TITLE:	Investigating the Use of Transcranial Magnetic Stimulation (TMS) for Primary Progressive Apraxia of Speech (PPAOS)
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INSTRUCTIONS:

1) **Protocol Title**

Investigating the Use of Transcranial Magnetic Stimulation (TMS) for Primary Progressive Apraxia of Speech (PPAOS)

2) **IRB Review History***

None

3) **Objectives***

The purpose of this study is to explore the extent to which TMS can improve speech in patients with PPAOS.

We hypothesize that the use of TMS will improve AOS measures on the AOS rating scale.

4) **Background***

Apraxia of speech (AOS) is a motor speech disorder affecting the programming of motor speech production. It is characterized by the impaired ability to coordinate the sequential, articulatory movements necessary to produce speech sound. AOS can result from left hemisphere stroke; however AOS can also occur as a primary speech disorder, usually associated with neurodegenerative disease. When AOS is the only sign or symptom of a neurodegenerative condition, it is called primary progressive AOS (PPAOS). The anatomical localization of PPAOS is thought to be primarily the the left superior motor and supplementary motor cortex as seen in prior studies by hypometabolism in Fluorodeoxyglucose positron emission tomography (FDG-PET), and patterns of atrophy on MRI (Josephs et al. 2006, Josephs et al. 2012, Whitwell et al. 2013). Another study identified the left premotor and motor cortices as common areas of infarct in stroke patients presenting with AOS without associated aphasia (Graff-Radford et al. 2014)

When AOS is related to stroke, linguistic rehabilitation has shown to be beneficial to improve language performance. However, there is limited benefit of linguistic rehabilitation in patients with PPAOS or AOS related to primary progressive aphasia (PPA). In many neurological diseases including primary progressive aphasia, the activity of certain brain areas has been shown to be altered. In these cases, individuals have experienced improvements in motor and cognitive symptoms when non-invasive brain stimulation was applied to restore balance in the brain (Finocchiaro et al 2006, Cotelli et al. 2012, Trebbastoni et al. 2013, Wang et al. 2013, Tsapkini et al. 2014, Gervits et al. 2016, Teichman et al. 2016). Trancranial Magnetic Stimulation (TMS) is perhaps the most common form of neurostimulation technique. In a non-invasive manner, it utilizes magnetic energy to induce very mild electrical currents in the brain, which can be used to evaluate the activity level of a specific brain area, or to alter the activity area of a specific brain area transiently.

To date, there is only one case report examining the role of TMS in language performance in PPAOS in a patient with an underlying diagnosis of progressive supranuclear palsy (PSP) who also presented with primary progressive nonfluent aphasia (PPNFA) (Spagnolo 2013). After 14 sessions of TMS targeting the left Broca/dorsolateral prefrontal cortex and bilateral prefrontal cortices over a 4-week period, the patient was noted to have increased metabolism on FDG-PET in the left posterior cingulate and left inferior frontal gyrus one day after treatment along with improvement in several cognitive domains on neuropsychological testing. There have been several other reports in the literature suggesting benefit of TMS in patients with primary progressive aphasias (Finocchiaro et al 2006; Cotelli et al. 2012; Trebbastoni et al. 2013,) Based on these previous studies, we believe there may be a role for TMS in improving speech output in patients with PPAOS.

5) Inclusion and Exclusion Criteria*

Patients will be recruited from the Neurology clinic at the University of Miami.

Inclusion Criteria

- Adults ages 18 and above who are able to consent or have a proxy who is willing to consent on their behalf
- Diagnosis of primary progressive apraxia of speech based on neurological evaluation

Exclusion Criteria

- Any uncontrolled medical condition expected to limit life expectancy or interfere with participation in the trial (i.e. unstable cancer, severe depression or anxiety by DSM-IV criteria)
- Abnormal stress test, as determined by the treating physician (unless cardiology clearance provided)
- Active substance abuse or alcohol dependence
- Uncorrected vision or hearing deficits that would preclude administration of the cognitive measures
- Unwilling or unable to provide written informed consent and do not have an appropriate proxy who is able to provide consent on their behalf
- History of fainting spells of unknown or undetermined etiology that might constitute seizures
- History of seizures, diagnosis of epilepsy, history of abnormal (epileptiform) EEG or family history of treatment resistant epilepsy
- No medication is an absolute exclusion from TMS. Medications will be reviewed by the responsible MD and a decision about inclusion will be made based on the following:

