caregiver.

The 6-month follow-up visits may be conducted via tele-assessment.

For in-person follow-up visits (i.e. not conducted via tele-assessment), the final day of the follow-up testing may include a brief tele-assessment, time permitting and with the subjects approval. This tele-assessment will consist of some combination of the tests (listed under Visits 1 and 2) conducted via video software; study personnel will conduct this tele-assessment from a nearby room.

6.4.5 Visit 18, 19 & 20 (12-week follow-up)

The same battery of tasks administered in visits 1 and 2 will be administered in these visits, which will occur at 12 weeks after the end of TMS. The anticipated time of these visits is 120-180 minutes. Additionally, for those subjects who had an MRI at the beginning of the study, a repeat MRI scan

The 12-week follow-up visits may be conducted via tele-assessment.

For in-person follow-up visits (i.e. not conducted via tele-assessment), the final day of the follow-up testing may include a brief tele-assessment, time permitting and with the subjects approval. This tele-assessment will consist of some combination of the tests (listed under Visits 1 and 2) conducted via video software; study personnel will conduct this tele-assessment from a nearby room.

6.6 Subject Withdrawal

Patients are free to withdraw from the study at any time if they no longer wish to participate. Additionally, patients may be withdrawn from the study prior to the expected completion date for a number of reasons:

1) Any adverse outcome or event which may represent a possible health risk to the patient
2) Failure of the patient to adhere to protocol requirements

3) Worsening of motor strength, language abilities, or worsening cognition or mood.

Abrupt discontinuation of TMS is not associated with rebound effects or other adverse outcomes, so no alternative treatment or transitional therapy will be required if patient discontinue the protocol.

6.6.1 Data Collection and Follow-up for Withdrawn Subjects

Some patients may wish to stop receiving TMS per the protocol. In this case, attempts will be made to obtain permission to continue collecting data from motor and cognitive testing in a way that mirrors patients who are receiving TMS as specified by the protocol. Should patients wish to withdraw from the study entirely, attempts will be made to seek permission to obtain survival data on such patients throughout the protocol defined follow-up period. It will be a high priority to try to obtain at least survival data on all patients lost to follow-up. A number of attempts will be made to contact a patient by various means before he or she will be considered lost to follow-up. These methods will consist of three or more of phone calls to patient, followed by a phone call to next-of-kin if possible, followed by a certified letter. Should all of these efforts fail to elicit a response the patient will be considered lost to follow-up.

6.7 Early Termination Visits

All subjects that decide to leave the study early or are asked to by the investigator will be strongly encouraged to continue follow-up visits, but early termination visits are not planned.

7 Study Evaluations and Measurements

7.1 Medical Record Review

- Date of birth
- Address
- Contact information
- Hospital admission date and date of brain injury
- Past medical history as it relates to stroke and other neurologic conditions, cardiac status, and surgery
- Results of neuroimaging studies and dates, including MRI and/or CT exams
- Current and past medications or therapies

7.2 Physical Examination

A routine physical examination will be performed at the time of admission to the study. Should subjects report new complaints or a change in their neurologic/language status, an examination will be performed by the PI or other neurologist working on the project.

7.3 Laboratory Evaluations

All subjects who have not had high quality brain imaging in the 3 months prior to entry to the project will undergo either MRI or CAT brain imaging at the University of Pennsylvania. MR examination will include structural imaging T1- weighted magnetization prepared rapid gradient echo (MP RAGE; TR=1620 ms, TE=3.08 ms; flip= 15; FOV = 280 x 280mm, 1.0 x 1.0 x 1.0 mm voxels; 160 slices); Coplanar T2 (TR=4010 ms, TE=76ms, flip=150, FOV=256 x 256 mm, slice thickness = 2.6 mm, 48 slices); T2 –weighted resting BOLD sequence (TR = 0.5s, TE = 30ms, 230x230 mm^2 FoV, 128x128 acquisition matrix) and a fast fluid attenuated inversion recover scan

or FLAIR (TR=9190 ms; TE=102 ms ; flip =180; FOV= 180 x 240; 1.3 x 0.8 x 4.0 mm; 40 slice) . We will also obtain diffusion imaging (HARDI; 2.5 x 2.5 x 2.5 mm voxels, 54 slices, 60 direction b-value=2500ms/mm2); and pseudo-continuous arterial spin labeling (pCASL; TR=4000 ms; TE=18 ms; 3.4 x 3.4 x 5 mm; flip angle 90; 16 slices, matrix=64 x 64). To avoid phase wrap artifact in subjects with large heads the slice thickness may be adjusted upwards slightly.

For subject unable or unwilling to undergo MRI imaging a high-resolution CAT (60 axial slices, 3mm thick, matrix =512 x 512) without contrast will be acquired.

