

University of Pittsburgh
Institutional Review Board

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<http://www.irb.pitt.edu>

Memorandum

To: Carmen Andreescu, MD
From: Margaret Hsieh, MD, Vice Chair
Date: 5/16/2018
IRB#: [PRO18020214](#)
Subject: A Pilot fMRI Study of TMS in Late-Life Severe Worry

At its full board meeting on 4/25/2018, the University of Pittsburgh Institutional Review Board, Committee H, reviewed the above referenced research study and approved it pending minor modifications. Your responses to these comments have been reviewed and the research submission, in its currently modified form, adequately addresses the concerns of the IRB and is therefore approved.

Please note the following information:

The IRB has approved the waiver for the requirement to obtain a written informed consent.

The risk level designation is Greater Than Minimal Risk .

Approval Date: 5/16/2018
Expiration Date: 4/24/2019

For studies being conducted in UPMC facilities, no clinical activities can be undertaken by investigators until they have received approval from the UPMC Fiscal Review Office.

Please note that it is the investigator's responsibility to report to the IRB any unanticipated problems involving risks to subjects or others [see 45 CFR 46.103(b)(5) and 21 CFR 56.108(b)]. Refer to the IRB Policy and Procedure Manual regarding the reporting requirements for unanticipated problems which include, but are not limited to, adverse events. If you have any questions about this process, please contact the Adverse Events Coordinator at 412-383-1480.

The protocol and consent forms, along with a brief progress report must be resubmitted at least one month prior to the renewal date noted above as required by FWA00006790 (University of Pittsburgh), FWA00006735 (University of Pittsburgh Medical Center), FWA00000600 (Children's Hospital of Pittsburgh), FWA00003567 (Magee-Womens Health Corporation), FWA00003338 (University of Pittsburgh Medical Center Cancer Institute).

Please be advised that your research study may be audited periodically by the University of Pittsburgh Research Conduct and Compliance Office.



[\[reviewer notes-\]](#)

Provide a short title for this study (200 characters or less):

A Pilot fMRI Study of TMS in Late-Life Severe Worry

T1.0

Select the type of application:

New Research Study

T2.0

Is the proposed research study limited to the inclusion of deceased individuals?

* No

T2.1

Are any research activities being conducted at the VA Pittsburgh Healthcare System or with VA funds?

* No

[\[reviewer notes-\]](#)

T3.0

What is the anticipated risk to the research participants?

Greater Than Minimal Risk

[\[reviewer notes-\]](#)

CS1.0 What is the reason for this submission?

New Research Protocol Submission

CS1.1 Has this research study been approved previously by the University of Pittsburgh IRB?

* No

CS1.1.1 Has this research study (or a substantially similar research study) been previously disapproved by the University of Pittsburgh IRB or, to your knowledge, by any other IRB?

* No

[\[reviewer notes-\]](#)

CS2.0**Title of Research Study:**

A Pilot fMRI Study of TMS in Late-Life Severe Worry

CS2.0.1**Requested approval letter wording:**

N/A

CS2.1**Research Protocol Abstract:**

We propose a study that will test a novel intervention through experimental therapeutic approach. We plan to use fMRI-directed repetitive transcranial magnetic stimulation (rTMS) for the treatment of severe, uncontrollable worry. While worry is a universal human experience, severe and excessive worry has been recently linked to increased risk of stroke and other cardiovascular diseases, increased risk of conversion to Alzheimer's disease as well as to higher risk of all-cause mortality in midlife and late-life. Severe, uncontrollable worry has been repeatedly associated with reduced quality of life and impaired functioning. Current treatment choices (antidepressant/anxiolytic medications and psychotherapeutic interventions) have been proven moderately efficacious in reducing anxiety/depression burden, but ineffective in reducing worry severity, a phenomenon that may contribute to the high relapse rates associated with mood and anxiety disorders. Our research indicated that worry severity is associated with hyperactivation in specific regions such as orbital frontal cortex, superior parietal gyrus, amygdala and parahippocampal gyrus. In this pilot study, we aim to explore the efficacy of targeting one of these regions with rTMS. Based on our results, the most accessible target is the right superior parietal gyrus (rSPG) – a region that remained significantly associated with severe worry after controlling for effects of comorbid depression or overall anxiety. As this region showed an increased in cerebrovascular flow in association with worry severity, we propose to use inhibitory rTMS (low frequency rTMS at 1 Hz, 5/wk for 2 weeks) to modulate cortical plasticity in this region and consequently, to reduce worry severity).

TMS during wakefulness has been shown to alter subsequent sleep [4], Further, changes in sleep in response to TMS has been associated with how participants respond to the TMS as a treatment [5]. Thus, we plan to measure sleep throughout the protocol to determine whether sleep changes as a function of TMS and whether sleep changes are associated with treatment response.

CS2.2**Select the category that best describes your research:**

Hybrid - includes aspects of BOTH types of research (check this option if your research is mainly social/behavioral but also involves specimen collection or blood draws to look at biological measures)

[\[reviewer notes-\]](#)

CS3.0**Name of the Principal Investigator:**

[Carmen Andreescu](#)

Note: Adjunct faculty of the University, including lecturers and instructors, are not permitted to serve as a PI or Faculty Mentor but may serve as co-investigators. Refer to [Chapter 4](#) on the HRPO website for more information.

CS3.1**Affiliation of Principal Investigator:**

UPitt faculty member

If you chose any of the **Pitt options**, please indicate the specific campus:

[Main Campus - Pittsburgh](#)

If you chose the UPitt faculty member option, provide the PI's **University Faculty Title**:

Associate Professor of Psychiatry

CS3.2

Address of Principal Investigator:

[REDACTED]

Pittsburgh, PA 15213

CS3.3

Recorded Primary Affiliation of the Principal Investigator:

U of Pgh | School of Medicine | Psychiatry

CS3.4

Identify the School, Department, Division or Center which is responsible for oversight of this research study:

[U of Pgh](#) | [School of Medicine](#) | [Psychiatry](#)

CS3.5

Telephone Number of Principal Investigator:

[REDACTED]

CS3.6

Recorded Current E-mail Address of Principal Investigator to which all notifications will be sent:

[REDACTED]

CS3.7

Fax Number:

[REDACTED]

CS3.8

Does this study include any personnel from Carnegie Mellon University, and/or use any CMU resources or facilities (e.g., Scientific Imaging and Brain Research Center (SIBR))?

* No

CS3.9

Is this your first submission, as PI, to the Pitt IRB?

* No

[reviewer notes-].

CS4.0**List of Co-Investigators:**

Last	First	Organization
Aizenstein	Howard	U of Pgh School of Medicine Psychiatry
Ferrarelli	Fabio	U of Pgh
Karim	Helmet	U of Pgh Faculty of Arts and Sciences Biological Sciences
Wilckens	Kristine	U of Pgh School of Medicine Psychiatry

[reviewer notes-].

CS5.0**Name of Primary Research Coordinator:**[Rachel Berta](#)**CS5.1****Address of Primary Research Coordinator:**

[REDACTED]

CS5.2**Telephone Number of Primary Research Coordinator:**

[REDACTED]

CS6.0**Name of Secondary Research Coordinator:**

Dana Williams

CS6.1**Address of Secondary Research Coordinator:**

[REDACTED]

CS6.2**Telephone Number of Secondary Research Coordinator:**

[REDACTED]

CS6.3**Key Personnel/Support Staff (Only list those individuals who require access to OSIRIS):**

Last	First	Organization
Buente	Kara	UPMC Hospital Divisions WPIC
Devine	David	UPMC Hospital Divisions WPIC
Kaskie	Rachel	UPMC Other
Lagattuta	Sally	U of Pgh School of Medicine Psychiatry
Ojewuyi	Ifeoluwadolapo	UPMC Other
Peng	Christine	UPMC Other
Tamburo	Erica	UPMC Hospital Divisions WPIC

[\[reviewer notes-\]](#).

CS7.0 Will this research study use any [Pediatric PittNet](#) or Clinical and Translational Research Center (CTRC) resources?

Yes

CS7.1 Please select the sites you intend to use:

CTRC - Neuroscience Clinical and Translational Research Center (N-CTRC)

[\[reviewer notes-\]](#).

CS8.0 Select the entity responsible for scientific review.

WPIC SRC - Western Psychiatric Institute and Clinic Scientific Review Committee. Note: Please upload the Research Committee approval notification in the "Supporting Documentation" section.

[\[reviewer notes-\]](#).

CS9.0 Does this research study involve the administration of an investigational drug or an FDA-approved drug that will be used for research purposes?

* No

CS10.0 Is this research study being conducted under a University of Pittsburgh-based, sponsor-investigator IND or IDE application?

* No

If YES, you are required to submit the IND or IDE application and all subsequent FDA correspondence through the Office for Investigator-Sponsored IND and IDE Support (O3IS). Refer to applicable University policies posted on the O3IS website (www.O3IS.pitt.edu).

[\[reviewer notes-\]](#)**CS11.0**

Use the 'Add' button to upload one or more of the following:

- the sponsor protocol (including investigator initiated studies) and/or other brochures
- the multi-center protocol and consent form template, *if applicable*

Name Modified Date

Is this research study supported in whole or in part by industry? This includes the provision of products (drugs or devices).

* No

Is this a multi-centered study?

* No

[\[reviewer notes-\]](#)**CS12.0**

Does your research protocol involve the evaluation or use of procedures that emit ionizing radiation?

* No

CS13.0

Does this research study involve the deliberate transfer of recombinant or synthetic nucleic acid molecules into human subjects?

* No

Upload Appendix M of NIH Guidelines:

Name Modified Date

CS14.0

Are you using UPMC facilities and/or UPMC patients during the conduct of your research study?