- The subject's past medical history, drug dose, history of recent medication changes or duration of treatment, and combination with other CNS active drugs.
- The published TMS guidelines review medications to be considered with TMS

- Any metal in the brain, skull or elsewhere unless approved by the responsible MD
- Any medical devices (i.e. Cardiac pacemaker, deep brain stimulator, medication infusion pump, cochlear implant, vagal nerve stimulator) unless otherwise approved by the responsible MD
- Substance abuse or dependence within the past six months
- Absence of corticospinal functional integrity
- Inability to provide informed consent or have an appropriate proxy provide consent on their behalf
- Age younger than 18 years
- Pregnancy
- Prisoners

6) Number of Subjects*

This is a single center study with 10 planned subjects.

7) Study Timelines*

After having a potential research participant has been identified, we will call him/her to discuss the study and determine both eligibility and interest in participating in the study. Participants will undergo TMS safety screening to ensure that they are eligible to participate, following the TMS Safety Guidelines (Rossi et al. 2009). Participation will involve a pre-study fMRI scan to identify a target for TMS application, and pre-study neuropsychological testing. The proposed timeline of TMS will be 10 sessions over a 2-week period, followed by a second, post-TMS neuropsychological testing session to assess for improvement. Patients who do not have significant benefit or change in symptoms after the first 10 sessions of rTMS may be offered an additional 10 sessions where the brain region being targeted will be changed based on fMRI data and the investigators' clinical impression. We will then plan to follow up with patients at 1 month to assess duration of effects of the treatment. The patients will be re-scored using the Apraxia of Speech Rating Scale and will undergo a second neuropsychological testing battery. We will also identify any post-treatment adverse effects during this visit.

8) Study Endpoints*

The primary study endpoint will be improvement on the language performance measured by neuropsychological testing and the Apraxia of Speech Rating Scale (a tool designed to measure the presence and severity of apraxia of speech that uses a 5-point rating scale to assess 16 items (see attached material, [Strand et al.

2014]).We will also look at global activity levels of the brain utilizing single-pulses pre- and post- TMS.

9) Procedures Involved*

Participants will undergo a pre-test assessment (consisting of neuropsychological performance and will be scored using the Apraxia of Speech Rating Scale). Following this visit, participants will receive 10 sessions of repetitive TMS in a 4 week period. After that, participants will undergo a post-test assessment in which they will be rescored using the Apraxia of Speech Rating scale and reassessed on neuropsychological testing. We will collect this information, along with demographic and basic medical information (age, gender, race, handedness, education level, and medical comorbidities) from the participants' medical records. This information will be important for reporting results (demographic information), scoring the neuropsychological testing (education level), and in determining eligibility to undergo TMS (medical comorbidities).

Single Pulse TMS

Prior to and following each TMS visit, a pre TMS side effects questionnaire will be performed..

We will use the TMS machine to assess the global activity levels of the brain utilizing single-pulses and to set the parameters for the repetitive TMS. TMS will be delivered using a biphasic figure of eight coil. This stimulation phase will consist of 3 batches of 30 TMS pulses delivered every 5-7 seconds at 120% of resting motor threshold (RMT). This is the standard way of setting the parameters of the TMS. We define the RMT as the intensity at which 5 responses are obtained (about 50 μV) when we give 10 stimulation pulses.

Repetitive TMS

Repetitive TMS will be delivered at 90% of the resting motor threshold at 20 Hz (50 trains, 40 pulses with 28 second inter-train interval), which was based on parameters used in prior studies including one prior case report in which rTMS was previously used and reported to lead to improvements in speech in an individual with PPAOS (Spagnolo et al. 2013), and two studies in which rTMS was used in primary progressive aphasia, a similar condition in which the same target was stimulated (Cotelli et al. 2012, Antczak et al. 2018).

10) Data and Specimen Banking*

We will not plan to collect or bank any specimens with this study.