7.4 Pregnancy Testing

There is no known risk to a mother or fetus from TMS or MRI, but due to the fact that the safety of the technique in pregnant women has not been fully studied, pregnant women are excluded from the study. If the female subject is of child-bearing age, a urine pregnancy test will be performed before the first TMS sessions.

7.5 Other Evaluations, Measures

The following battery of language and cognitive tasks will be administered prior to TMS and at 3 and 6 months after the completion of TMS: (1) The *Western Aphasia* Battery (WAB: 121) samples a number of different language functions and generates a summary score between 0-100 (Aphasia Quotient, AQ), interpretable as general aphasia severity. The WAB will be administered on two occasions prior to treatment to obtain a stable baseline. (2) The *Philadelphia Naming Test* (PNT) is a 175-item test of common object (picture) naming designed to measure retrieval of known words. Computational models have been developed that relate an individual's performance on the PNT (accuracy and error breakdown) to the integrity of semantic and phonological stages of naming (38, 136), thus producing a psycholinguistic diagnosis of the word production impairment. (3) Word and non-word repetition tests from the Moss Psycholinguistic Aphasia Database (MAPPD; 77) will be used to further assess lexical and post-lexical phonological encoding (31, 89). Word repetition will also be used to quantify instances of consonant distortion, prosodic alteration, and other features of speech apraxia (e.g., 105, 115). (4) The Pyramids and Palm Trees test (Picture version; 52) will be used to assess core semantic memory. (5) The Communication Confidence Rating Scale for Aphasia (144) will be administered to assess changes in quality of communication in daily life. (6) Narrative discourse as an indicator of functional communication will be assessed with the Cinderella story (145, 146). *(7*) Finally, 2 pre-treatment baselines will be obtained on the stimuli used for CILT. We note that the baseline sessions (T1 and T2, Figure 2) may require more than one day to complete; the entire series of baseline sessions (T1, T2 and T3) will be completed in 2 weeks or less.

One might speculate that improvements in language associated with TMS to the right IFG would be associated with adverse effects in other domains. We found no evidence of this in our previous work, nor are we aware of reports of such a phenomenon. To address this possibility, we will administer the Ruff Figural Fluency Test (108), which has been shown to be sensitive to dysfunction of the right prefrontal cortex.

While there has been research on the effects of TMS on motor recovery for patients with stroke-induced hemiparesis, we do not expect our stimulation location to have an effect on

motor ability. However, given the possibility for changes in motor ability in the hemiparetic arm, we will take a measure of grip strength using a dynamometer, and a measure of figure flexibility using the finger-tapping test. We will administer these measures at baseline, on the first, 5th and 10th day of treatment, and at the 3-month and 6-month follow up.

7.5.1 Specific Measurements for the AD Sub-Study

Subjects in the AD sub-study will undergo the same battery of language and cognitive tasks as those in the Aphasia study, with the addition of the *Repeatable Battery for the Assessment of Neuropsychological Status* (RBANS) (147), which will be used to assess attention, language and visuospatial/constructional abilities, as well as immediate and delayed memory. Semantic fluency will be assessed by asking subjects to name as many animals and tools as possible in 1 minute intervals.

7.6 Efficacy Evaluations

No interim analyses for efficacy are planned, as previous work suggests that the maximal benefit is likely to be obtained at the 6 month endpoint and there is no additional risk to the subject after the TMS is completed.

7.7 Genetic Testing

Exploratory genetic testing will take place. Saliva samples will be collected with an OG-100 Oragene collection kit (DNA Genotek, Ontario, Canada), and DNA will be extracted using standard methodology. All subjects that consent to have genetic samples taken will have marked on their consent form that they consent to the collection and storage of their genetic sample; they will be assigned a separate coded identification number. Saliva samples will be de-identified and transported to the Penn Genomic Analysis Core for genotyping.

Storage of DNA will be conducted in the lab. DNA samples will not become part of the clinical record and will not be made available for commercial use. Identifiers for the DNA samples will not be directly traceable to any name, but rather to another coding system. The second coding system will be used to link behavioral and neurophysiologic outcomes. There are no known risks involved in saliva collection.

Once the study is complete, all samples will be destroyed.

7.8 Safety Evaluations

Subject safety will assessed throughout the course of the study by asking subjects if they have experienced adverse effects from the interventions. Although we consider the risk to be low, TMS is the most likely study intervention to be associated with adverse effects. As any adverse effects of TMS are likely to occur at the time of stimulation, we will ask all subjects before and immediately after TMS if they note any symptoms of concern. This will be documented for each subject for each TMS session.

