Title: Treatment of Post-Chemotherapy Cognitive Impairment with Transcranial Magnetic Stimulation

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1) Background

"Chemo-brain" or Post-Chemotherapy Cognitive Impairment (PCCI) is defined as cognitive changes including impairment of memory, learning, concentration, reasoning, executive function, attention and visuovisio-spatial skills that occur during or after chemotherapy treatment (Argyriou, Assimakopoulos, Iconomou, Giannakopoulou, & Kalofonos, 2010). Additionally, anxiety and depression often co-exist with the cognitive symptoms and may be an inseparable component of the disease. The extent and duration of PCCI varies from transient, subtle manifestations to sustained, long-term cognitive effects that can have long-lasting impact on patient quality of life (Ahles & Saykin, 2007; Ahles et al., 2003; Cimprich et al., 2010; Dietrich, Monje, Wefel, & Meyers, 2008; Jacobsen et al., 2004; Vearncombe et al., 2009; Wefel et al., 2004). PCCI is also a heavy financial and social burden on our society (Artherholt & Fann, 2012; Boykoff, Moieni, & Subramanian, 2009; Lucas, 2010; Siegel et al., 2012; Wertheimer, 2010). Its cost is not only from consumption of resources for treatment of symptoms but also indirect costs from loss of productivity. With more patients surviving longer with cancer or beating cancer entirely, PCCI will become an ever important issue in cancer survivorship. There is no treatment, thus research into the understanding and treatment of PCCI need to keep pace with our continuously improving treatment of cancer and the side effects of therapy.

A number of studies have sought to better understand PCCI through imaging. Structural and functional imaging studies utilizing MRI and specialized PET imaging have shown alterations in brain tissue after systemic anti-cancer therapy. PET scanning with O-15 labeled water was acquired during performance of control and memory-related tasks in subjects treated 5-10 years previously with adjuvant chemotherapy with/without adjuvant Tamoxifen for breast cancer. Cerebral blood flow in regions of the frontal cortex and cerebellum was significantly altered in chemotherapy-treated subjects versus untreated subjects (Silverman et al., 2007). A study in breast cancer patients post chemotherapy that assessed brain gray matter density (GMD), a structural measure, by voxel-based morphometry using MRI in a prospective, longitudinal design found decreases in GMD in bilateral frontal, medial temporal and cerebellar regions at one month post completion of chemotherapy compared with baseline, with return to baseline levels in some but not all regions at one year after completion of chemotherapy. No changes were seen by MRI analysis in breast cancer patients not receiving chemotherapy or in healthy controls (McDonald, Conroy, Ahles, West, & Saykin, 2010). A prospective, longitudinal study utilizing functional MRI to assess cognitive task-related brain activation in breast cancer patients who did and did not receive chemotherapy reported frontal white matter hyper-

activation prior to receiving systemic adjuvant therapy compared to controls. Furthermore, chemotherapy-treated patients after completing chemotherapy were unable to maintain this hyper-activation, which the authors presumed were related to impairment of brain function due to chemotherapy (McDonald, Conroy, Ahles, West, & Saykin, 2012). Additionally, a multi-center trial in breast cancer found a potential link between elevated levels of cytokines IL-6 and IL-1 and PCCI {Cheung:2015kc}. These studies support a causal relationship between systemic therapy and PCCI.

Transcranial magnetic stimulation (TMS) is a painless and safe magnetic brain stimulation technique. Since its introduction about 30 years ago, more than 10,000 articles on TMS have been published. In clinical practice, a number of TMS devices and protocols have been approved by the FDA for the treatment of medication-refractory depression and migraine, as well as approved for pre-surgical motor and language mapping. Currently, TMS has been under investigation as a treatment tool in diverse disease states including Parkinson's disease, Alzheimer's disease, schizophrenia, stroke, epilepsy, autism, and tinnitus (for a review, see Miocinovic, Somayajula, Chitnis, & Vitek, 2013; Schulz, Gerloff, & Hummel, 2013). TMS is considered safe and well tolerated. It does not involve any form of general anesthesia or sedation (Tor and Mok 2016).