11) Data Management*

There is only one document that lists the individual's name and the subject number that will be assigned to him/her upon giving informed consent to participate in this

study. This document will be kept at the Principal Investigator's Office at 5915 Ponce de Leon Blvd, Coral Gables, FL, 33146. Data will be stored for a minimum of 3 years, and in accordance with University Policies thereafter. We would like to keep de-identified data, so that other studies may benefit from these after study completion. De-identified data will be stored at the Professional Arts Center (1150 NW 14th Street, Suite 602-B, Miami, FL 33136) and Clinical Research Building (1120 NW 14th Street 13th Floor, Miami, FL 33136). It will be kept in a locked cabinet, and the only people who will have access to this data are personnel approved by the IRB to work on this study.

12) Provisions to Monitor the Data to Ensure the Safety of Subjects*

Data monitoring

Only authorized personnel will have access to the data collected during the study. Participants' information will not be shared with any party without IRB-approval. Research data will not be released to the participants.

Data collection will be halted if the participant requests it. If this occurs, subject will be taken off the study and the reason of discontinuation will be documented. Data collected before will be kept by the investigator.

Monitoring the safety of participants with respect to TMS

TMS has been used in a growing number of laboratories worldwide since 1984. A series of adverse events have been identified since then, and have been thoroughly reviewed for the development of recommended safety guidelines and precautions for the use of TMS, first at a consensus conference at the NIH in June, 1996 and, more recently, in 2008 in Siena (Italy), in a meeting of an international panel of TMS experts (The Safety of TMS Consensus Group).

The principal investigator will ensure that these guidelines are well-known by all study investigators and will carefully follow these updated safety guidelines in the present study.

13) Withdrawal of Subjects*

As the greatest risk to subjects with TMS as documented in prior literature, is seizure, the development of a seizure during or immediately following TMS will be grounds for withdrawal from the study. Similarly, the development of a new risk factor for seizure during the study period will be grounds for withdrawal (including new stroke/structural brain lesion, central nervous system infection such as meningitis or encephalitis, or traumatic brain injury).

14) **Risks to Subjects***

Risks associated with TMS:

TMS has been used in a growing number of laboratories worldwide since 1984. A series of adverse events have been identified since then, and have been thoroughly reviewed for the development of recommended safety guidelines and precautions for the use of TMS, first at a consensus conference at the NIH in June, 1996 and, more recently, in 2008 in Siena (Italy), in a meeting of an international panel of TMS experts (Rossi et al. 2009). We will carefully follow these updated safety guidelines in the present study.

More Common

- Headaches and/or Neck Pain: Up to 20%-40% of subjects undergoing TMS experience headaches or neck pain, which are believed to be due to muscle tension. All prior cases of headaches induced by TMS have promptly resolved with a single dose of acetaminophen (Tylenol®) or a nonsteroidal anti-inflammatory drug (NSAID). In some cases TMS may cause facial discomfort on the same side of stimulation.

Rare

- Seizures: TMS can cause a seizure; however, this is an extremely rare problem. Repetitive TMS can induce a seizure even in the absence of pre-existing brain lesions, epilepsy, or other seizure risk factors, both in patients and healthy subjects. From the several thousands of studies that have used TMS to date, a total of 16 cases have been reported, of which 9 cases occurred after the 1998 safety guidelines. Based on the available data, the reported risk of seizures is less than 1 in 1000 for repetitive TMS. Additionally, TMS has been rarely associated with seizure-like events and syncope. Nevertheless, this is a very concerning complication and to make the subjects' risk as small as possible, the investigators will follow precautions that are recommended by the International Society for Transcranial Stimulation and mentioned in the 2008 updated safety guidelines of The Safety of TMS Consensus Group. Several investigators are neurologists, and at least one of them will be present during the TMS and able to run a rapid response and treat the patient in case of seizure.