8 Statistical Plan

8.1 Primary Endpoint

The primary endpoint will be overall change in WAB-AQ between the first baseline visit and the 6 month follow-up visit

8.2 Secondary Endpoints

Change in naming accuracy on the PNT will serve as a secondary outcome measure

8.3 Sample Size and Power Determination

To calculate power, we started from an ambitious but realistic estimate of the population available at the participating recruitment sites. We intend to recruit up to 83 subjects to achieve a post-attrition sample size of 75. This attrition estimate is based on past experience. In previous treatment studies involving TMS (e.g., 76) and tDCS (119) we have had very low attrition; we attribute this to the fact that PWA are often very motivated by the opportunity to participate in a study with potential benefit.

Subjects (or will be allocated to TMS and CILT and sham TMS and CILT in a 2:1 ratio. Assuming a type I error rate of α=0.05, we will have 80% power to detect a difference in mean change of 0.7 standard deviation units based on a two-sample t-test at 6 months. A 2:1 ratio was selected to provide more information about outcomes among patients randomized to TMS+CILT and as an incentive to recruitment since prospective participants are more likely to enroll in sham-controlled trials when the probability of receiving active treatment is greater. Efficiency loss associated with unequal allocation is minimal, amounting to an additional 6 participants required relative to 1:1 randomization for our design. Maher et al. (unpublished) report a standard deviation of change in the WAB AQ of 5.7 points in groups treated with Constraint Induced Language Therapy (see below). Assuming that our patients are similar, we are powered to detect a difference of 4 points in mean change in the WAB AQ between TMS+CILT and sham TMS+CILT arms. Note that our assumed effect size of 0.7 is conservative; Ren et al. (103) reported a Standard Difference of Means (a measure of effect size) of 1.26 for the general measure of severity of impairment (e.g., BDAE, Aachen Aphasia Test) based on a meta-analysis of 5 trials including a total of 96 subjects in which rTMS was compared to sham rTMS. The statistical analyses employ methods for longitudinal data in which 3 and 6 month assessments are considered simultaneously, thereby providing additional power to detect smaller effects.

8.3.1 AD Sub-Study Sample Size and Power Determination

Given the time and budget constraints that characterize a supplement, we propose to recruit to achieve an ultimate sample size of 30; given our historical attrition rate, we expect attrition of approximately 15%. The 30 subjects will be allocated to TMS + SLT and sham TMS + SLT in a 2:1 ratio, as this will provide more information about the effects of TMS and SLT and will serve as an incentive to recruitment. As noted above, loss of efficiency associated with unequal allocation is minimal relative to a 1:1 randomization for our design.

We have no preliminary data on the basis of which to calculate power. We note, however, that the meta analysis of Chen et al. (152) found a “moderate” effect size for TMS treatment for cognitive function in subjects with AD. We also note that Lee et al. (164) found a significant group effect favoring the TMS group in a study of 27 subjects with mild-moderate AD treated for impaired cognition with TMS or sham TMS and randomized in a 2:1 ratio. This project will permit us to determine an effect size that will inform sample determination for future trials.

8.4 Statistical Methods

8.4.1 Statistical Analysis of Primary Outcomes

Prior to analysis, the presence of outliers will be determined by examining descriptive statistics and graphical summaries of primary and secondary outcomes. As noted, the primary end-point will be the change in WAB AQ from the baseline for the treatment and sham groups. An intent-to-treat analysis will be performed using Linear Mixed Models for repeated-measures outcomes using outcomes at 3 and 6 months simultaneously. LMM is a regression-based approach that is suitable for repeated assessments, unlike generalized linear model regression. Additionally, unlike ANOVA, it is robust to missing data under the missing at random (MAR) assumption and sphericity assumptions. The primary outcome model will include change from baseline on the WAB AQ as the response and intervention, assessment end-point, and the interaction of intervention and end-point as fixed effects. The model will also include the baseline WAB AQ score as a predictor to increase efficiency and account for baseline imbalances in aphasia severity. A random intercept and end-point slope will be included to reflect between-subject heterogeneity in changes in WAB AQ scores. To examine possible bias in estimated intervention effects due to data missing not at random, sensitivity analyses, such as shared parameter and pattern mixture models, will be used. Secondary analyses will adjust for covariates that are imbalanced between intervention arms as well as demographic and clinical variables such as age, history of depression, lesion size, aphasia type, gender, and aphasia severity. In an exploratory analysis, we will evaluate whether there is a direct treatment effect on the WAB AQ that is not mediated by changes in response to CILT stimuli by further adjusting our primary outcome model for changes in CILT stimuli (67).

The statistical modeling of the secondary outcome (PNT) will involve similar analyses, but with items and participants modeled as random effects. Item-level response types will be analyzed separately (e.g., correct vs. incorrect; semantic error versus other response, etc.) to allow for determination of intervention effects specific to response type.