TMS was first introduced by Barker et al in 1985 (Barker, Jalinous, & Freeston, 1985). This neurostimulation technique is based on Faraday's principle of electromagnetic induction. More specifically, the TMS coil discharges quick (200-300μs), powerful (0.2-4.0 T) and focal magnetic pulses at the surface of the scalp, which creates a secondary electrical current that abruptly modulates the excitability of the underlying neurons and, thus, neural activity within specific regions of the brain (Tatti, Rossi, Innocenti, Rossi, & Santarnecchi, 2016). Notably, to provide a point of reference, the magnetic field generated by the TMS coil is analogous to those employed by conventional MRI scanners (1.5-3.0 T).

TMS has a number of different protocols. The repetitive TMS (rTMS) paradigm is one of the commonly used TMS protocols. It utilizes trains of pulses to induce cortical effects that outlast the stimulation duration. rTMS allows researchers and clinicians to induce long-lasting changes in cortical reactivity and plasticity. In 2008, the FDA approved the use of rTMS for treating medically refractory or treatment-resistant depression (FDA approval K061053). This FDA approval was finalized after a sham-controlled randomized clinical trial was performed among a population of 300 patients who had failed to respond to medication and other forms of therapy. The trial consisted of medication-free patients undergoing rTMS treatment daily for 4-6 weeks, and this therapeutic intervention showed statistically significant improvements among several clinical measures (O'Reardon et al., 2007). Findings from this study were supported by a larger, multi-site study sponsored by the NIH several years later (George et al., 2010). Notably, these studies, along with many others, demonstrate that rTMS is a safe practice even

when performed many times over in therapeutic paradigms. Currently, hundreds of clinics in the United States use an FDA-approved TMS system to treat depression.

In addition to improving depression and relieving pain, TMS can also be applied to enhance cognitive performance. Cumulative evidence has indicated the effectiveness of high-frequency (excitatory) rTMS over the left dorsolateral prefrontal cortex (DLPFC) in improving cognitive performance in psychiatric/neurological diseases or healthy volunteers (Guse, Falkai, & Wobrock, 2010).

DLPFC is chosen as the rTMS target because it is the most widely used one in the literature. DLPFC is a key element of many high-order brain functions including inhibition control, attention, working memory, and decision-making. High-frequency rTMS increases brain activity of the stimulation site, which may then help improve these complex functions and subsequently improve the associated brain disease condition such as PCCI. Moreover, DLPFC is both structurally and functionally connected to many cortical and sub-cortical regions. Thus, stimulating the DLPFC can also provide a means to assess the remote effects of rTMS through either connectivity or network-wise interactions.

PCCI is not surprisingly very difficult to study and is still not well understood including PCCI and MRI changes. We hope that this work including the MRI will add to the knowledge on PCCI but there is no specific MRI “signature”. Diagnostic criteria for PCCI has been a topic of recent NIH RFA but it will likely be years before the publications come out from those grants.

2) Purpose

In this pilot study, we propose to test the efficacy of rTMS for the treatment of PCCI. Efficacy measures will include baseline and post-rTMS neuropsychological testing, functional MRI and biometry data using body worn sensors.

3) Lay Summary (approximately 400 words)

Transcranial magnetic stimulation (TMS) is a safe and non-invasive brain stimulation technique. It uses a magnetic coil to stimulate brain tissue painlessly using only a magnet (no electrodes or electrical wires) in a procedure that does not involve any surgery or sedation. TMS is currently FDA approved to treat depression and migraines. Although this technology is applicable to many other brain conditions as well, it has not been systematically examined in individuals with "Chemo-brain". Chemo-brain or Post-Chemotherapy Cognitive Impairment (PCCI) is defined as cognitive changes including impairment of memory, learning, concentration, reasoning, executive function, attention and visuo visio-spatial skills that occur during or after chemotherapy treatment.

In this study, we will:

1) use high-resolution magnetic resonance imaging (MRI) of individuals' brains to determine precisely where to place the TMS magnetic coil in order to stimulate the target brain region based off their unique brain structure.
2) use TMS to stimulate the target region of the brain.
3) take high-resolution MRI pictures of the brain both baseline and post-TMS to study whether the brain activity of the target region changes as a result of the TMS stimulation.
4) perform neuropsychological tasks baseline and post-TMS to study if performance is improved following stimulation of the target brain region.
5) collect data from completing Frailty assessments, baseline and post-TMS.
6) study the short-term and long-term treatment effects.
7) collect subject's daily activity and sleep/wake patterns from watch style device (http://www.actigraphy.com/solutions/actiwatch/actiwatch-plus-specifications.html).
8) perform behavioral assessments, baseline and post-TMS, to study whether there are measurable changes following stimulation of the target brain region.