- Hearing Problems: TMS produces a loud clicking sound when the current is passed through the stimulation coil. This loud click can result in concurrent ringing in the ear and short-term decreased hearing if no protection is used. In order to prevent this potential adverse effect subjects will be given earplugs. Animal and human studies have demonstrated that earplugs can effectively prevent the risk of hearing disturbance due to TMS. In order to inform and protect the subjects, we will take the following precautions:

- Inform subjects of the risk of permanent hearing loss, if an earplug should loosen, become detached, or fall out.
- Inform subjects that they should immediately report to the investigator any loosening or detachment of an earplug during TMS.
- Immediately stop TMS to replace earplugs if the subject reports or if an investigator observes that an earplug has loosened or has fallen out.
- Ask the subject if they are experiencing any hearing problems following every session of TMS
- Prompt referral for auditory assessment of all individuals who complain of hearing loss, tinnitus, or aural fullness following completion of TMS.

The risk of hearing loss with our TMS coil is very low with no reported incidence of transient or lasting problems using the methods outlined in this study.

- Syncope: Syncope can occur due to anxiety and psycho-physical discomfort during testing and treatment with TMS. This is reported less than seizure activity. Subjects will be monitored for feeling any signs or symptoms of a pending syncopal event (i.e. feeling dizzy or lightheaded). TMS will immediately be stopped and the subject will be assisted.

- Memory: TMS could induce short-term changes in memory, attention and other cognitive and mental functions. This is a rare risk, as safety studies conducted found these events to be rare and transient.

- Mood: Acute psychiatric effects have been described in patients receiving rTMS. Although single cases suggest a causal relationship between rTMS and mania, the overall rate (13 cases) across 53 randomized controlled studies (combined N=520) in depression appears to be low (0.84% mania for active rTMS vs. 0.73% for sham rTMS) and even below natural switch rates in patients with bipolar disorders receiving mood stabilizers (2.3–3.45%). Similarly, cases of rTMS induced psychotic symptoms, anxiety, agitation, suicidal ideation and insomnia, have been reported, but it is unknown whether these occur at higher rates compared to the natural course of disease being treated or associated with other interventionPsychotic symptoms and suicidal ideation have never been described in normal subjects during or after rTMS. Subjects with psychiatric problems will not be included in this study, so mood changes are not anticipated.

- Dental Pain: The possibility of dental pain during rTMS has been reported. This potential adverse effect of TMS would occur during the stimulus. We will encourage the participant to alert the study investigator should such discomfort occur. In that case, the stimulation session will be terminated immediately, and the participant will be encouraged to seek a dental evaluation. This is a very rare occurrence, but it may point to the presence of a

cavity that may require care. This adverse effect should not lead to any lasting problems or complications.

- Finally, even though TMS has been used in several laboratories worldwide since 1984, there could be some unforeseen complications, and the patients will be informed about this possibility.

Electromyography (EMG):
The sticky pads used for the test may cause skin irritation or redness. Taking the sticky pads off causes discomfort similar to when taking off a band-aid.

Breach of Confidentiality
There is also a risk of breach of confidentiality if personal health information gathered during the study is accessed by persons not involved in the study. To guard against this, information about study patients will be kept confidential and managed according to HIPAA requirements. Only persons involved in the study will be granted access to the information.

15) Potential Benefits to Subjects*

Based on prior case reports documenting improvement of language function with TMS in PPAOS primary progressive aphasias and post-stroke language disorders, we believe that there is a potential for TMS to improve speech function (as measured by neuropsychological testing and the Apraxia of Speech Rating Scale) in study participants with primary progressive apraxia of speech. This benefit is potentially better than benefits that they could expect to achieve with speech therapy alone (the current standard of care and only other available treatment available outside of a research protocol). However, given that this is a research study, we cannot guarantee any direct benefit.

16) Vulnerable Populations*

Cognitively-impaired adults will be able to participate in this study, provided that the participant has an appropriate proxy who is able to sign a consent form on his or her behalf. We will put in place specific plans to closely monitor these participants (outlined in detail under section 23).

17) Multi-Site Research*

We are not planning to include any additional sites in this study.

18) Community-Based Participatory Research*

We do not have plans for community involvement in the design of this study, at this time.

19) Sharing of Results with Subjects*

We will share the results of the fMRI study, neuropsychological testing, motor cortex excitability findings, and Apraxia of Speech Rating Scale scores with the patients at all follow up visits.