8.4.2 Identifying Predictors of Treatment Response

As in our primary analyses, we will use Linear Mixed Modeling (LMM) to identify the strongest clinical/linguistic predictors of response to TMS+CILT as compared to sham TMS+CILT from among variables like chronicity, severity, gender, depression severity, naming accuracy, apraxia of speech, core semantics, and sentence processing. Although we will be underpowered for formal tests of interaction given our moderate sample size, we will refit our primary endpoint model by adding interactions of the intervention indicator and potential predictors of response to therapy to see which are suggestive of differential intervention effects. We expect that these analyses will illuminate the clinical/linguistic predictors of treatment response, thereby defining the ideal “target population” for a future Phase 3 clinical trial.

Network Neuroscience measures of response to TMS+SLT

Subjects who can undergo MRI will have studies obtained prior to treatment and at 6 months after the completion of TMS. We will construct brain networks for each individual based on their baseline and post treatment BOLD fMRI data. We will use both the AAL (132) and Glasser et al. (40) parcellations and subject-specific lesion masks to exclude lesioned areas prior to atlas registration within each subject. Then, we will extract time series data from each region following modern preprocessing practices designed to reduce the influence of motion on BOLD time series (24). Across all pairs of region time series, we will compute wavelet coherence, which is well-suited for non-stationary data such as BOLD fMRI (128), to construct an adjacency matrix A that represents the pairwise coherence across all regions within the frequency band 0.01 to 0.10 Hz,

which is robust to physiological noise and evinces reliable functional network organization (44). We will constrain our analysis to the functional connections observed among regions identified to be involved in language processing (34) and their homotopic regions. Within each subject, we will compute a within-subjects t-test for elements (connections) in A_3 (final timepoint) versus A_1 (baseline) in the language and homotopic systems corrected for multiple corrections using a false discovery rate correction with a nominal corrected p-value of 0.05. This will allow us to detect the connections most modified by treatment and determine whether mechanism 1, 2, or 3 is supported.

8.4.3 AD Sub-Study Network Neuroscience

Subjects who can undergo MRI will have scans obtained prior to treatment and at 6 months after the completion of TMS. All other details are as stated above, however, subject-specific lesion masks will not be relevant.

8.1.4 Safety Analysis

All data on any and all adverse events occurring during the baseline testing, 2 week period in which TMS is being administered, and the 6-month interval between the end of TMS and completion of the study will be used for an overall study safety analysis.

8.5 Subject Population(s) for Analysis

The subject population that will be subject to analysis will be the randomized population. Subjects that are non-compliant with treatment will be encouraged to continue with follow-up and these measurements will be enter into analysis (see 8.4.1 for details on the analysis of non-compliant subjects)

9 Safety and Adverse Events

9.1 Definitions

9.1.1 Adverse Event

An **adverse event** (AE) is any symptom, sign, illness or experience that develops or worsens in severity during the course of the study. Inter-current illnesses or injuries should be regarded as adverse events. Abnormal results of diagnostic procedures are considered to be adverse events if the abnormality:

- results in study withdrawal
- is associated with a serious adverse event
- is associated with clinical signs or symptoms
- leads to additional treatment or to further diagnostic tests
- is considered by the investigator to be of clinical significance

9.1.2 Serious Adverse Event

Adverse events are classified as serious or non-serious. A **serious adverse event** is any AE that is:

- fatal
- life-threatening
- requires or prolongs hospital stay
- results in persistent or significant disability or incapacity
- an important medical event

9.2 Recording of Adverse Events

At each contact with the patient, the investigator will seek information on adverse events by specific questioning and, as appropriate, by examination. Information on all adverse events will be recorded immediately in the source document, and also in the appropriate adverse event module of the case report form (CRF). All clearly related signs, symptoms, and abnormal diagnostic procedures results will be recorded in the source document.

All adverse events occurring during the study period will be recorded. The clinical course of each event will be followed until resolution, stabilization, or until it has been determined that the study treatment or participation is not the cause. Serious adverse events that are still ongoing at the end of the study period will be followed up to determine the final outcome. Any serious adverse event that occurs after the study period and is considered to be possibly related to the study treatment or study participation will be recorded and reported immediately to the chair of the DSMB.

9.3 Relationship of AE to Study

The relationship of each adverse event to the study procedures will be determined by the PI, who is a neurologist. Based on his expertise with TMS, he will make a determination about the relationship of the adverse event to the study procedures.

9.4 Reporting of Adverse Events, Adverse Device Effects and Unanticipated Problems

9.4.1 Follow-up report

If an SAE has not resolved at the time of the initial report and new information arises that changes the investigator's assessment of the event, a follow-up report including all relevant new or reassessed information (e.g., concomitant medication, medical history) should be submitted to the IRB. The investigator is responsible for ensuring that all SAEs are followed until either resolved or stable.

9.4.2 Investigator reporting: notifying the study sponsor

A serious adverse event will be reported to the IRB and chair of the DSMB by telephone within 24 hours of the event. A Serious Adverse Event (SAE) form will be completed by the investigator and faxed to the IRB within 24 hours. The investigator will keep a copy of this SAE form on file at the study site.