4) Resources: Describe the resources (personnel, facilities, time, emergency resources, etc.) available to recruit, consent, conduct study procedures, and analyze data.

Our clinical collaborators will participate in patient recruitment. MRI scans, TMS treatment, neuropsychological assessment, and assessments with body worn devices will be done at the Biosciences Research Laboratories (BSRL) at 1230 N Cherry Ave. All persons assisting with the study have received appropriate training and are or will be knowledgeable in their study-related duties and functions.

Ying-hui Chou, Assistant Professor, Cognition and Neural Systems, and her team will be involved in the neuropsychological testing as well as the TMS treatments. Her research focuses primarily on 1) characterizing the mapping between brain organization and behavior, and 2) studies of transcranial magnetic stimulation (TMS) techniques for modulation of human brain function and behavior.

5) Study Population

12 participants with PCCI will be recruited to participate in this trial.

Inclusion Criteria:
• Adult (>=18).
• PCCI diagnosis (see information below).
• Right Handed (We will not enroll left-handed dominant people because they tend to have more symmetric brain function and thus targeting the left frontal region may not be as effective.)
• English speaking.
• Cancer treatment completed and considered curative with the exception of endocrine therapy after chemotherapy.
• Able to attend daily intervention (Monday-Friday) for 2 weeks.
• Not enrolled in another interventional study within 6 months prior to beginning this study.

Exclusion Criteria:
• Pregnancy or thinking of becoming pregnant.
• Undergoing active treatment for cancer.
• Routine contraindications for MRI (including incompatible medical implants or metal fragments in the body at risk for migration or heating with application of the magnetic field) including severe claustrophobia.
• History of brain metastasis or other brain tumor.
• History of stroke or traumatic brain injury.
• Frequent or severe headaches.
• Cognitive or mood disorder prior to chemotherapy (i.e. dementia or depression).
• History of epilepsy, or other seizure disorders.
• History mental health disorders, such as substance misuse, bipolar disorder or psychosis.
• Taking medication for seizures or that could lower seizure threshold if withdrawn.
• Inability to complete neuropsychological testing.
• Prior treatment with rTMS. We will enroll subjects without prior experience with rTMS.

PCCI Diagnosis: Given lack of universally accepted criteria, we will initially follow commonly used criteria for mild cognitive impairment (MCI). The following revised Mayo clinic criteria for MCI will be used: (a) self- or informant-reported cognitive complaint; (b) objective cognitive impairment; (c) preserved independence in functional abilities; and (d) absence of dementia. The MCI diagnosis will be supported by the measures of general cognitive function using Mini-Mental State Exam (MMSE) 24-27 points (inclusive); (2) Montreal Cognitive Assessment (MoCA) 18-26 points (inclusive); and (3) Clinical Dementia Rating Scale score of 0.5. In addition, the Jak/Bondi actuarial neuropsychological test method and NACC UDS 3.0 Neuropsychological battery will be used identify MCI (i.e., 1 standard deviation below the mean for their age and education matched peers on normative data in at least 2 memory tasks). We will not include those with unstable medical condition, contraindications to MRI and TMS, clinical evidence of stroke, psychiatric disorder, and other neurological disorders or head injury.

6) Recruitment Methods and Consenting Process

Recruitment will begin after IRB approval and other approval requirements are complete. We plan to recruit for approximately 2 years or until we have recruited and completed 12 subjects, whichever comes first.

Our Banner University Medical Center clinical collaborators will participate in patient recruitment. When the physicians are seeing cancer patients as part of their routine standard of care, potential subjects will be identified.

Pre-screening in clinic is currently envisioned to be the combination of both the patients' symptoms and physicians' assessment consistent with "chemobrain." The patient will then be asked by the oncologist or staff if they are interested in a clinical trial for the treatment of "chemobrain" or whatever terminology the oncologist feels will best describe the symptoms the patient is describing (in other words, the oncologist does not need to use the exact term

"chemobrain"). If the patient is interested in participating, contact information will be collected on a consent to contact form and provided to the research staff. We hope that signing the consent to contact form rather than the full consent will save time and minimize disruption of the clinic's workflow.