20) Setting

Describe the sites or locations where your research team will conduct the research.

Identification and recruitment of subjects, as well as all follow up visits will take place at the University of Miami Neurology Clinic in the Professional Arts Center building. The address is 1150 NW 14th Street, Miami, Florida 33136. TMS will be performed at the Neuromotor Plasticity Laboratory and neuropsychological testing will take place in the neuropsychological testing suite at the same address.

At this time, there are no plans for a community advisory board or research performed at any additional sites.

21) Resources Available

Dr. Joyce Gomes-Osman PhD, PT is a research neuroscientist with extensive experience in clinical research and non-invasive brain stimulation approaches, which include transcranial magnetic stimulation (TMS) and electroencephalography (EEG). Dr. Gomes-Osman is the Director of the Neuromotor Plasticity Laboratory, at the University of Miami Miller School of Medicine and has a publication record that include many studies utilizing non-invasive brain stimulation by means of transcranial magnetic stimulation and transcranial direct current stimulation to characterize the neurophysiology and induce neurostimulation (as a potential therapeutic approach) in individuals with neurologic impairments and healthy individuals. Dr. Gomes-Osman has expanded her knowledge in Neurology and non-invasive brain stimulation techniques during her postdoctoral fellowship with Dr. Alvaro Pascual-Leone, an internationally recognized leader in this field, at the Berenson-Allen Center for Non-Invasive Stimulation at Beth Israel Deaconess Medical Center at Harvard Medical School. She remains affiliated as a research scholar, and is currently conducting studies to investigate the effects of aerobic exercise on neuroplasticity and cognitive function in healthy individuals. In addition, she is a lecturer at the "Intensive Course in Transcranial Magnetic Stimulation", organized by this Center.

22) Prior Approvals

We will not need to obtain prior approvals prior to starting this study.

23) Recruitment Methods

Subjects will be recruited from the University of Miami Neurology clinic after having been identified by a neurologist in that practice as having the diagnosis of primary progressive apraxia of speech during regularly scheduled clinic appointments to receive care. When a potential patient is identified, the neurologist will discuss the study briefly with the patient and assess his/her interest in participating during the regularly scheduled clinic visit. If the patient is interested in learning more, the neurologist will forward the patient's name and contact information to the study investigators, who will contact the patient by phone to explain the study in more detail and determine if the patient is eligible to participate. There will not be any supplemental materials used to recruit subjects.

There are no plans for payments to subjects in exchange for participation in this study.

Recruitment of Cognitively Impaired Adults:

We will allow certain cognitively impaired subjects to participate in the study. If a potential subject is interested in participating, he/she must have an appropriate proxy who is willing and able to sign a proxy consent form on his/her behalf. Subjects will be evaluated for capacity to provide consent at the screening visit, which will be conducted by a board-certified neurologist. Assent will be obtained from all subjects. If he/she is capable, the subject will personally sign the written informed consent, documenting his/her assent. Based on the natural history of the underlying conditions associated with primary progressive apraxia of speech, we do not expect that the ability of the patient to provide consent will change during the course of the study. The details of the study will be discussed at the screening visit at a level compatible with the participant's understanding. Participants deemed to lack capacity to give consent for participation will be closely monitored at each visit for development of side effects or change in ability to provide consent, including questioning of the proxy, if necessary, to provide additional information. Participants will be withdrawn from the study if they appear to be unduly distressed by participation.

24) Local Number of Subjects

We will plan to recruit a total of 10 patients to participate in the study at the University of Miami.

25) Confidentiality

There is only one document that lists the individual's name and the subject number that will be assigned to him/her upon giving informed consent to participate in this study. This document will be kept at the Principal Investigator's Office at 5915 Ponce de Leon Blvd, Coral Gables, FL, 33146. Data will be stored for a minimum of 6 years following study closure, and in accordance with

University Policies thereafter. It will be kept in a locked cabinet, and the only people who will have access to this data are personnel approved by the IRB to work on this study.