* Yes

If Yes, upload completed Research Fiscal Review Form:

Name Modified Date

[TINA UPMC Fiscal Form Updated .docx](#)

3/14/2018 8:06 AM

[\[reviewer notes-\]](#)**CS15.0**

Indicate the sites where research activities will be performed and/or private information will be obtained.

Choose all sites that apply and/or use **Other** to include sites not listed:

Sites:

[University of Pittsburgh](#)

UPMC

University of Pittsburgh

Campus: _____

Main Campus - Pittsburgh

List university owned off-campus research sites if applicable:

UPMC

Sites: _____

UPMC Presbyterian

UPMC Western Psychiatric Institute & Clinic

If you selected **School, International** or **Other**, list the sites:

***For research being conducted at non Pitt or UPMC sites, upload a site permission letter granting the researcher permission to conduct their research at each external site:**

Name Modified Date

CS15.1 Have you, [Carmen Andreescu](#), verified that all members of the research team have the appropriate expertise, credentials, and if applicable, hospital privileges to perform those research procedures that are their responsibility as outlined in the IRB protocol?

* Yes

CS15.2 Describe the availability of resources and the adequacy of the facilities to conduct this study:

* This study brings together a highly experienced research team with experience in study coordination, recruitment, psychiatric evaluations, administration of research quality assessments and tools, and the actual implementation and conduct of studies. There is sufficient private office space available for investigators and project staff.

Geriatric Psychiatry Neuroimaging Lab (GPN) (Directors: Howard Aizenstein, M.D., Ph.D., Carmen Andreescu, M.D.) http://www.gpn.pitt.edu/GPN/About_Us.html): GPN uses structural and functional magnetic resonance imaging (fMRI) to study the brain changes associated with aging. On-going functional magnetic resonance imaging (fMRI) studies aim to relate the cognitive and affective symptoms in the elderly to the functional neuroanatomy. The GPN Lab is located in Thomas Detre Hall, the main building of Western Psychiatric Institute and Clinic (WPIC), and is fully equipped to conduct neuroimaging analyses and data management. The GPN image processing lab consists of 15 multi-processor Macintosh workstations connected on a GB local area network. The computers share two RAID arrays containing a total of 20 terabytes of storage. The data are backed up weekly to tapes, which are stored off-site. The workstations have all necessary software for structural and functional neuroimaging analysis, including Matlab, AFNI, NIS, ITK, VTK, MIPAV, ImageJ, and FSL. Additionally, the computers run the Microsoft Office software suite, including Word, PowerPoint, and Excel. All

computers are connected (via a 100 MB line) to the UPMC network (in addition to the GB LAN). All computers in the GPN utilize the WPIC office of Academic Computing (OAC) Network.

The GPN office space includes twelve offices and a computer lab, which contains networked image processing workstations. Office space is provided for faculty, research staff, post-doctoral fellows, and graduate and undergraduate students.

Magnetic Resonance Research Center (MRRC) of the University of Pittsburgh Medical Center (<http://www.mrctr.upmc.edu/mrrc/home/overview>): The MRRC at Presbyterian Hospital and the Biomedical Science Tower, Pittsburgh is a state-of-the-art facility with space for imaging systems, support laboratories, technical support staff, image processing, and offices. The building housing the scanners is located in close proximity to our offices at WPIC. Scanning Instrumentation: The MRRC houses two 3T Siemens full-body parallel imaging systems equipped with an ultra-fast gradient system (maximum amplitude: 40 mT/m, slew rate 400 T/m/s, rise time: 100 us) as well as a 7T scanner. The scanners have full conventional images capabilities (T1/T2; High Resolution T1 (MPRAGE); FLAIR; DTI; BOLD). The instrumentation is designed to handle the high data rates and storage required by fMRI. All researchers conducting studies at the MRRC are provided with accounts on the computational cluster. Computers for stimulus presentation, equipment for acquisition of physiological data, and a computer laboratory for data analysis are all available at the MRRC. Quality assurance and safety activities include daily signal stability scans and required safety training sessions for all researchers. All conventional and echo planar MR imaging and MR angiographic functions are supported with optimized image contrast and signal at 3T and 7T strength. For fMRI scanning, echo planar imaging with the shortest echo spacing is provided with an automatic correction of B0 drift during the acquisition. The magnet rooms are magnetically, acoustically, and RF shielded. Quality assurance procedures are in place. These include daily signal stability scans for echo planar imaging (maximum 1% peak-to-peak over a continuous eight-minute acquisition with a 64x64 matrix size) and daily signal-to-noise measurements with the standard RF head coil and cylindrical phantom. The MR Center has maintenance agreements with Siemens that guarantee service whenever daily stability scans fail to meet the required specifications. The systems are interfaced to a high-speed local area network (CDDI-based LAN) for data transfer to the computers in GPN lab in for analysis.

Transcranial Magnetic Stimulation. Under supervision of Co-I Ferrarelli, the Neuroscience Clinical and Translational Research Center (N-CTRC) recently purchased a state-of-the-art, research-dedicated Transcranial Magnetic Stimulation (TMS) device capable of delivering the Theta Burst Stimulation (TBS) protocols. The system includes aMagVenture MagPro X100 with MagOption and a figure-of-8 coil (coil model: MCF-B65) which provides relatively focused stimulation and is specifically designed to deliver demanding stimulation protocols without the need for external cooling. The device includes an integrated active sham protocol which passes current through two surface electrodes placed on the scalp. The electrodes can be placed under the coil for both the real and sham stimulation sessions, though they will only be active during sham stimulation. For sham stimulation the coil is flipped 180 degrees, placing the active face away from the scalp while the scalp electrodes are active. In this configuration the inactive face makes contact (maintaining pressure) and the TMS coil still fires (generating equivalent sound) which very effectively maintains participant blinding. Additional services and resources at the N-CTRC include computing resources (PCs in each room, stimulus presentation control room). An exam room is available to conduct participant assessments, blood draws with basic processing, 12-lead EKGs, and other nursing functions.

[reviewer notes-]

CS16.0 Special Research Subject Populations:

Categories

None

[reviewer notes-]

CS17.0 Does your research involve the experimental use of any type of human stem cell?

* No

[reviewer notes-]

NIH Definition of a Clinical Trial

A research study¹ in which one or more human subjects² are prospectively assigned³ to one or more interventions⁴ (which may include placebo or other control) to evaluate the effects of those interventions on health related biomedical or behavioral outcomes.⁵

¹ See Common Rule definition of research at [45 CFR 46.102\(d\)](#) .

² See Common Rule definition of human subject at [45 CFR 46.102\(f\)](#) .

³ The term "prospectively assigned" refers to a pre-defined process (e.g., randomization) specified in an approved protocol that stipulates the assignment of research subjects (individually or in clusters) to one or more arms (e.g., intervention, placebo, or other control) of a clinical trial.

⁴ An intervention is defined as a manipulation of the subject or subject's environment for the purpose of modifying one or more health-related biomedical or behavioral processes and/or endpoints. Examples include: drugs/small molecules/compounds; biologics; devices; procedures (e.g., surgical techniques); delivery systems (e.g., telemedicine, face-to-face interviews); strategies to change health-related behavior (e.g., diet, cognitive therapy, exercise, development of new habits); treatment strategies; prevention strategies; and, diagnostic strategies.

⁵ Health-related biomedical or behavioral outcome is defined as the pre-specified goal(s) or condition(s) that reflect the effect of one or more interventions on human subjects' biomedical or behavioral status or quality of life. Examples include: positive or negative changes to physiological or biological parameters (e.g., improvement of lung capacity, gene expression); positive or negative changes to psychological or neurodevelopmental parameters (e.g., mood management intervention for smokers; reading comprehension and /or information retention); positive or negative changes to disease processes; positive or negative changes to health-related behaviors; and, positive or negative changes to quality of life.

CS18.0 * Based on the above information, does this study meet the NIH definition of a clinical trial?

Yes No

If Yes, click Save and then [Click Here For Study Team's CITI Training Records](#) . Please ensure all personnel's training is up to date

[\[reviewer notes-\]](#)

1.1 Objective: What is the overall purpose of this research study? (Limit response to 1-2 sentences.)

We propose a pilot study that will test the use fMRI-directed TMS for the treatment of severe, uncontrollable worry in older adults.

1.2 Specific Aims: List the goals of the proposed study (e.g., describe the relevant hypotheses or the specific problems or issues that will be addressed by the study).

AIM 1: Test target engagement (decreased right orbito-frontal cortex (rOFC) activation following low-frequency rTMS).

H 1: Low-frequency rTMS will be associated with a relative decrease in BOLD signal in the rOFC, during a worry-induction fMRI task.

H2: Low-frequency rTMS will be associated with a relative decrease in worry-rest rOFC-rAmygdala functional connectivity.

1.3 Background: Briefly describe previous findings or observations that provide the background leading to this proposal.

Twenty percent of older adults in the community report severe worry. While worry is a universal human experience, severe and excessive worry in older adults has been recently linked to increased risk of stroke and other cardiovascular diseases, increased risk of conversion to Alzheimer's disease as well as to higher risk of all-cause mortality. As worry is a transdiagnostic construct, it is present in several mood and anxiety disorders, including major depressive disorder and generalized anxiety disorder. Current treatment choices in late-life (antidepressant/anxiolytic medications and psychotherapeutic interventions) have been proven moderately efficacious in reducing anxiety/depression burden, but ineffective in reducing worry severity, a phenomenon that may contribute to the high relapse rates associated with mood and anxiety disorders in the geriatric population. These elements support the need for novel, experimental interventions specifically designed to target the neural basis of severe worry in late-life. In our current research (R01 MH108509) we focus on describing the behavior of canonical neural networks during resting state and during worry induction in participants with low-to-high worry. Our research indicates that simple induction of worry activates a distinct set of regions (caudate/thalamus, visual cortex, dorsal anterior cingulate). Given the universality and potential evolutionary benefits of worry, we believe that the neural network associated with worry induction supports a normal, physiologic experience. However, the regions involved in maintaining worry (hippocampus, thalamus) as well as those associated with severe worry (orbitofrontal cortex, superior parietal gyrus, amygdala, parahippocampal gyrus) support a pathological phenomenon and may represent ideal targets for interventions.