The research staff will contact the individuals using the consent form as a script to describe the study. During this phone conversation, the inclusion and exclusion criteria will be reviewed with the patient to verify eligibility.

The identified individuals will be given ample time to review the consent and time commitment before consenting to the project. The patient will then receive a detailed schedule of research appointments. The first appointment will include the neuropsychiatric exams and pre-determined cut-offs (previously described) will be used to select appropriate subjects. The selection is based on multiple neuropsychiatric tests.

Any information collected during this phone-screening process will be secured under lock and key to ensure confidentiality. If the participants withdraw from the study, all personal information collected will be destroyed in a shredding machine to protect confidentiality of any PHI or sensitive data that may have been recorded.

7) Consenting Process

The consent will be obtained in a private setting to preserve confidentiality. All patient questions will be answered and no procedures will be completed before consent form is signed. No undue pressure will be applied to obtain consent.

This consent process will occur with a trained member of the research staff. The Consent Form will be reviewed by both the participant and the member of the research staff. The participant will be encouraged to ask any questions that arise while reviewing the informed consent form. Upon completion of the consent form and additional oral explanation provided by the research staff, the research participant will be asked to sign the consent form and a copy will be provided to them.

Throughout this consent process, the research staff will communicate the participant's right to withdraw from the study at any time without penalty. No minors or participants unable to consent will be included in this trial.

8) Research Procedures Involved in the Human Research

Subjects will undergo testing at baseline prior to TMS treatments and once more at the end of the 2-week intervention. All study activities will occur at the Biosciences Research Laboratories (BRSL) Building, located at 1230 N. Cherry Ave., Tucson, AZ 85721.

Child-bearing females will be required to take a urine pregnancy test and requested that adequate birth control be used during the treatment phase of the study.

A) Brain imaging data
We will acquire diffusion weighted imaging (DWI), resting-state fMRI, and T1 structural MRI. The MRI technician will ensure that participants have proper ear protection in the scanner (e.g., protective headphones so we can still communicate with them for the duration of the scan). The MRI technician will take measures to optimize the comfort of the participant (e.g., warm blankets, back support cushion). Foam pads will also be used to reduce head motion. Diffusion weighted MRI and resting-state functional MRI will be used to measure structural and functional connectivity, respectively. During resting-state fMRI scans, participants will be instructed to rest and remain awake with their eyes fixated on the cross hair presented before them. Total MRI scan time will require approximately 30 minutes.

B) Neuropsychological data and demographic data (see attached document: NACC UDS 3.0 Neuropsychological battery.pdf)
We will use a selection of MMSE, CDR, and NACC UDS 3.0 Neuropsychological battery. The NACC UDS Battery includes MoCA, Craft Story 21 Recall (Immediate), Benson Complex Figure Copy (Immediate), Number Span Test (Forward and Backward), Category Fluency, Trail Making Test, Craft Story 21 Recall (Delayed), Benson Complex Figure Copy (Delayed), MINT, and Verbal Fluency – Phonemic Test, to assess cognitive performance. Additionally, AVLT (Immediate Recall, Delay Recall), NAART (North American Adult Reading Test), and Stroop will also be applied for measuring cognitive function. Some of these tasks require audio recording for ease of scoring. Besides, demographics data, health history, medications, family history, and handedness questionnaire, will be collected. Acquiring neuropsychological and demographical data will take approximately 2 to 3 hours.

C) Memory tasks (see attached document: Memory tasks 20190318.docx)
A selection of the following memory tasks, which include Face Name Associative Memory Exam, Memory Capacity Test, Short-Term Memory Binding test, Behavioral Pattern Separation-Object test, Spatial Pattern Separation task, Discrimination and Transfer task, Dual tasking task, and other similar memory tasks (Rentz et al.), will be used to assess memory function. These memory tasks contain various shapes, colors, numbers, letters, objects, background (e.g., environments in our daily life), names, occupation titles, and ordinary faces. The memory task will require approximately 30 minutes.