At the time of the initial report, the following information should be provided:

- Study identifier
- Study Center
- Subject number
- A description of the event
- Date of onset
- Current status
- Whether study treatment was discontinued
- The reason why the event is classified as serious
- Investigator assessment of the association between the event and study treatment

Within the following 48 hours, the investigator will provide further information on the serious adverse event in the form of a written narrative. This will include a copy of the completed Serious Adverse Event form, and any other diagnostic information that will assist the understanding of the event. Significant new information on ongoing serious adverse events will be provided promptly to the IRB and chair of the DSMB.

9.4.3 Investigator Reporting: Notifying the Penn IRB

Reports of all serious adverse events (including follow-up information) will be submitted to the IRB within 10 working days. Copies of each report and documentation of DSMB/IRB notification and receipt will be kept in the Clinical Investigator's binder.

9.5 Unblinding Procedures

Patients will be told which treatment (real TMS+CILT vs. sham TMS+CILT) they received at the completion of the entire study. If a serious adverse event should occur, the patient will be unblendedunblinded.

9.6 Stopping Rules

The trial may be stopped for safety concerns or poor study performance, including failure to recruit and/or retain subjects. Subjects who report significant discomfort from TMS, seizure, or worsening of language or cognition during TMS will remain in the study with treatment discontinuation. Two sources of information about short-term adverse effects of TMS on language function will be available. First, subjects and family will be asked if they see evidence of deterioration in language or other faculties each day they return for TMS. Second, the SLP will see the subject during each treatment session. S/he will be instructed to inform the PI if s/he observes a clinically significant worsening in language function. If the SLP is concerned, the WAB will be repeated. If this supports a decline from baseline (operationally defined as more than 5 points below baseline), the adverse effect will be reported and the subject will be withdrawn from treatment. In order to support the intention-to-treat analysis, all such subjects will be strongly encouraged to continue follow-up.

9.7 Medical Monitoring

It is the responsibility of the Principal Investigator to oversee the safety of the study. 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. Medical monitoring will include a regular assessment of the number and type of serious adverse events.

9.7.1 Data and Safety Monitoring Plan

A committee of three investigators with experience with non-invasive brain stimulation will serve as the Data and Safety Monitoring Committee. The DSMB will meet with the PI every 6 months to review study progress and discuss any adverse events. The BAC group, under the guidance of the faculty statisticians, will provide safety reports every six months to this monitor and the PI. These reports will be blinded as to treatment assignment, unless unblinding for individual events is requested by the monitor. All SAEs will also be reported to the IRB.

10 Study Administration, Data Handling and Record Keeping

10.1 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
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI.

PHI (see below) as well as data from the studies to be performed during the study will be kept in an institutionally secured server or in a locked cabinet.

The following protected health information (PHI) will be collected: name, age, contact information (including telephone number), PMH (including information regarding the participant's stroke), SSN, as well as demographic information and results of neuroimaging.

Dr. Coslett and the research team conducting the study will have access to the subject's PHI as well as data generated during the study. Information contained in publications and presentations will be de-identified. The Institutional Review Board (IRB) as well as the FDA and NIDCD may access information regarding participants should they desire. Although we will strive to protect the privacy of participants, we cannot guarantee absolute privacy.

Subjects will be contacted by the PI to determine if they are interested in participating in the study. Subjects will be referred from multiple sources including colleagues at MossRehab Research Institute, Temple University, and UPHS physicians. Only subjects who have indicated their willingness to consider participating in the study or learn about the study will be contacted by the PI. Most potential subjects will be contacted by the PI who will use the phone script attached to this application.

Subjects will interact with the PI and other members of the research team in the process of obtaining consent, during the testing before and after the treatment as well as during the administration of TMS and CILT.

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.

10.2 Data Collection and Management

Source documents will be kept in a secure location. Paper-based records will be kept in a locked cabinet and will only be accessible to personnel involved in the study. Most of the information will take the form of computer files; these will be de-identified by using a coding process under which subjects are identified by an assigned subject number. These files will be stored on an institutionally secured and managed device or server. Participants will be voice and video recorded during baseline testing, CIILT treatment, and follow-up testing for the purposes of data analysis. Audio recordings will be transcribed and be saved on password-protected computers. Video recordings will be stored in an encrypted drive to be

used by the study team for data coding and data analysis. All audio and video data will be stored on School of Medicine managed and secured computer devices.

10.3 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.

11 Study Monitoring, Auditing, and Inspecting

11.1 Study Monitoring Plan

As noted above, a DSMB consisting of 3 members will be established and will meet with the PI every 6 months

11.2 Auditing and Inspecting

The investigator will permit study-related monitoring, audits, and inspections by the 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.