In this pilot proposal we intent to test the engagement of therapeutic targets during rTMS. Based on our preliminary results, the most accessible and relevant target is the right orbito-frontal cortex (rOFC) – a region that in our K 23 sample remained significantly associated with severe worry after controlling for effects of comorbid depression or overall anxiety. As rOFC cerebrovascular flow increased in association with worry severity, we propose to use inhibitory TMS [low frequency TMS at 1 Hz] to modulate cortical plasticity and consequently reduce worry severity. To test target engagement, we will use the in-scanner worry induction paradigm designed by Dr. Andreescu and her mentors during her K23 award and currently use to probe worry induction in the R01 MH108509. Given the exploratory nature of this proposal and based on our preliminary data, we will use two measures of target engagement: 1) the relative decrease in BOLD signal in rOFC and 2) the relative decrease in rOFC-rAmygdala functional connectivity.

1.4 Significance: Why is it important that this research be conducted? What gaps in existing information or knowledge is this research intended to fill?

1. Severe worry in late-life carries a significant health care risk.

Worry is defined as a complex affective and cognitive process, negative-affect laden, and

relatively uncontrollable [6]. While worry is a universal human experience that may confer an evolutionary advantage by modifying threat-related decision-making, severe and excessive worry has been recently linked to increased risk of conversion from mild cognitive impairment to Alzheimer's disease [7], and with increased risk of stroke and other cardiovascular events, after controlling for depression and vascular risk factors. Severe worry is also associated with interruption in functioning and reduced quality of life and with a higher risk of all-cause mortality in midlife and late-life.

2. Severe worry in late-life responds poorly to traditional interventions.

Traditionally, severe worry has been confined to categories such as Generalized Anxiety Disorder (GAD) and Major Depressive Disorder (MDD), multiple lines of research support the presence of severe worry in other several other anxiety and mood disorders. Thus, while GAD is built around the concept of severe, uncontrollable worry, only 20% of severe older worriers qualify for a GAD diagnosis. This evidence supports a major recent shift in the conceptualization of worry as a transdiagnostic entity most suitable for dimensional investigations. Current late-life GAD treatment choices, including cognitive-behavioral therapy (CBT) and antidepressant pharmacotherapy, have proven moderately efficacious in reducing overall burden of anxiety but ineffective in reducing worry severity. The ineffectiveness of current treatments in reducing worry severity may be at the root of the chronic, relapsing course of late-life GAD, which is one of the least likely mental disorders to remit and most likely to relapse.

3. Novel circuit-based targets for intervention.

Several neuroimaging studies have investigated both activation and functional connectivity among various brain regions involved in GAD – in adolescents and young adults. Our team has published exclusively on the neural markers of GAD in older adult participants. Also, very few studies used fMRI paradigms specifically tailored to induce worry or analyzed specifically the effect of worry severity at rest or during task. Our current results point toward two different networks that may benefit from targeted interventions: the one associated exclusively with severe worry (amygdala-parahippocampus- rOFC- rSPG) and the one associated with maintenance/the protracted quality of worry (insula-caudate/thalamus-amygdala-parahippocampus).

We decided to target in this application the network associated with worry severity due to both the richer literature regarding the pernicious effect of severe worry on both public health and treatment response but also due to accessibility for TMS of two of the nodes (OFC and SPG). Overall, the worry severity network seems to implicate excessive limbic/paralimbic activation potentially amplified by the cognitive anticipation of the negative affective value of future events processed through the OFC as well as probable attempts to cognitively control the arousal and dysphoria through structures such as SPG. This speculation is in line with newer interpretations of pathologic worry that suggest severe worriers both maintain arousal in order to seek out potential solutions to the anxiogenic source while attempting to inhibit representations of the potential bad outcomes. In other words, the severe worry network involves an ignition key (limbic/paralimbic), a gas pedal (OFC) and an ineffective break (SPG).

[\[reviewer notes-\]](#)

2.1 Does this research study involve the use or evaluation of a drug, biological, or nutritional (e.g., herbal or dietary) supplement?

* No

[\[reviewer notes-\]](#)

2.2 Will this research use or evaluate the safety and/or effectiveness of one or more devices?

* Yes

2.2.1 Does this research study involve an evaluation of the safety and/or effectiveness of one or more devices not currently approved by the FDA for general marketing?

* Yes

If **YES**, describe your **plan to prevent unauthorized use of the investigational device**:
The device will be operated as per current safety guidelines.

2.2.1.1 List each of the unapproved devices being evaluated in this research study.

Specify for each listed device the corresponding Investigational Device Exemption (IDE) number or provide a justification for why you feel that this device and its use, as proposed in this research study constitute a non-significant risk (i.e., to include potential failure of the device) to the research subjects:

Unapproved IDE device	#	Non-significant risk justification
View Repetitive Transcranial Magnetic Stimulation System		The study of the TMS device does not present a potential for serious risk to the health, safety, or welfare of a subject. TMS involves stimulating directly and non-invasively a cortical area while EEG allows measuring the response of that area and the rest of the brain to TMS. TMS has been introduced about 30 years ago, and although some initial studies reported more serious side effects, including the occurrence of single episode seizure in a handful of participants, there have been no reported significant side effects since safety guidelines have been initially introduced in 1998[1], and then again updated in 2008[2]. Our study will perform TMS well within the safety guidelines, and the co-investigator leading the TMS component of this study (Fabio Ferrarelli) has more than a decade long experience with this technique, and has used it in the past in studies involving both healthy subjects [3-5] and patients with schizophrenia[6, 7]. Additionally, this device is being evaluated as a potential treatment for anxiety. It will be made clear that participants may not experience any benefit and are able to pursue other treatment options at any time.

[\[reviewer notes-\]](#)

2.2.2 Does this research study involve the use or evaluation of the safety and/or effectiveness of one or more devices approved by the FDA for general marketing?

* Yes

2.2.2.1 Does this research study involve an evaluation of one or more FDA-approved devices for a clinical indication, subject population, and/or operational parameter that is not specified in the current FDA-approved product labeling for that device (i.e., for an "off-label" indication)?

* Yes

2.2.2.1.1 List each of the devices being evaluated for an "off-label" indication. Specify for each listed device the corresponding Investigational Device Exemption (IDE) number for this device/research study; or provide a justification for why you feel that this device and its "off-label" use, as proposed in this research study (i.e., to include potential failure of the device) constitute a non-significant risk to the involved research subjects.

*

Device	IDE #	Non-significant risk justification
View Transcranial magnetic stimulation		The study of the device does not present a potential for serious risk to the health, safety, or welfare of a subject.

[\[reviewer notes-\]](#)

2.3 Summarize the general classification (e.g., descriptive, experimental) and methodological design (e.g., observational, cross-sectional, longitudinal, randomized, open-label single-blind, double-blind, placebo-controlled, active treatment controlled, parallel arm, cross-over arm) of the proposed research study, as applicable.

This is an experimental, cross-sectional study.

2.3.1 Does this research study involve a placebo-controlled arm?

* No

[\[reviewer notes-\]](#)

2.4 Will any research subjects be withdrawn from known effective therapy for the purpose of participating in this research study?

* Yes

2.4.1 Provide a justification for discontinuing subjects from known effective therapy for the purpose of study participation.

Benzodiazepine use 48 hours prior to the MRI will affect the neural networks, activation, and response to emotional stimuli.

2.4.2 Describe the risks to subjects associated with discontinuing them from known effective therapy for the purpose of study participation.

Because there is well-recognized risk of withdrawal symptoms if benzodiazepine therapy is interrupted abruptly, we are planning on doing two things:

- 1) Excluding participants with dosages greater than or equivalent to 2 mg of lorazepam
- 2) Conducting a physician-monitored taper for those with lower doses that are willing to withhold benzodiazepine medications 48 hours prior to scanning.

[\[reviewer notes-\]](#)

2.5 Will screening procedures (i.e., procedures to determine research subject eligibility) be performed specifically for the purpose of this research study?

* Yes

2.5.1 List the screening procedures that will be performed for the purpose of this research study. Do NOT include the inclusion/exclusion criteria in this section as they will be addressed in section 3; questions 3.13 and 3.14.

We plan to recruit up to twenty participants with moderate and severe worry (e.g. Penn State Worry Questionnaire of 55 or higher) from the current R01 MH108509. This measure will be re-administered at the screening visit to ensure that participants still meet this criterion.

Prior to the screening visit, a phone screen that includes MRI safety screening questions will be administered. This will be done to assess the possibility of any new implants since their participation in R01 MH108509.

Should the participant have any history of surgeries involving implants, following consent, we will obtain a copy of any medical records related to the procedure/s to confirm whether he/she may safely complete the MRI scans.

The day of the MRI scan, women of child bearing potential will be asked to complete a pregnancy test. All participants will undergo a secondary MR safety screen administered by MRRC personnel.

[\[reviewer notes-\]](#)

Provide a detailed description of all research activities (e.g., all drugs or devices; psychosocial interventions or measures) that will be performed for the purpose of this research study.

This description of activities should be complete and of sufficient detail to permit an assessment of associated risks.