D) Frailty assessment (see attached document: Frailty Meter device manual BioSensics.pdf)
Frailty will be assessed by measuring motion of forearm and upper-arm via wearable motion sensors attached to the upper extremity (tri-axial wearable gyroscope sensor, BioSensics LLC, Cambridge, MA). Participants will perform fully elbow flexion and extension with their dominant arm repetitively and as quickly as they can within 20 seconds. Motion score will be estimated with the following variables: (a) speed; (b) flexibility; (c) power; (d) rise time; (e) moment; (f) speed variability; (g) speed reduction, (h) flexion number, (i) BMI; and (j) Age. The

whole assessment will take around 10 minutes to complete. This will be done pre and post treatment.

E) TMS treatment

The purpose of the study is to test the acceptability and practicality of rTMS for the treatment of PCCI. Efficacy measures will include baseline and post-rTMS neuropsychological testing, functional MRI and biometry data using body worn sensors. All study activities will occur at the Biosciences Research Laboratories (BRSL) Building, located at 1230 N. Cherry Ave., Tucson, AZ 85721.

Theta burst stimulation (TBS) is a safe and patterned repetitive TMS protocol. In this project, we will apply the intermittent TBS (iTBS) protocol at the left dorsolateral prefrontal cortex. The iTBS paradigm consists of 3 pulses of 50 Hz stimulation repeated at 200-ms interval (i.e., 5 Hz) for 2 seconds (30 stimuli for 2 seconds). The 2-second train of stimulation will repeat every 10 seconds for 190 seconds (600 stimuli in total). A single session of iTBS induces transient effects on the targeted brain structures/networks that tend to last approximately 60 minutes following a single application. Structural MRI for TMS target localization and baseline functional MRI (fMRI) will be performed.

After the conclusion of baseline data acquisition, the research team will analyze each participant's unique structural and functional connectivity patterns to determine stimulation site for TMS in future study sessions.

The subjects will receive 10-sessions (1 session per day, M-F over 2 consecutive weeks).
The treatment itself lasts approximately only 190 seconds but we are conservatively planning an hour slot in order to not rush the daily planning/positioning.
After the last rTMS session, follow-up neuropsychological testing, behavioral assessments, and fMRI will be performed.
At 30, 90 and 120 days post the last rTMS session, a selection of neuropsychological and behavioral assessments will be mailed to the patients for the subject to complete and mail back. These assessments may be done alternatively over the phone.

F) Actiwatch

Data will be collected using Actiwatch spectrum plus (hardware) over a period of up to 2 weeks from our subjects. This data will be stored in a computer and processed using Actigraph (software licensed from Philips Respironics). The equipment is off the shelf commercial products with FDA approvals.
The subject will wear Actiwatch on their wrist and perform regular activities: sleeping, sitting, running, walking, etc. After finishing data collection, the Actiwatch will be returned to the study staff. The study staff will use USB cord to download the data to computer with actigraph software. This assessment is optional.

G) Behavioral Assessments

A selection of the following assessments may be performed, either on paper, electronically or over the phone. Assessments include PRO-CTCAE and the PSQI Sleep Questionnaire. See details in file "Behavioral assessments.pdf". These assessments will require approximately 30-60 minutes.

9) Cost to Subjects

There is no monetary or financial cost incurred by participants who enroll in this trial. Participants will, however, be responsible for their own travel to the research laboratory. While the participants will not be reimbursed for travel, the research team will cover the cost of parking.
Though no other monetary/financial costs are affixed with participation in this trial, there is a **significant "time cost"** associated with completing this trial. Given the nature of this trial, we understand that this may place a burden on the participant's scheduling and whereabouts.