12 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 the IRB in agreement with local legal prescriptions, for formal approval of the study conduct. The decision of the 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.

All patients for this study will be provided a consent form describing this study and providing sufficient information for patients to make an informed decision about their participation in this study. This consent form will be submitted with the protocol for review and approval by the IRB for the study. The formal consent of a patient, using the IRB-approved consent form, will be obtained before that patient is submitted to any study procedure. This consent form will be signed by the patient or legally acceptable surrogate, and the investigator-designated research professional obtaining the consent.

12.1 Risks

12.1.1 Potential Risks

Potential risks of the behavioral and motor tasks are minimal and easily addressed (see below). The major risk associated with genetic testing is a loss of confidentiality.

There are well-known but rarely encountered risks from brain imaging with MRI and CT, or standard X-Ray exams. For the former, the risks include contrast administration (not relevant here), dislodging a metal object in the patient, interfering with an implanted device (e.g., pacemaker) and moving metallic objects in the scanner room. Protocols to deal with these issues are described below. The major risk from CT or X-rays is exposure to small amounts of ionizing radiation.

A variety of potential risks from repetitive TMS, including daily TMS administrations, have been identified (see 106 for a recent review); these include the following:

1. Seizures: Seizure induction represents the most serious known risk of TMS. The risk of seizures is quite low in subjects receiving single pulse TMS. Based on an extensive review of the literature, guidelines have been developed that specify the number of stimulations that may safely be given as a function of stimulus intensity (% of Motor Evoked Potential) and frequency of stimulation (138; see also Rossi et al, 2009). Using these guidelines there have been no published reports of seizures or evidence of after-discharge or spread of excitation in normal subjects receiving low-frequency repetitive TMS. We will adhere to the published guidelines.

It is plausible that a TMS-induced seizure could adversely affect a patient's ability to obtain health insurance, obtain or retain a driver's license, or obtain or retain employment. For example, physicians in the state of Pennsylvania are required to report patients who have experienced seizures to the Department of Transportation. Because seizures induced by TMS are considered to be provoked single events that do not convey an additional risk of developing epilepsy, patients who have a seizure due to TMS would presumably be considered exempt from the restrictions on driving that the Department of Transportation sometimes enforces on other seizure patients. If such a problem were to arise, Dr. Coslett or Hamilton would contact the appropriate institutions, explain the circumstances under which the patient experienced a provoked seizure, and express our professional opinion that a single TMS-induced seizure does not put a patient at significantly higher risk for spontaneous future events. Patients will also be provided with a letter stating that their seizure was experimentally induced. We cannot, however, guarantee patients that our advocacy on their behalf will convince employers, insurers, or other organizations that they are not at risk for future seizures.

2. Effects on Cognition: A number of studies have attempted to identify adverse neuropsychological consequences of TMS. Several such studies demonstrated a trend for performance to be better on cognitive measures after TMS (see 43). Two studies demonstrated minor adverse effects of TMS lasting up to one hour (Greenberg et al [cited in 128]; 36). Both studies, however, employed involved rapid repetitive TMS with stimulus parameters that would no longer be considered acceptable in light of current guidelines.

3. Effects on Mood: Dysphoria with crying has been induced after left prefrontal stimulation (92). In contrast, high frequency stimulation of right prefrontal cortex may transiently improve mood. TMS has been shown to be a safe and effective treatment in patients with depression that was unresponsive to other types of treatment. There are no reports of lasting changes of mood after single pulse or low frequencyTMS.

4. Effects on Hearing and Tinnitus: Animals have shown permanent increases of the auditory threshold after single pulse TMS (28) and humans have shown transient increases. Foam earplugs were effective in avoiding changes in the auditory threshold in a safety study of TMS (94). There has been one report of a subject who reported permanent hearing loss from TMS after a study in which his foam earplug became dislodged (142). In response to this, we altered our Informed Consent Form to list this as a possible adverse effect and stress to subjects that they should notify the investigators so that the study can be halted if an earplug becomes loose of dislodged. We will also stop stimulation at the 10 minute mark to check that the earplugs are

securely in place. We have routinely used foam earplugs in our investigations and have had no complaints regarding hearing loss. Pascual-Leone (personal communication) noted that tinnitus increased in one subject who received TMS to the dorsolateral prefrontal cortex and that tinnitus recurred in a second subject after a three-year absence with stimulation to the same location. Because of these concerns, no subject with tinnitus will be included in the investigations.

5. Scalp Burns: Rapid rate and high stimulus intensity TMS may cause the coil to heat resulting in scalp burns. The MagVenture stimulator that we use incorporates a temperature sensor in the coil and will cease operation should the coil exceed 140°. An air-cooled coil is used in our lab for TMS studies.