At a minimum the description should include:

- **all research activities**
- **personnel (by role) performing the procedures**
- **location of procedures**
- **duration of procedures**
- **timeline of study procedures**

Clinical Assessments

The following measures will be administered both before and after the TMS intervention:

- 1) Penn State Worry Questionnaire (PSWQ)
- 2) Montgomery-Asberg Depression Rating Scale (MADRS)
- 3) Hamilton Anxiety Rating Scale (HARS)

Sleep and Physical Activity Monitoring

Participants will be asked to complete a sleep diary and wear an actigraphy monitor for 1 week prior to and throughout the TMS intervention. This is to determine their in and out of bed times and sleep onset and wake times and how these may change during the TMS intervention.

TMS

Transcranial Magnetic Stimulation Protocol. Low frequency rTMS will be delivered through a MagPro X100 magnetic stimulator with a MCF-B70 static-cooled coil. rTMS will be targeted to the right OFC based on neural navigation software. rTMS will be delivered 1 hr/day, five days a week for two weeks, for a total of ten sessions.

MRI scan

The MRI scan will take place within 2 weeks of completion of the TMS sessions and will last approximately 1 hour. Scanning will be conducted on a 3 Tesla Siemens PRISMA scanner located in the MR Research Center at the University of Pittsburgh, using a 32-channel head coil (the same scanner and coil that is used for the current R01 study). We will gather functional MRI data (during rest and task) and structural MRI data including gray-matter volumetric estimates from T1-weighted images, white matter hyperintensity volume (WMH) estimated from T2-FLAIR images and white matter microstructure integrity estimates from diffusion tensor imaging (DTI).

Functional MRI: The fMRI acquisition includes a 10-minute resting state acquisition (eyes open) followed by the worry induction task. We have chosen to use a 10-min acquisition as recent data has showed that the reliability is improved by increasing the scan length from 5 to 10 minutes. T2*-weighted BOLD-contrast functional image acquisition will use multiband (acceleration of 3) gradient-echo echoplanar imaging (EPI): TR/TE = 1800ms/30ms, Matrix= 96x96 with 60 slices, Voxel size = 2.5x2.5x2.5 mm³, parallel to AC-PC. The most inferior functional scan will be inferior to the most inferior aspect of the temporal lobes.

Note regarding psychotropic medications:

Participants will be required to be medication free at the time of scanning (e.g., antianxiety and antidepressant medications). Participants will be asked to refrain from benzodiazepines 48 hours prior to the MRI. We will review participants' lists of medications at their clinical visit and will inform them whether it will be necessary for them to refrain from any of their usual medications. Participants will be told (as per the consent form) that they may decide that they do not wish to refrain from taking such medications prior to their scan. If so, they will be considered ineligible for the study. Participants on high doses of benzodiazepines (e.g., greater than or equivalent to 2 mg of lorazepam) will be excluded, given the complexity and potential complications of benzodiazepine taper/withdrawal.

Individuals who are needing to refrain from benzodiazepines 48 hours prior to the MRI will be given a taper plan by a physician investigator. At this time, participants will additionally

be provided with a phone number (our 24-hour participant line) to call if they experience any concerns or difficulties during the taper process. Additionally, the day prior to the MRI scan, research staff will contact the participant to ensure that the taper is well tolerated. Participants will be told that they may resume taking their medication at any time. Research staff will again follow-up with participants the day of the scheduled scan (Monday if scheduled scan was a Friday). In the case where there is imminent risk to the participant, the participant will be referred to Re:Solve or the WPIC ER (please see suicide risk assessment flow charts in "Supporting Documentation").

Participants who have decompensated and are requiring further treatment/monitoring will be advised to follow-up with their prescribing doctor. Until it is determined that the participant has returned to their normal state and/or is under the care of another provider, follow-up calls will be made by research staff.

2.6.1

Will blood samples be obtained as part of this research study?

* No

*If submitting a protocol for expedited review, it should be clear that the planned blood draws are within the parameters described here:

<http://www.hhs.gov/ohrp/policy/expedited98.html> (see Expedited Research Category #2)

If **Yes**, address the frequency, volume per withdrawal, the total volume per visit, and the qualifications of the individual performing the procedure:

Study Flow Chart:

Name

[TMS_Worry_Flow_Chart.pptx](#)

Modified Date

3/8/2018 12:27 PM

[[reviewer notes](#)].

2.7

Will follow-up procedures be performed specifically for research purposes? Follow-up procedures may include phone calls, interviews, biomedical tests or other monitoring procedures.

* Yes

Detailed procedures listed in the textbox below:

A follow-up call will be made the day following the MRI scan (Monday for scans occurring on a Friday) for participants needing to taper off medications.

Additionally, a follow-up call will be made 1 month following their last TMS session. The 1-month follow-up call will include a general assessment of well-being and potential adverse reactions, along with over the phone administration of the HARS and MADRS. Research staff will mail (including a postage-paid envelope) a copy of the Penn State Worry Questionnaire for the participant to complete and return.

The call templates are attached in 2.8.

[\[reviewer notes-\]](#)**2.8 Does this research study involve the use of any questionnaires, interview or survey instruments?**

* No

Upload a copy of all materials except for the SCID or KSADS which are on file at the IRB. The use of all instruments must be addressed in question 2.6 and/or question 2.7 (except for an exempt submission where they should be addressed on the appropriate uploaded exempt form).

Name	Modified Date
hars.doc	2/9/2018 1:08 PM
Sleep Diary.pdf	2/27/2018 2:01 PM
PSWQ_1to5.pdf	2/9/2018 1:27 PM
1-Month Follow-up Call	5/14/2018 2:36 PM
TMS Worry Medication Taper Documentation.docx	5/14/2018 12:44 PM
08 MADRS.pdf	2/27/2018 1:35 PM

Previously the name and publisher for commercially available materials were listed in the textbox below but effective 9/1/2015, all materials (except for the SCID and KSADS) must be uploaded using the Add button above.

[\[reviewer notes-\]](#)**2.9 If subjects are also patients, will any clinical procedures that are being used for their conventional medical care also be used for research purposes?**

* no

If **Yes**, describe the clinical procedures (and, if applicable, their frequency) that will be used for research purposes:

2.10 The blood sample question was moved to 2.6.1.[\[reviewer notes-\]](#)**2.11 What is the total duration of the subject's participation in this research study across all visits, including follow-up surveillance?**

* up to 5 weeks

[\[reviewer notes-\]](#)**2.12 Does this research study involve any type of planned deception?**

If Yes, you are required to request an alteration of the informed consent process (question 4.7)

* No

[reviewer notes-].

2.13 Does this research study involve the use of UPMC/Pitt protected health information that will be de-identified by an IRB approved "honest broker" system?

* No

[reviewer notes-].

2.14 Will protected health information from a UPMC/Pitt HIPAA covered entity be accessed for research purposes or will research data be placed in the UPMC/Pitt medical record?

* Yes

If you answer **Yes**, you are required to submit this study to the Center for Assistance in Research using e-Record (CARE). Per UPMC Policy HS-RS0005, all research projects that access or involve UPMC electronic protected health information (e-PHI) must be submitted to CARE, with the exception of clinical trials that are contracted through the UPMC Office of Sponsored Programs and Research Support (OSPARS).

Complete the online submission form at <https://care.upmc.com/request.aspx>. After the study is submitted in OSIRIS, a CARE representative will conduct a review. You will be notified once your CARE review is complete or if anything further is needed.

Studies that will access only paper-based medical records (not in combination with any electronic records) do not need to be submitted to CARE.

For additional information, please see <https://care.upmc.com>.

Describe the medical record information that will be collected from the UPMC/Pitt HIPAA covered entity and/or the research-derived information that will be placed in the medical records.

Should participants have any history of surgeries involving implants, we will review any records related to the procedure/s to confirm whether he/she may safely complete the MRI scan. We will not be placing any information in participants' medical records.

We may also access medical histories to confirm that participants are eligible to safely participate.

Medical record review will only take place following consent.

2.14.1 Will protected health information from a non-UPMC/Pitt HIPAA covered entity be obtained for research purposes or will research data be placed in the non-UPMC/Pitt medical record?

* Yes

If Yes, describe how the HIPAA requirements will be met:

For participants that have had surgeries involving implants outside of the UPMC system, we

will ask participants to sign a release of information form. We will then request paper copies of medical records from the facility that performed the surgery. The paper copies will be kept separately from the research data, since records will contain identifiers. The medical records will be used to determine whether participants can safely complete fMRI procedures. We will not be placing research data into participants' medical records.

We may also access medical histories to confirm that participants are eligible to safely participate.

Medical record review will only take place following consent.

I, Carmen Andreescu, certify that any member of my research team accessing, reviewing and/or recording information from medical records have completed the CITI Privacy & Information Security course or, if completed within the past year, the Internet-Based Studies in Education and Research (ISER) HIPAA for Researchers (Formerly RPF Module 6). The HIPAA certificates must be available for review if audited but do not need to be uploaded into this OSIRIS application.

* Yes

2.14.2

Are you requesting a waiver of the requirement to obtain written HIPAA authorization for the collection of the PHI?

* No

[\[reviewer notes-\]](#).

2.15 Does this research study involve the long-term storage (banking) of biological specimens?

* No

[\[reviewer notes-\]](#).

2.16 Will research participants be asked to provide information about their family members or acquaintances?

* No

[\[reviewer notes-\]](#).

2.17 What are the main outcome variables that will be evaluated in this study?

- 1) T2-T1 differences in BOLD changes across MRI task conditions (rest/worry induction) in the region of interest (rOFC);
- 2) Change in worry severity from baseline to post-treatment as measured by the PSWQ.
- 3) We will determine whether sleep time and sleep efficiency (amount of time spent in bed actually sleeping) change in response to and during TMS and whether these changes are associated with how well participants respond to TMS in terms of anxiety and fMRI response.