26) Provisions to Protect the Privacy Interests of Subjects

Information about study patients will be kept confidential and managed according to HIPAA requirements. Regulations require a signed patient HIPAA Authorization informing the participant of the following:

- What protected health information (PHI) will be collected
- Who will have access to that information and why
- Who will use or disclose that information

If a participant withdraws consent or revokes authorization to collect or use PHI, following regulations, the investigator retains the ability to use all information collected prior to revocation of patient authorization.

27) Compensation for Research-Related Injury

By following the recommended safety guidelines and precautions for the use of TMS developed by an international panel of TMS experts (The Safety of TMS Consensus Group), we will carefully monitor any adverse effects that may arise and no not expect research-related injury to occur.. Individuals will be instructed to follow-up with their medical insurance in the event of an injury.

28) Economic Burden to Subjects

The subjects will be responsible for their own transportation to and from the study-related visits, and for parking costs related to the visits.

29) Consent Process

Patients will review a consent form with one of the primary investigators at the first visit, to ensure all questions are answers with regards to their participation in the study, and any potential risks. They will have the opportunity to ask additional questions at any of the visits, and can revoke consent to participate in the study at any time. We will plan to follow SOP: Informed Consent Process for Research (HRP-090).

Non-English Speaking Subjects

All patients must be fluent in English to participate in this study.

Children under the age of 18 will be excluded from this study.

30) Process to Document Consent in Writing

We will plan to obtain written consents of all patients participating in this study according to the SOP: Written Documentation of Consent (HRP-091).

31) Drugs or Devices

Device: Magpro X100, MagVenture Corporation, Farum, Denmark

- The Transcranial Magnetic Stimulator is the original device developed by the *Magstim Corporation* for the purpose of electromagnetic neural tissue stimulation in 1984. The devices consist of a bank of capacitors that can be charged up to a predetermined amount of energy and then quickly discharge via solid state switches into a coil of copper wire. This coil of copper wire is encased in plastic. As the current passes through the coil, a magnetic field is generated following Faraday Laws. This magnetic field will in turn induce a secondary current in any tissue with capabilities to conduct electricity that is placed in the proximity of the induced magnetic field. For the purpose of brain stimulation, the coil is held over the subject's head and as the current passes through it, i.e., a magnetic field is generated that penetrates the scalp and skull without being attenuated. This magnetic field induces a flux of current in the brain. This secondary current induced in the brain influences neuronal activity by virtue of mostly transsynaptic effects. The effects induced by the stimulation of the brain depend on the site of stimulation, since different areas of the brain control different functions. In addition, stimulation parameters such as focality of the magnetic field, stimulus intensity and stimulus frequency also condition the induced effects in the brain. The Transcranial Magnetic Stimulator has no electric contact with the patient or subject. There is no failure mode of the device that could result in the delivery of an excessive amount of stimulation intensity or number of stimuli given a circuit breaking safety device. Therefore, the device allows noninvasive stimulation of the human brain without the use of direct electrical contact between the device and the subject. In principle, this device provides the means of an electrodeless, noninvasive, and painless stimulation of the human brain. It is used in cognitive research and treatment of some neurologic and psychiatric conditions.

Support for non-significant risk device

The non-invasive brain stimulation device (TMS) utilized in the present study has been cleared by the FDA for the treatment of depression. There have been nearly 2,000 research studies published utilizing this technique, and the safety of this device has been established. The First International Safety Conference on Transcranial Magnetic Stimulation took place at the National Institutes of Health in Bethesda, MD, in June 1996.

Representatives of the Food and Drug Administration (FDA) were present at that meeting and they shared the consensus that the evidence accumulated over the

previous 10 years supports the safety of TMS. More recently in 2008, an international panel of TMS experts (The Safety of TMS Consensus Group) met for a consensus conference to review and update safety guidelines in TMS based upon review of published data (Rossi et al., 2009). The evidence reviewed by this group of experts in the field continues to support the safety of TMS with the application of recommended guidelines. In the present study, we are applying it for a different purpose and we will strictly follow the Safety Guidelines to TMS.

Storage and usage of device

- The Magpro X100 will be stored at the Department of Neurology Clinic located at 1150 NW 14th Street, Suite 609, Miami, FL 33136. The device will be used by the principal investigator, and only be used by other study investigators following adequate training.

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