6. Neck Pain and Headache: Head and neck pain related to stimulation of underlying muscle and nerves occurs in approximately 10% of subjects. The incidence and severity is a function of stimulus site and intensity but is most common over fronto-temporal regions. The symptoms are self-limited and usually treated with minor analgesics.

7. Histotoxicity: Studies from animals as well as study of subsequently resected anterior temporal lobes of humans subjected to direct cortical stimulation or TMS have failed to demonstrate evidence of histotoxicity. For reasons reviewed by Wasserman (139), there appears to be very little likelihood of this.

8. Kindling: Kindling is a process by which repeated administration of an initially subconvulsive stimulus results in a progressive intensification of induced neuroelectrical activity resulting in a seizure. This has not been reported with TMS and appears unlikely for several reasons. Kindling is most readily obtained with high rate repetitive stimulation (e.g., 60 Hz), requires pulse duration of 1 ms (longer than that of TMS) and is easiest to produce in the amygdala and hippocampus. Kindling of neocortex in animal models of epilepsy is very difficult to achieve. There is no evidence that kindling can be produced by TMS.

9. Exposure to Magnetic Fields: The maximal field strength generated by commercially available stimulators such as the MagVenture machine to be used in our lab is in the 2 Tesla range. The field is induced for a brief period only and the strength of the field falls off rapidly with distance from the coil. There is no evidence of adverse effects from magnetic field exposure during TMS.

As the proposed studies involve TMS to subjects with brain lesions it is important to note that TMS has been used extensively in subjects with brain pathology since the 1990s (e.g., 26). Significant adverse effects in subjects with stroke are rare. For example, Hoyer and Celnik (53) reviewed studies in which TMS was administered to either the lesioned (13 studies) or contralesional (12 studies) hemisphere for treatment of hemiparesis. No significant adverse effects were reported in these studies; in many of the studies (e.g., 61), TMS was administered with high frequency stimulation over the lesioned hemisphere, a procedure that is generally considered to be more likely to be associated with adverse effects than the 1 Hz stimulation we propose.

Also of relevance is that rTMS has been administered for the treatment of aphasia to over 250 subjects in more than 20 studies, including studies done at Penn by our group; while most studies involved 1 Hz stimulation over the contralesional hemisphere (as we will be doing), several studies employed more aggressive procedures such as high frequency repetitive stimulation over the lesioned hemisphere (e.g., 62; 126). No significant side-effects were reported in any of the studies, including studies where TMS was administered in 10 daily sessions; furthermore, there is no report of an aphasic subject withdrawing from a study because of adverse effects. Thus, on the basis of data reported to date, we believe that the procedures to be employed in this study are safe in subjects with stroke and aphasia.

Under the AD Sub-Study, the decision to stimulate at 10 Hz is motivated by the fact that several studies demonstrating benefit on the ADAS-Cog in subjects with AD employed this frequency (e.g., 149, 150, 164, 170, 171). We note that the stimulation parameters that we

propose are within the guidelines proposed by Rossi et al. (106). Rapid repetitive TMS of the type that we propose to employ has been used in at least 11 studies with subjects with Alzheimer Disease; no seizures or other major adverse events have been reported.

Finally, we note that TMS with normal subjects and subjects with stroke (e.g., protocol #826841) has been considered to be non-significant risk at Penn.

12.1.2 Adequacy of Protection Against Risks

Behavioral and Motor Tasks: To protect against fatigue subjects will be permitted to rest or discontinue testing at any time. Should subjects appear to be made anxious by the tasks, testing will be terminated. Subjects will be told that they are free to withdraw from the testing at any time. The PI is not aware of any significant adverse effect from behavioral or motor testing of the type proposed in more than 30 years of work with brain-lesion subjects.

Genetic Testing: See the above "Genetic Testing" section

Brain Imaging: No contrast agents will be administered. The major risk from MRI is that the strong magnetic field will dislodge a metallic object inside the subject's body (e.g., aneurysm clip) or interfere with an implanted device (e.g., cardiac pacemaker). Standard protocols have been developed at the University of Pennsylvania to ensure that subjects at risk do not undergo an MRI scan. This protocol includes an extensive checklist that is completed by the subject or family member; additionally, the MRI technician interviews subjects prior to entering the MRI suite. A second potential concern comes from loose metallic objects in the MRI suite that can serve as missiles if they are drawn to a powerful magnet. Metallic objects that are not secured to the floor or wall are not permitted in the MRI suite. We note that these procedures have been employed in the clinical and research settings at the University of Pennsylvania for many years; no adverse effects from MRI scanning have been experienced to date. Subjects who are or think they might be pregnant will be excluded because the safety of MRI in pregnancy has not been established. The major risk from CAT scan is a small dose of ionizing radiation. This procedure has been approved by the Penn IRB and subjects will be asked to sign a consent form in which the potential risks are discussed.

TMS: The following steps will be taken to minimize risks from TMS identified above.