2.18 Describe the statistical approaches that will be used to analyze the study data.

* Addressed below:

Repeated measures ANOVA analysis for responders vs. non-responders using T2-T1 differences in BOLD changes across MRI task conditions (rest/worry induction) in the region of interest (rOFC). Response = decrease of 30% in PSWQ.

Repeated measures ANOVA, correlation, and regression will be used to test changes in sleep patterns and their association with anxiety and fMRI response.

Analysis of Structural MRI

We will collect measures of gray matter volume (MPRAGE), WMH load (T2-weighted FLAIR), and white matter micro-structural integrity (DTI). These structural measures will be extracted using methods developed and validated by the Co-I Dr. Aizenstein to take into account the variability of elderly brain images. These methods include assessment of regional gray matter volume using Automatic Labeling Pathway (ALP), regional WMH volume, and tract-based spatial statistics (TBSS) estimates of fractional anisotropy (FA) for the WM tracts. Regional WMH volumes: The automated WMH segmentation method developed by the Co-I Dr. Aizenstein is an iterative algorithm that automatically selects 'seeds' of WMH lesions and applies fuzzy connectedness to segment WMH lesions around the seeds (8). Using an automated method, the segmented WMH voxels are localized to the different white matter tracts defined on the Johns Hopkins University (JHU) White Matter Atlas (9). The WMH matter extraction algorithm has been shared with the neuroimaging community through our website (<http://www.gpn.pitt.edu>), where it can be requested for download. The same atlas used for localizing the WMH volumes is also used for generating tract-specific DTI measures. The DTI data is first pre-processed using tract-based spatial statistics. DTI summary measures are then generated using a 4-tissue class model, which treats normal appearing white matter as distinct from WMH. The other 2 classes (gray matter and CSF) are included to ensure accurate segmentation, but are not part of the planned analyses for this study. The global WMH burden and FA will be included as primary variables in Aim 3. As described above, we will also extract regional DTI and WMH measures for all white matter tracts. Secondary analyses will explore the role of tract-specific white matter alterations in tracts associated with emotion regulation (e.g. uncinate fasciculus, cingulum bundle).

Analysis of functional MRI

Our primary analyses of the BOLD-contrast fMRI dataset will follow a ROI approach that has been optimized by our group for analyzing fMRI in the elderly. We will also perform full-brain voxelwise secondary analyses. All standard processing steps are done in SPM8 [<http://www.fil.ion.ucl.ac.uk/spm/software/spm8>]. Additional custom software for alignment of elderly brain MRI's will also be used.

Preprocessing. (1) Functional images for both rest and task are realigned using a two-pass procedure to correct for head movement; (2) Each subject's T1 weighted structural image is co-registered across the sessions to the mean realigned EPI; (3) The T1-weighted volume is then segmented to generate a non-linear deformation mapping from native to MNI space; (4) EPI are then normalized to the ICBM MNI template using the non-linear deformation field; (5) Normalized functional images are then smoothed by using a 8-mm FWHM Gaussian kernel to reduce spatial noise and accommodate inter-subject anatomical variability. All preprocessing output files are then inspected to verify that all steps worked. Residual head motion and related global signal fluctuations are then estimated and the outlier time points saved for use in the first-level model as nuisance variables using the Artifact Detection Tool (ART) to detect and adjust for motion outliers in the fMRI time series data [http://www.nitrc.org/projects/artifact_detect/]. Our group has shown how, by using highly deformable registrations, we can get accurate segmentation and reduce Type 1 error in fMRI studies of elderly participants. Level One Analyses for Resting State: Resting BOLD time series will be de-trended, de-spiked, mean-centered and adjusted for the confounding covariance due to hemodynamic response, movement and physiological noise. The hemodynamic response will be modeled by the SPM default canonical hemodynamic response function and its derivative. The movement parameters from realignment are used as the movement regressors. The physiological noise will be modeled using the component base model (10) with 5 principal components of the BOLD time series from a white matter mask and 3 principal components from a CSF mask. The masks are constructed using the SPM MNI template of 95% and 75% probability map for white matter and CSF respectively; they are further eroded to avoid the partial volume effect. The adjusted time series are then band-pass filtered to the resting state frequency domain, ranging from 0.01 to 0.1HZ. For the functional connectivity analyses we will use the primary eigenvariate of the time-series extracted from the anatomic ROI using REX (<http://web.mit.edu/swg/rex/rex.pdf>). This

method extracts the time series that explains the maximum variance of all the time-series in the ROI (12). The eigenvariate time-series for each ROI will be correlated (Pearson correlation) with the eigenvariate time-series for the corresponding seed for each network-of-interest. The correlations will be transformed to Fisher Z statistics for group analysis. In addition, functional connectivity map for each seed and subject will also be generated by using the general linear model (GLM) with the seed time-series as independent variable and the movement parameters generated in the realignment as nuisance variables for exploration analysis. Level Two Analyses for Resting State: The resulting connectivity measures (Fisher Z transform of the Pearson correlation) will be exported to R [<http://www.r-project.org>], where statistical analyses will be conducted to test the association of each of these measures with the identified clinical factors. For the exploratory whole brain seed-to-voxel analysis, the functional connectivity maps will be analyzed across individuals using second-level design matrices. Level One Analyses for the Worry Regulation Task: The BOLD-contrast time-series images will first be filtered with a high pass filter of 128 sec. Condition effects for the worry regulation task will be determined in SPM8 for each subject using contrasts analysis (e.g., 'worry induction > rest') employed in the GLM framework. Specifically, the hemodynamic response of each condition will be modeled by a boxcar function convolved with the SPM canonical HRF with time delay as covariate to allow for increased variability in HRF with age. The movement parameters will be included in the GLM as nuisance variables. The GLM, which contains regressors of hemodynamic response for each task and the movement parameters, will be solved using robust regression to minimize the effect of outliers. The contrast maps representing the effects of tasks on the BOLD-contrast signal compared with that at baseline will be generated and tested in level two analyses.

Psychophysiological interaction (PPI) analyses will be used to test Aims 2-3. These analyses enable us to examine the degree to which the worry regulation conditions (induction/ reappraisal/ reappraisal+acceptance) affect the temporal covariation of the BOLD signal between the ROIs in the SN and ECN. For PPI analyses, we will use as seed regions the RAI and the right dIPFC. The RAI seed is extracted from the right insula cortex defined in the Automated Anatomical Labeling (AAL) atlas in the WFU Pick-Atlas (11). From the insular cortex, we extract the right AI cortex (landmarked anterior of the central insular sulcus) using ITK165. The right dIPFC is defined as the right Brodmann area (BA) 46 in the Talairach Daemon database from the WFU Pick-Atlas (11). Each seed time-series is extracted from the first principal component of BOLD signal in all voxels within the RAI and within the right dIPFC seed. Next, each seed time-series is mean-centered and submitted to a deconvolution algorithm using the canonical SPM8 HRF. Following deconvolution, an interaction vector is created, representing the product of the deconvolved BOLD signal time-series and a vector coding for task condition. The interaction vector is subsequently re-convolved with the SPM8 HRF, creating a PPI vector. Finally, all three vectors, corresponding to the PPI task-by-seed activity term, the seed activity, and the HRF convolved task vectors are entered as regressors in an individual GLM design matrix wherein one PPI GLM is executed for each participant and seed region. Individual GLMs are then estimated, and the contrast maps, which represent the modulation effect of worry regulation on connectivity (PPI map), are generated for Level 2 analysis. Second Level Functional Connectivity Analyses for the Worry Regulation Task: As a result of first level analysis, the PPI maps generated for each individual identify regions exhibiting greater functional connectivity with the RAI in the worry induction as compared with the rest condition, and with the RAI and the dIPFC in the worry reappraisal as compared to the rest. Individual PPI maps are then entered into regression analyses, wherein we test the association of task-related effects ('worry induction>rest') on functional connectivity with worry severity as measured by PSWQ. For PPI analyses, we maintain an FDR corrected threshold of 0.05 within the ROI volumes relevant for the SN (left AIns, dACC, right and left amygdala) and for the ECN (dACC, RAI, right and left Posterior Parietal Cortex).

[reviewer notes-].

2.19

Will this research be conducted in (a) a foreign country and/or (b) at a site (e.g., Navajo Nation) where the cultural background of the subject population differs substantially from that of Pittsburgh and its surrounding communities?

* No

Note that copies of training records, licenses, certificates should be maintained in the study regulatory binder and are subject to audit by the Research Conduct and Compliance Office (RCCO).

In addition, individuals planning to conduct human subject research outside the United States must complete an optional module on the CITI training website: International Studies. [Click here](#) to access the instruction sheet for accessing optional CITI modules.

[reviewer notes-].

2.21

Will this research study be conducted within a nursing home located in Pennsylvania?

* No

[\[reviewer notes-\]](#)

Section 3 - Human Subjects

3.1 What is the age range of the subject population?

50 to 85

3.2 What is their gender?

* Both males and females

Provide a justification if single gender selected:

3.3 Will any racial or ethnic subgroups be explicitly excluded from participation?

* No

If **Yes**, identify subgroups and provide a justification:

3.4 For studies conducted in the U.S., do you expect that all subjects will be able to comprehend English?

* Yes

[\[reviewer notes-\]](#)

3.5 **Participation of Children:** Will children less than 18 years of age be studied?

* No

If **No**, provide a justification for excluding children:
This research study is investigating anxiety in older adults.

[\[reviewer notes-\]](#)

3.6 Does this research study involve prisoners, or is it anticipated that the research study may involve prisoners?

* No

[\[reviewer notes-\]](#)

3.7 Will pregnant women be knowingly and purposely included in this research study?

* No

[\[reviewer notes-\]](#)**3.8 Does this research study involve neonates of uncertain viability or nonviable neonates?**

* No

[\[reviewer notes-\]](#)**3.9 Fetal Tissues: Does this research involve the use of fetal tissues or organs?**

* No

[\[reviewer notes-\]](#)

--->

3.10 What is the total number of subjects to be studied at this site, including subjects to be screened for eligibility?

Note: The number below is calculated by summing the data entered in question 3.11. Any additions or changes to the values entered in 3.11 will be reflected in 3.10.