10) Risks to Subjects

There are no know long-term health risks to the use of magnetic resonance imaging (MRI) when operated within FDA guidelines. There are no known long-term health risks to the use of TMS when operated within consensus safety guidelines (Rossi et al. 2009). In 2008, the FDA approved the use of high frequency rTMS in the treatment of depression. In 2013, the FDA approved the use of single-pulse TMS in the treatment of migraine.
Although seizure is a theoretical risk with repetitive TMS, "the occurrence of seizures has been extremely rare, with most of the few new cases receiving rTMS protocols exceeding previous guidelines, often in patients under treatment with drugs which potentially lowered the seizure threshold" (Rossi et al. 2009). As Rossi et al. delineate, "rare" means that 16 cases (out of tens of thousands of rTMS sessions over the last two decades) of seizure related to rTMS have been reported (~ 0.1%). Notably, eight of these adverse events occurred before safety parameters were established in 1997 and, of the other eight reports, six occurred either when the safe rTMS parameters were exceeded or other safety guidelines ignored, and the actual occurrence of a seizure has been questioned in the other two (i.e., convulsive syncope or pseudoseizure may have occurred). In a workshop convened by the National Institute for Neurological Disorders and Stroke (NINDS) in 1996, researchers in the field agreed upon a set of rTMS consensus safety guidelines (Wassermann 1998), including recommended stimulation parameters and contra-indications, and these consensus guidelines have been recently updated (Rossi et al. 2009). Widespread adherence to the 1996 guidelines has resulted in the virtual elimination of inadvertent seizures in rTMS studies (Rossi et al. 2009). The levels of stimulation used in this protocol are well within safety guidelines (Wassermann 1998; Rossi et al. 2009).

Actiwatch: There is no known risk involved in this experiment. The Actiwatch and actigraph are FDA approved.

11) Potential Benefits to Subjects and Society

We do not expect any direct benefits to the participants.

12) Provisions to Protect the Privacy of Subjects and the Confidentiality of Data

The risks are minimized by using standard clinical safety procedures. Procedures will be performed by trained personnel.

MRI checklist will be completed before each MRI to make sure no metal or other contraindications exist for the subject. We will not perform the MRI if such risks are identified.

All testing and interviews will be done in a private setting by individuals who have completed CITI and HIPAA training.

The federal regulations define 'private information' as "information about behavior that occurs in a context in which an individual can reasonably expect that no observation or recording is taking place, and information which has been provided for specific purposes by an individual and which the individual can reasonably expect will not be made public (e.g., a medical or education record)." In consideration of protecting the privacy of participants, we will follow these provisions:

- Only use the recruitment methods listed above; no cold-calling
- Have a private, welcoming environment for research practices
- Only key personnel will be present during research procedures
- Limit the number of personnel present for certain procedures (e.g., consent process)
- Obtain informed consent prior to any research practices
- Data will be de-identified and participants will be given randomized ID code

13) Access to Private Information

In addition to protecting the privacy of the participant, we will also take measures to protect the confidentiality of the data and private information that has been collected. A major component in the pursuit of protecting confidentiality involves formulating an agreement between the investigator and research participant about 1) how their data will be used, 2) who will have access to it, 3) what procedures will be put in place to ensure only authorized individuals will have access to the information, and 4) the limitations (if any) to these confidentiality procedures. This "agreement" will be discussed during the informed consent process so participants can be properly informed. Protecting confidentiality, then, relies on the research team carefully following through on all components of this agreement.

For this study, we have the following provisions in place to protect data confidentiality:

- Pertaining to information collected prior to informed consent:
    - Those who are eligible and enroll will receive random subject ID number. For those who are not eligible or who no longer wish to enroll in the study, we will adequately destroy all information recorded (e.g., shredding).

- All paper information will be kept under double lock and key in the coordinator's office. Only key personnel will have access to this data.
- Digital records will be stored in password protected files, on university maintained servers that undergo regular and secured back-up. Any sensitive data will be encrypted.
- All laboratory computers will be protected with a sign-in password.
- Any data shared will collaborators will be de-identified.
- No data will be shared with collaborators without the approval of an additional IRB amendment.
- Pursuant of University guidelines, research records will be stored for six years after the completion of the research.
- A key limitation of this agreement would arise in the event of an audit.
    - If the study is randomly chosen to be audited, regulatory officials would have access to all study records. This is the only instance in which non-key personnel would have access to data collected in this study.

14) Subject Compensation

Participants will not be compensated for being a part of this feasibility study.

15) Withdrawal of Subjects

Participants can be withdrawn from the study at any time with no penalty. The participants can prompt this withdrawal themselves if they no longer wish to continue with the trial or their participation in the study can be terminated by the research investigators for any reason. Participants will be informed of this during the consent process. This arrangement for withdrawal without penalty will promote participant safety and the accuracy of the data collected by the investigator.