1. We will use train durations and stimulus intensities that fall within the guidelines recommended by the NIH consensus meeting (see 127).
2. Subjects will be monitored during and after TMS stimulation for involuntary movements that could represent focal motor seizures. Should suspicious motor activity be observed or a change in level of responsiveness occur, the session will be terminated and the subject withdrawn from the study.
3. A physician will be available by phone during all site-finding and whenever TMS is being delivered.
4. All subjects will wear foam earplugs during testing sessions.
5. In the unlikely event that a seizure is observed, the subject will be evaluated by a physician within minutes. In the entire experience with TMS throughout the world, we are unaware of any reports if seizures that were not self-limited; because of this we do not anticipate giving medications. In the event of a seizure, subjects will be asked to undergo an EEG and a MRI scan and may be asked to stay in the hospital overnight for observation.

12.2 Benefits

The objective of the study is to determine if TMS paired with CILT improves chronic aphasia; subjects randomized to the TMS+CILT treatment group may benefit from the treatment. We note that the study is also potentially of benefit to those who randomize to the sham TMS+CILT group as they will receive two weeks of CILT, an accepted form of speech therapy for which there is evidence of efficacy. The study is also of potential benefit to other subjects with chronic aphasia as it may identify an effective therapy for this disabling condition.

12.3 AD Sub-Study Benefits

The objective of the sub-study is to determine if TMS paired with CILT improves verbal communication in AD; subjects randomized to the TMS+CILT treatment group may benefit from the treatment. We note that the study is also potentially of benefit to those who randomize to the sham TMS+CILT group as they will receive two weeks of CILT, an accepted form of speech therapy for which there is evidence of efficacy. The study is also of potential benefit to other subjects with AD as it may identify an effective therapy for impaired verbal communication.

12.4 Risk Benefit Assessment

We believe that the investigations are likely to demonstrate that TMS in conjunction with CILT is beneficial for the treatment of chronic aphasia. The studies, therefore, are important as they are likely to provide evidence of efficacy for a new approach to the treatment of chronic aphasia. We believe that the potential scientific and clinical value of the information to be obtained justifies the small risk of the investigations.

12.5 AD Sub-Study Risk Benefit Assessment

We believe that the investigations are likely to demonstrate that TMS in conjunction with CILT is beneficial for the treatment of impaired verbal communication in AD. The sub-study, therefore, is important as it is likely to provide evidence of efficacy for a new approach to the treatment of impaired verbal communication in AD. We believe that the potential scientific and clinical value of the information to be obtained justifies the small risk of the investigations.

12.6 Informed Consent Process / HIPAA Authorization

All subjects will be provided a consent form describing the study providing sufficient information for subjects to make an informed decision about their participation in this study. The nature and goals of the proposed research will be explained to the subjects and, as appropriate, to their families. The formal consent of a subject, using the IRB-approved consent form, must be obtained before that subject undergoes any study procedure. The subject must sign the consent form to participate. The Principal Investigator or study staff obtaining consent will additionally sign the form. Subjects will be consented by the study Principal Investigator, or appropriate designee, in a room we have selected in which to perform consent, which is located outside of the clinic. Potential subjects will review the consent form in detail with the person designated to consent and have the ability to take the consent home for further review. We note that the PI has worked with subjects with aphasia for more than 30 years and has extensive experience assessing the capacity of subjects with aphasia to provide and obtaining informed consent.

Since potential subjects will be recruited by phone, email or letter, and PHI will necessarily be collected to conduct screening, we will be using a verbal consent script which will be completed before any PHI is collected.

To reduce the burden of in-person visits during COVID-19, as well as for potential participants for whom travel for single visits is burdensome, we will conduct informed remote consent via

Bluejeans. The consent form will be provided through RedCAP survey webpage, and may also be shared as a pdf. The video call will involve identification of the participants of the call, and then will move into a full review of the IRB-approved consent form by either the Principal Investigator or study staff. The Principal Investigator will confirm that the participant is informed and willing to participate. The participant will then provide an e-signature via RedCAP; the document will then also be e-signed by the Principal Investigator or the study staff.

13 Study Finances

13.1 Funding Source

This study will be funded through a grant obtained from the US National Institutes of Health (1R01 DC016800-A1).

13.2 Conflict of Interest

All University of Pennsylvania Investigators will follow the University of Pennsylvania Policy on Conflicts of Interest Related to Research.

13.3 Subject Stipends or Payments

Subjects will be reimbursed for their time at a rate of $15/hour and their transportation costs will be paid, up to $50 per visit.

14 Publication Plan

Results of the study will be published by the PI and colleagues in peer-reviewed journals.

15 References

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16 Attachments

- Sample Consent Form
- Study Procedures Flowchart/Table
- CILT Manual

17 Appendix

17.1 Magventure MagPro Manual