* 30

3.11 Identify each of the disease or condition specific subgroups (include healthy volunteers, if applicable) that will be studied.

Click on the "Add" button and specify for each subgroup:

- 1) how many subjects will undergo research related procedures at this site; and
- 2) if applicable, how many subjects will be required to undergo screening procedures (e.g., blood work, EKG, x-rays, etc.) to establish eligibility. **Do Not include subjects who will undergo preliminary telephone screening.**

*

Subgroup	Number to undergo research procedures	Number to undergo screening procedures
View Anxious older adults	20	30

3.12 Provide a statistical justification for the total number of subjects to be enrolled into this research study at the multicenter sites or this site.

* Described below:

This is a pilot study aiming to explore neural signatures of treatment response. It is not statistically powered.

[reviewer notes-].

3.13 Inclusion Criteria: List the specific criteria for inclusion of potential subjects.

Participants must have completed Dr. Andreescu's study R01MH108509/PRO15080120.

Penn State Worry Questionnaire score of 55 or above.

3.14 Exclusion Criteria: List the specific criteria for exclusion of potential subjects from participation.

1) Any form of psychosis or Bipolar Disorder, dementia, a history of substance abuse within the last six months, or subjects treated with psychotropic medications (SSRIs, SNRIs, and similar; benzodiazepines okay) within the past two weeks (six weeks for fluoxetine).

2) Unable to complete MRI scans: presence of ferromagnetic metal in the body, claustrophobia

3) Contraindications for TMS:

a. Presence of a neurologic disorder or medical condition known to alter seizure threshold (e.g., stroke, aneurysm, brain surgery, structural brain lesion, brain injury, frequent/severe headaches)

b. Recurrent seizures or epilepsy in participant

c. Pregnancy

d. Metallic implants in body located at 30 cm or less from the position of the magnetic coil; presence in the

body of other devices that may be affected by magnetic field (e.g. pacemakers).

4) Unable to temporarily discontinue benzodiazepines 48 hours prior to MRI scan.

Participants on high doses of benzodiazepines (e.g., greater than or equivalent to 2 mg of lorazepam) will be excluded, given the complexity and potential complications of benzodiazepine taper/withdrawal.

3.15 Will HIV serostatus be evaluated specifically for the purpose of participation in this research study?

* No

If **Yes**, provide a justification:

[\[reviewer notes-\]](#)

- 4.1** Select all recruitment methods to be used to identify potential subjects:
Other Strategies: Described below

- 4.2** **Provide a detailed description of your recruitment methods, including identifying and initiating contact with participants:**

Participants with a Penn State Worry Questionnaire score of 55 or above will be invited to participate by a staff member who is listed on the consent form for both this study and PRO15080120. This will take place either over the phone or in-person. In-person this could occur at any of the visits associated with PRO15080120 once it is determined that the participant has a qualifying PSWQ score. Please see 4.6 for script/screen.

Note: Questions jump from 4.2 to 4.6 as questions 4.3-4.5 have been removed and the information is now captured in 4.1

[\[reviewer notes-\]](#)

- 4.6** **Are you requesting a waiver to document informed consent for any or all participants, for any or all procedures? (e.g., a verbal or computerized consent script will be used, but the subjects will not be required to sign a written informed consent document. *This is not a waiver to obtain consent.***

* Yes

- 4.6.1** **Identify the specific research procedures and/or the specific subject populations for which you are requesting a waiver of the requirement to obtain a signed consent form.**

Addressed below:

If not all, identify the specific procedures and/or subject populations for which you are requesting a waiver:

We have requested a waiver of the requirement to obtain signed informed consent for the screening process. We believe we meet the following criteria: The respective research procedures present no more than minimal risk of harm to the involved participants and involve no procedures for which written consent is normally required outside of the research context. We believe the information being obtained is the same type of information that would be collected on patients setting up an appointment for their condition.

- 4.6.2** **Indicate which of the following regulatory criteria is applicable to your request for a waiver of the requirement to obtain a signed consent form.**

45 CFR 46.117(c)(2)

45 CFR 46.117(c)(1) That the only record linking the subject and the research would be the consent document and the principal risk would be potential harm resulting from a breach of confidentiality. Each subject will be asked whether the subject wants documentation linking the subject with the research, and the subject's wishes will govern; or

45 CFR 46.117(c)(2) That the research presents no more than minimal risk of harm to subjects and involves no procedures for which written consent is normally required outside of the research context.

4.6.2.1

Address why the specific research procedures for which you are requesting a waiver of the requirement to obtain a signed consent form present no more than minimal risk of harm to the research subjects:

The screening questions present no more than minimal risk of harm to the involved participants and involve no procedures for which written consent is normally required outside of the research context. The information being obtained is the same type of information being collected on patients setting up an appointment for their anxiety. In addition, written informed consent will be obtained at the screening visit prior to any research activities.

4.6.2.2

Justify why the research listed in 4.6.1 involves no procedures for which written informed consent is normally required outside of the research context:

The screening document will act as documentation of verbal consent for the screening interview. We will first read the screening script followed by (with permission from the participant) the screening questions. The script will then be reviewed and a determination would be made as to whether the participant is appropriate for study. At this point, if s/he is eligible and interested in enrolling in this research study, s/he will be invited for further evaluation, at which time the formal study consent form will be signed.

4.6.3

Address the procedures that will be used and the information that will be provided (i.e., script) in obtaining and documenting the subjects' verbal informed consent for study participation:

The phone screening will act as documentation of verbal consent for the screening interview. After the script is reviewed and all of the participant's questions/concerns are answered, if the participant is interested in participation, the study staff will explain that to determine eligibility, we will need to ask him/her some screening questions. The research staff member will explain that he/she may choose not to answer any questions that make him/her feel uncomfortable and may end the screening at any time.

Upload Scripts:

Name	Modified Date
Phone screen TMS worry.docx	5/11/2018 11:17 AM

[\[reviewer notes-\]](#)

4.7 Are you requesting a waiver to obtain informed consent or an alteration of the informed consent process for any of the following?

* No

4.7.1 If Yes, select the reason(s) for your request:

There are no items to display

General Requirements: The Federal Policy **[45 CFR 46.116 (d)]** specifies in order for a waiver of consent to be approved, the request must meet four criteria. For each request, you will be asked to provide a justification addressing how each of these criterion is met.

[\[reviewer notes-\]](#)

4.8 Are you requesting an exception to the requirement to obtain informed consent for research involving the evaluation of an 'emergency' procedure?

Note: This exception allows research on life-threatening conditions for which available treatments are unproven or unsatisfactory and where it is not possible to obtain informed consent.

* No

[\[reviewer notes-\]](#)

4.9

Upload all consent documents for watermarking:

Draft Consent Forms for editing:

Name	Modified Date
TMS Worry Consent 5.11.18.doc	5/16/2018 12:00 PM

Approved Consent Form(s):

Name	Modified Date
TMS Worry Consent 5.11.18.doc	5/16/2018 12:03 PM

[\[reviewer notes-\]](#)

4.10 Will all potential adult subjects be capable of providing direct consent for study participation?

*

Yes

[\[reviewer notes-\]](#)

4.11

At what point will you obtain the informed consent of potential research subjects or their authorized representative?

After performing certain of the screening procedures, but prior to performing any of the research interventions/interactions

4.11.1

Address why you feel that it is acceptable to defer obtaining written informed consent until after the screening procedures have been performed.

The screening questionnaire will allow the investigators to determine the potential subject's eligibility as well as his or her safety in undergoing an MRI scan (e.g. metal in body). Conducting this interview with brief screening would reduce participant burden by eliminating an extra visit to the research site should they not be eligible to participate. The screening script will include obtaining verbal consent prior to asking the screening questions.

4.11.2

Taking into account the nature of the study and subject population, indicate how the research team will ensure that subjects have sufficient time to decide whether to participate in this study. In addition, describe the steps that will be taken to minimize the possibility of coercion or undue influence.

Participants will be allowed as much time as they need to consider participation after the consent form is reviewed. They will be encouraged to voice any questions or concerns at that time, prior to signing the consent form. Subjects will be provided with a clear explanation of the objectives, procedures, risks and benefits of the study and all questions will be answered. Because we believe that consent is an ongoing process in any study, we will continue to educate subjects about the nature of the research and address any questions that may arise throughout the course of the study. All members of our research team who have contact with potential participants will receive training in the importance of not coercing or otherwise unfairly influencing individuals to participate in this study.

[reviewer notes-].

4.12 Describe the process that you will employ to ensure the subjects are fully informed about this research study.

* Addressed below:

This description must include the following elements:

- who from the research team will be involved in the consent process (both the discussion and documentation);
- person who will provide consent or permission;
- information communicated; and
- any waiting period between informing the prospective participant about the study and obtaining consent

In addition, address the following if applicable based on your subject population:

- process for child assent and parental permission
 - continued participation if a child subject turns 18 during participation
- process for obtaining proxy consent and assent for decisionally impaired subjects
 - continued participation if subject regains capacity to consent

A physician investigator who is also a co-investigator will review the consent form with the participant. The purpose of the research study, the procedures involved in the conduct of the study, potential risks and benefits, and the rights of study participants will be discussed with the potential subject prior to the attainment of written informed consent. Questions will be asked of subjects to ensure they understand the nature of the research, the risks and potential benefits of participation, and their rights as research subjects. Participants will be given as much time as needed to decide whether they wish to sign the consent form. Participants will also be informed that signing the consent form does not bind them to complete any part of the study- they can always change their mind.