In the event of participant withdrawal: 1) participants will be asked whether they are willing to complete the follow-up testing and surveys, and 2) the research team will thoroughly document the event. In cases that abrupt withdrawal is necessary, participant safety will remain our ultimate goal and we will follow protocols to ensure participants are not put at increased risk.

16) Sharing of Results with Subjects

Results will not be shared with research participants. However, exceptions may be made with raw MRI image file if research participants specifically request a picture of their brain as study memento.

17) Clinical Trials.gov Information

Registration pending

18) Statistical Analysis Plan

Repeated measures ANOVA will be employed. The independent variable is rTMS treatment. The primary outcome measure is cognitive function, and the secondary outcome measures is brain functional connectivity. Alpha = 0.05 will be used as the significance level for all analyses. Results will be corrected for multiple comparisons.

19) **SCHEDULE OF EVENTS**

Study stage	**Baseline**	**Treatment** Week #1		**Treatment** Week #2	**Final Treatment**	**Follow-Up**		
Study event	**Day 0**	**Day 1**	**Day 2-5**	**Day 8-11**	**Day 12**	**Day 42 +/- 7**	**Day 102 +/- 25**	**Day 132 +/- 25**
Consent	X							
Neuropsychological testing	X				X	X	X	X
Behavioral testing	X				X	X	X	X
Urine Pregnancy test	X							
Structural MRI	X							
Functional MRI	X				X			
TMS treatment*		X	X	X	X			
Actiwatch[1]		X	X	X	X			
Frailty task		X			X			
*The TMS treatment sessions do not need to start immediately after Baseline. [1]Optional tasks, subjects can opt out this task.								

Appendix 1: Data and Safety Monitoring Plan:

1. **Identification of the DSMB obligated for oversight responsibilities:**
   The University of Arizona Cancer Center Data and Safety Monitoring Board (DSMB) will provide ongoing oversight for this trial. This study has been assigned a Medium Risk level by the DSMB.

2. **Identification of the entity obligated for routine monitoring duties:**
   Routine monitoring will be provided by the Quality Assurance/Quality Control (QA/QC) Program to ensure that the investigation is conducted according to protocol design and regulatory requirements.

   This trial will also undergo real-time monitoring by the PI and study team, including documentation of real-time monitoring of any new or ongoing safety issues.

   The trial will have a AE/SAE log that will be reviewed and signed by the PI in a timely manner of the knowledge and documentation of the occurrence of an AE/SAE. SAEs will be reviewed within 24 hours of notification of event.

3. **Monitoring progress and data review process:**
   Routine monitoring of subject data will be conducted at least quarterly.
   The first routine monitoring visit will include at a minimum:
   - Informed consent – 100% of cases enrolled;
   - Subject eligibility – 50% of cases, up to two subjects;
   - Data review – 50% of cases, up to two subjects.

   All subsequent monitoring visits will consist of randomly selected subject cases based on current enrollment and include continuing review of previously selected cases, as applicable.

   A monitoring visit report and follow-up letter will be completed approximately two weeks after the routine monitoring visit; a copy will be maintained in the study file. The monitor will request additional source documentation, clarification, information, or corrections to the CRF and/or regulatory records from the Clinical Research Coordinator (CRC) or other applicable staff responsible for the study and resolution of queries/findings. Documentation of such a request will be maintained with a copy of the monitor's visit report for follow-up at the next monitoring visit. Electronic records will be available in the institutional database or provided by the QA/QC Program staff.

   The Principal Investigator will ensure the accuracy, completeness, legibility and timeliness of the data reported in the Case Report Form (CRF). Source documentation

supporting the study data should indicate the subject's participation in the trial and should document the dates and details of study procedures, adverse events, and patient status.
Case report forms will be created to include study data points and the adverse event forms and be completed using the institution database or other acceptable data formats. All subject forms and study files will be stored in a secure area limited to authorized staff.

Note: Routine monitoring of regulatory documents and test article will be conducted at least annually.

4. Process to implement study closure when significant risks or benefits are identified:

We do not anticipate any additional significant risks or benefits associated with the research. If there is a reason to close the study before the planned study end, there are no additional risks to the subjects for sudden withdrawal.
This research is not part of the subject's standard of care so if the study ends early, there would be no continuing interaction with the subject in the event we closed the study due to any newly identified significant information.