We believe that consent is an ongoing process in any study, and we will continue to educate subjects about the nature of the research and address any questions that may arise throughout the course of the study.

4.13

Are you requesting an exception to either IRB policy related to the informed consent process?

- For studies involving a drug, device or surgical procedures, a listed physician investigator is required to obtain the written informed consent unless an exception to this policy has been approved by the IRB
- For all other studies, a listed investigator is required to obtain consent (Note: In order to request an exception to this policy, the study must be minimal risk)

* No

If **Yes**, provide a justification and describe the qualifications of the individual who will obtain consent:

4.14

Will you inform research subjects about the outcome of this research study following its completion?

* No

If **Yes**, describe the process to inform subjects of the results:

[\[reviewer notes-\]](#)

5.1 Describe potential risks (physical, psychological, social, legal, economic or other) associated with screening procedures, research interventions/interactions, and follow-up/monitoring procedures performed specifically for this study:

*

View	<p>Research Activity: Rating scales, questionnaires, and cognitive assessments</p> <p>Common Risks: <i>No Value Entered</i></p> <p>Infrequent Risks: Some inconvenience and or anxiety may occur due to time required to complete formal rating scales and questionnaires.</p> <p>Other Risks: <i>No Value Entered</i></p>
View	<p>Research Activity: Actiwatch sleep monitoring device</p> <p>Common Risks: <i>No Value Entered</i></p> <p>Infrequent Risks: Mild discomfort from wearing watch</p> <p>Other Risks: <i>No Value Entered</i></p>
View	<p>Research Activity: Collection of private information</p> <p>Common Risks: <i>No Value Entered</i></p> <p>Infrequent Risks: There is a potential risk of breach of confidentiality that is inherent in all research protocols. There is a possibility that if research data were to become generally known, this knowledge could potentially impact a subject's future insurability, employability, or reproduction plans, or have a negative impact on family relationships, and/or in paternity suits or stigmatization.</p> <p>Other Risks: <i>No Value Entered</i></p>
View	<p>Research Activity: MRI</p> <p>Common Risks:</p> <p>Infrequent Risks: Some subjects experience discomfort associated with confinement and remaining stationary for a long period of time. Since the MRI is very noisy, there is the risk of hearing impairment. There is also the risk of injury related to metal attraction, since the MRI machine is a giant magnet.</p> <p>Other Risks: <i>No Value Entered</i></p>
View	<p>Research Activity: Temporary discontinuation of short-acting anti-anxiety medications</p> <p>Common Risks: Some people may develop "flu" like symptoms (e.g., nausea, achy, diarrhea). Your symptoms of anxiety may worsen. You will be given personalized instructions from one of the study physicians to reduce the risk of any negative effects.</p> <p>Infrequent Risks: <i>No Value Entered</i></p> <p>Other Risks: <i>No Value Entered</i></p>

Research Activity:	TMS
Common Risks:	Scalp discomfort. Experiencing mild headache during or immediately after the TMS procedure due to TMS activation of superficial scalp muscle. Possibility to develop a delayed onset headache, which usual resolves with single dose of common analgesics (i.e., acetaminophen, ibuprofen).
Infrequent Risks:	Seizure, although there have been no reported seizures in individuals undergoing the TMS protocol employed in this study (low frequency). Hearing loss, scalp burn, and adverse tissue reaction are risks that have on occasion been reported, but are rare and are even more unlikely to occur in this protocol.
Other Risks:	<i>No Value Entered</i>

[View](#)

5.1.1 Describe the steps that will be taken to prevent or to minimize the severity of the potential risks:

There is a potential risk of breach of confidentiality that is inherent in all research protocols. Procedures have been established, and will be followed, to minimize the risk of breach of confidentiality. Data will be entered into password-secured databases by staff authorized by the PI to do this, and they will abide by confidentiality regulations of the IRB. These data are password-secured for accessibility only by authorized personnel associated with the study. Subject anonymity will be preserved by the use of a code number (not related to name, social security number, or date of birth) on all questionnaires and reports. A list of subject names will be kept in a separate locked cabinet with access only to study personnel authorized by the PI. No subject will be identified by name in any published reports.

Rating scales will be performed by experienced research clinicians. If subjects experience emotional distress or undue burden during the administration of the assessments, collection of data will be postponed or minimized for that subject. With respect to minimizing the discomfort that may result from the interview, raters have been or will be selected on the basis of personal attributes and interpersonal skills as well as substantive knowledge. They will be further trained and periodically observed to ensure that they are respectful and sensitive to the needs and feelings of the subjects. Furthermore, they are trained to recognize signs of significant stress or irritability and will be instructed that they should gently terminate the interview whenever distress is observed.

Risks associated with MR imaging include claustrophobia, ringing in the ears, and the magnetic field which can attract ferromagnetic objects toward the magnet. Care will be taken to minimize distress due to claustrophobia by thoroughly training all project staff who come in contact with subjects, to ensure that they are sensitive to a subject's distress and will be capable of dealing with them in a courteous manner. In addition, subjects will be screened for potential contraindications for MR scanning, including metal in their body and claustrophobia, and will be excluded from the study when appropriate. Trained MR technologists will complete a thorough secondary safety screen about medical history to insure there is no metal in the participant's body that could potentially be attracted by the scanner. The presence of such metal is exclusionary. All subjects are required to wear ear plugs in the scanner to protect their hearing. Despite all preparation, some subjects experience discomfort associated with confinement and remaining stationary for a long period of time. Testing or scanning of any subject who becomes distressed will be terminated immediately.

To monitor for any potential side effect of TMS each participant will be interviewed at the beginning and at the end of the TMS protocol to assess for possible side effects. The risk of seizures is minimized by the low frequency TMS used in this study (there are no documented seizures in individuals undergoing the TMS protocol in this study). We will also have participants wear earplugs that will greatly attenuate the click sound generated from the discharge of the TMS coil. Furthermore, participants will also be asked to notify at any time during the assessment whether they experience any discomfort. All the most

commonly reported side effects related to TMS tend to occur during the stimulation or immediately afterwards. Very infrequently, some subjects have experienced a delayed onset headache due to the activation of superficial scalp muscles from the TMS coil. To address this issue, we will notify participants during the TMS protocol of this possibility and instruct them to take an analgesic if the pain were not to subside. Participants will be instructed to place ice on their scalp in the case prolonged scalp discomfort.

Additionally, there have been no reported significant side effects resulting from TMS since safety guidelines have been initially introduced in 1998[1], and then again updated in 2008[2]. Our study will perform TMS well within the safety guidelines, and the Co-I leading the TMS aspect of this study (Fabio Ferrarelli) has more than a decade long experience with this technique, and has used it in the past in studies involving both healthy subjects [3-5] and patients with schizophrenia[6, 7].

As far as participants who are tapering off of benzodiazepine medication, the risk to participants will be minimized as the taper plan will be supervised by a physician and our staff will be following up with participants throughout the process. Participants will also be able to contact us at any time with concerns through our 24-hour participant line.

5.2

What steps will be taken in the event that a clinically significant, unexpected disease or condition is identified during the conduct of the study?

*** Addressed below:**

Participants will be made aware of any unexpected events or conditions and appropriate referrals will be facilitated (either to PCP or other healthcare professional). Appropriate clinical follow-up will be made in the event that a clinically significant, unexpected disease or condition is identified during the conduct of the research study. In addition, participants who experience clinical deterioration or unexpected clinically significant psychiatric symptoms will be referred to the appropriate level of care (inpatient or outpatient).

Participants will be informed that the brain imaging scan used for this study is tailored for research purposes and should not be viewed as a clinical evaluation. If at the time of the scan the MRRC technologist detects a potential incidental finding, the MRRC Medical Director will be contacted immediately. The images will then be reviewed by a neuroradiologist in the Neuroradiology Reading Room. An investigator will share verbally results/impressions deemed clinically significant with the participant and a clinical follow-up referral will be provided as appropriate. If there is no provider, participants will be advised to seek a provider. Images will be sent to the participant's doctor with the written request of the participant (using a HIPAA authorization request).

Participants (or their insurance) will be responsible for all costs related to referrals for care for any incidental findings discovered during the course of this study.

5.3

All the risk questions (screening, intervention/interaction, follow-up) have been merged into one question (5.1).

[\[reviewer notes-\]](#)

5.4 Do any of the research procedures pose a physical or clinically significant psychological risk to women who are or may be pregnant or to a fetus?

* Yes

5.4.1 List the research procedures that pose a risk to pregnant women or fetuses:

There may be a possibility of risk in pregnancy from the MRI scans.

5.4.2 Describe the steps that will be taken to rule out pregnancy prior to exposing women of child-bearing potential to the research procedures that pose a risk to pregnant women or fetuses:

Any pre-menopausal females will have a urine pregnancy test performed before the MRI scans. If the test is positive, they will not be allowed to undergo the MRI procedure.

5.4.3 Describe the measures to prevent pregnancy, and their required duration of use, that will be discussed with women of child-bearing potential during and following exposure to research procedures:

Not applicable, If female participants are positive at the urine pregnancy test, they will be withdrawn from the study.

[\[reviewer notes-\]](#)

5.5 Do any of the research procedures pose a potential risk of causing genetic mutations that could lead to birth defects?

* No

[\[reviewer notes-\]](#)

5.6 Are there any alternative procedures or courses of treatment which may be of benefit to the subject if they choose not to participate in this study?

* Yes - Describe below:

If **Yes**, describe in detail:

Participants who choose not to participate in this study will be provided with referrals for alternative studies or open treatment as requested. These will include referrals for conventional firstline anxiety treatments that may be of benefit, including pharmacotherapy and cognitive-behavioral therapy.