5. Description of adverse events and reporting procedures:

ADVERSE EVENTS
An adverse event (AE) is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign, symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

Any and all adverse events will be recorded on the UACC adverse events record form and reviewed by the Principal Investigator.

All adverse events will be classified using either the MedDRA term or NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 and will address:

- Grade
- Relationship to study drug (not related, unlikely, possible, probable, definitely)
- Causality other than study drug (disease related, concomitant medication related, intercurrent illness, other)
- Date of onset, date of resolution
- Frequency of event (single, intermittent, continuous)
- Event outcome (resolved, ongoing, death)
- Action taken (none, held, dose reduced, discontinued, medication given)

SERIOUS ADVERSE EVENTS

A serious adverse event (SAE) is any untoward medical occurrence that at any dose:

1) Results in death;
2) Is life-threatening;
3) Requires in-patient hospitalization or prolongation of an existing hospital stay;
4) Results in disability persistent or significant disability/incapacity, or:
5) Is a congenital anomaly/birth defect.

Note: A SAE may also be an important medical event, in the view of the investigator that requires medical or surgical intervention to prevent one of the outcomes listed above.

All serious adverse events, regardless of attribution, and any deaths will be reported within 24 hours of notification of the event to the sponsor and, if applicable, any collaborating entity. All serious adverse events and any deaths will be reported to the DSMB and to the University of Arizona Human Subjects Protection Program per the guidelines set forth in University of Arizona Cancer Center Data and Safety Monitoring Board Charter, Table 5: Adverse Event Reporting.

All submitted serious adverse events will be processed by the DSMB Coordinator monthly for initial trend analysis and then reviewed by the DSMB Chair. The assigned QA/QC Monitor will review the SAE reporting process to confirm reporting requirements are met.

6. Plan for assuring data accuracy and protocol compliance:

Routine study activity and safety information will be reported to the DSMB quarterly, or more frequently if requested. These reports will include:

- Study activity, cumulative and for the period under review;
- Safety (narrative description on non-serious and serious adverse events, protocol pre-determined early stopping rules for safety or treatment-emergent adverse events);
- Predetermined protocol early stopping rules for efficacy/futility;
- Status of study in relationship to stopping rules;
- Current dose level of study agent;
- Routine monitoring and protocol compliance (describe the monitoring process and identify the status of the monitoring);
- Comments;
- Attachments (AE data reviewed by the PI to compile the report, SAE letters and reports, results of any review(s), applicable correspondence with the IRB or other regulatory agencies

Data, safety and study progress will be reported to:

- Human Subjects Protection Program (IRB) at least annually;
- Sponsor (if applicable) at least every six months.

7. Identification of the sponsor or funding agency, as applicable:

The PI will immediately notify; in writing, the funding agency, if applicable, any action resulting in a temporary or permanent suspension of the study.

A copy of this correspondence will also be forwarded to the DSMB and the SRC.

Appendix 2: List of contraindicated medications:

Drugs with potential Hazards for rTMS

Strong potential hazard	Relative hazard
Alcohol	Ampicillin
Amitriptyline	Anticholinergics
Amphetamines	Antihistamines
Chlorpromazine	Aripiprazole
Clozapine	BCNU
Cocaine	Bupropion
Doxepine	Cephalosporins
Ecstasy	Chlorambucil
Foscarnet	Chloroquine
Gamma-hydroxybutyrate (GHB)	Citalopram
Ganciclovir	Cyclosporine
Imipramine	Cytosine arabinoside
Ketamine	Duloxetine
Maprotiline	Fluoxetine
MDMA	Fluphenazine
Nortriptyline	Fluvoxamine
Phencyclidine (PCP)	Haloperidol
Ritonavir	Imipenem
Theophylline	Isoniazid
	Levofloxacin
	Lithium
	Mefloquine
	Methotrexate
	Metronidazole
	Mianserin
	Mirtazapine
	Olanzapine
	Paroxetine
	Penicillin
	Pimozide

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Strong potential hazard	Relative hazard
	Quetiapine
	Reboxetine
	Risperidone
	Sertraline
	Sympathomimetics
	Venlafaxine
	Vincristine
	Ziprasidone