[\[reviewer notes-\]](#)

5.7 Describe the specific endpoints (e.g., adverse reactions/events, failure to demonstrate effectiveness, disease progression) or other circumstances (e.g., subject's failure to follow study procedures) that will result in discontinuing a subject's participation?

* Describe below:

The investigators may remove someone from the study if we discover that s/he no longer meets study eligibility (e.g., has a surgery involving a metallic implant), for non-compliance with the study protocol, or if the study is not believed to be in her/his best interest.

[reviewer notes-]

5.8 Will any individuals other than the investigators/research staff involved in the conduct of this research study and authorized representatives of the University Research Conduct and Compliance Office (RCCO) be permitted access to research data/documents (including medical record information) associated with the conduct of this research study?

* Yes

5.8.1 Identify the 'external' persons or entity who may have access to research data/documents and the purpose of this access:

We may share de-identified information with other investigators in order to answer new research questions. If an individual has agreed (or does in the future) to participate in other studies, we will also share collected information between these studies. Each study would have already collected identifying information from the individual. Sharing information avoids duplication of certain interviews and tests, and it also provides new knowledge and allows us to answer new research questions.

5.8.2 Will these 'external' persons or entity have access to identifiable research data/documents?

*

Yes - Describe below:

If **Yes**, describe how they will protect the confidentiality of the research data: In the case of sharing data with other research studies in which the individual may be participating, these other studies would have already collected identifying information from the individual. When sharing actual data, however, research data/documents will only include the subject ID.

5.9 Has or will a Federal Certificate of Confidentiality be obtained for this research study?

* No

5.10 Question has been moved to 5.17

5.11 Question has been moved to 5.16

[\[reviewer notes-\]](#)

5.12 Does participation in this research study offer the potential for direct benefit to the research subjects?

Yes - Describe the direct benefit that subjects may receive as a result of study participation. Indicate if all, or only certain, of the subjects may derive this potential benefit.

Describe the benefit:

Participants in this study are subjects with severe worry. We anticipate a decrease in the level of experienced worry following TMS. There are however no known benefits of the TMS protocol at this time regarding reducing severity of worry. Participants will be informed in writing that there are no guarantees that they will benefit from study procedures. However, the potential benefits of participation in this study include receiving TMS that could be beneficial. Additionally, participants may derive benefits from the psychiatric evaluations by having the opportunity to talk about personal issues and concerns with a sympathetic listener and by having access to treatment referral services. Finally, participation in the proposed research may help inform and improve the development of novel treatment strategies that could ultimately benefit patients, including the participants themselves.

5.13 Describe the data and safety monitoring plan associated with this study. If the research study involves multiple sites, the plan must address both a local and central review process.

We will monitor accrual and any changes in the risk-to-benefit considerations of the study. A regular review of accrued data will be done to ensure the validity and integrity of the data and also to ensure that there is no change to the benefit-to-risk ratio of the study. All consents and assessment forms undergo a rigorous quality-assurance review. In addition, an ongoing review of study procedures will be done to ensure that the privacy of subjects and confidentiality of data is not violated. There will also be adequate provisions for monitoring the collected data to ensure the safety of subjects and to maintain the confidentiality of the research data. The PI and the clinical evaluators associated with the study will be responsible for these reviews during weekly research meetings in which each participant is discussed throughout the longitudinal course of their participation in the protocol. In addition subjects are not always compliant with the procedures despite the researchers' best efforts. We will report annually the deviations in completing research assessments related to subject safety. Any internal adverse events involving fatal or life-threatening circumstances, though none are anticipated, will be reported to the IRB within 24 hours of learning of the event. If only incomplete information is available, the IRB will, at a minimum, be notified of the adverse event during this time frame, with subsequent follow-up submission of a more detailed written report. All other internal Adverse Events will be reported to the IRB within 10 working days of the investigator learning of the event. Any external adverse events which are unexpected, serious, and suggest that the research places subjects or others at greater risk than was previously recognized, and related to the research intervention will be reported to the IRB within 30 working days of the investigator learning of the situation. Monitoring committee reports will be submitted to the IRB at the time of annual study renewal. Study procedures will comply with IRB policies for reporting of serious and unexpected adverse events.

[\[reviewer notes-\]](#)

Section 5 - Potential Risks and Benefits of Study Participation

5.14 What precautions will be used to ensure subject privacy is respected? (e.g. the research intervention will be conducted in a private room; the collection of sensitive information about subjects is limited to the amount necessary to achieve the aims of the research, so that no unneeded sensitive information is being collected, drapes or other barriers will be used for subjects who are required to disrobe)

Research interventions will be completed in private suites and offices. No unneeded sensitive information will be collected, except that which is necessary to achieve the aims of the research study.

The experimental procedures including during the MRI occur at the MR research center which is specifically equipped for research studies in order to maintain the confidentiality of subjects. Participants are provided with a locked, private room in which they can change their clothing and store their belongings in individually padlocked lockers.

5.15

What precautions will be used to maintain the confidentiality of the research data during collection, transmission and storage? It is important that you indicate the data security measures for all data types.

Go to the [A-Z Guidance](#), download the Data Security Assessment Form, complete, and upload using the Add button below. Depending on the data type, you may need to consult with your data manager to address some of the sections. Email irb@pitt.edu if you have any questions.

*** Upload Data Security Form:**

Name	Modified Date
Data Security Assessment Form 3.27.18	3/27/2018 9:59 AM

Address what precautions will be used to maintain the confidentiality of the research data collected in paper format if applicable:

Data will be entered into password secured data bases by staff authorized by the principal investigator to do this, and they will abide by confidentiality regulations of the IRB. These data are password secured for minimal access to authorized personnel associated with the study. No research documents will contain the names of participating subjects. Subject anonymity will be preserved by the use of a code number. Research records will be kept in a locked file. No subject will be identified by any published report.

5.15.1

Does your research study require a data security review? Answer Yes if any of the following conditions are met:

- Identifiable or *coded data will be collected, stored, or transmitted using any of the following technologies: mobile app, web-based site or survey, wearable device, text messaging, electronic audio, photographic, or video recording or conferencing **and/or**
- The IRB requested a data security review during their review of the study

* Yes

*** Coded:** Identifying information (such as name) that would enable the investigator to readily ascertain the identity of the individual to whom the private information or specimens pertain has been replaced with a code (number, letter, symbol, or any combination) and a key to decipher the code exists, enabling linkage of the identifying information to the private information or specimens

5.16

If the subject withdraws from the study, describe what, if anything, will happen to the subject's research data or biological specimens.

Any identifiable research or medical information which is recorded, which results from subject participation in this research study prior to the date that subject formally withdrew consent may continue to be used and disclosed by investigators.

5.17

Following the required data retention period, describe the procedures utilized to protect subject confidentiality. (e.g., destruction of research records; removal of identifiers; destruction of linkage code information; secured long-term retention)

Data will be entered into password secured data bases by staff authorized by the PI to do this and they will abide by confidentiality regulations of the IRB. These data are password secured for accessibility only by authorized personnel associated with the study. Subject confidentiality will be preserved by the use of a code number on all questionnaires and reports. Research records will be kept in a locked file accessible to only research personnel. A list of subject names and their associated subject ID's will be kept in our password protected database, which is also protected by our password protected server, which can only be accessed by individuals who have been assigned a username and password for computers connected to our server. No subject will be identified in any published report. After the retention period, we will maintain the deidentified data in a password-secured database.

[\[reviewer notes-\]](#)

6.1 Will research subjects or their insurance providers be charged for any of the procedures (e.g., screening procedures, research procedures, follow-up procedures) performed for the purpose of this research study?

*
No

[\[reviewer notes-\]](#)

6.2 Will subjects be compensated in any way for their participation in this research study?

* Yes

6.2.1 Describe the amount of payment or other remuneration offered for complete participation in this research study.

At the initial visit, participants will receive \$10 in travel reimbursement. Participants will receive payment for TMS sessions as follows. The first week participants will receive \$75 total. To promote retention, payments will increase the longer participants stay enrolled. Participants will receive \$125 for completing TMS sessions at the the end of Week 2. Participants will also receive \$75 for completing the MRI scan along with \$10 travel reimbursement.

Participants will receive a \$50 for bonus for sleep and physical activity monitoring as long as they complete 6/7 days each of the 3 weeks that they are asked to wear the watch.

Participants will receive \$15 for completion of the 1-month follow-up.

This will result in a total payment of up to \$360.

6.2.2 Describe the amount and term of payment or other remuneration that will be provided for partial completion of this research study.

Participants who miss TMS sessions will receive partial payment. This includes \$15 per session during Week 1, and \$25 per session during week 2.

Participants will receive payment for coming to the fMRI visit, even if the scan cannot be completed (i.e. technical issues). The scan will be rescheduled if at all possible.

Participants who do not complete 6/7 days each of the 3 weeks of sleep/actigraphy monitored will not receive any compensation for this task.

Participants will not be compensated if they do not complete the entire battery of assessments for the 1-month follow-up. This includes returning the Penn State Worry Questionnaire.

[reviewer notes-]

7.1 Summarize the qualifications and expertise of the principal investigator and listed co-investigators to perform the procedures outlined in this research study.

Carmen Andreescu, M.D., is an Associate Professor of Psychiatry at the University of Pittsburgh and geriatric psychiatrist who carries out research on anxiety and depression in elderly persons.

Howard J. Aizenstein, M.D., Ph.D., is a Professor of Psychiatry, Bioengineering, and Clinical and Translational Science at the University of Pittsburgh. Dr. Aizenstein is a geriatric psychiatrist and has research experience in the cognitive neuroscience and functional MRI of memory and learning systems. He has carried out studies of implicit learning using behavioral measures and also functional brain imaging.

Fabio Ferrarelli, M.D., Ph.D., is an Assistant Professor of Psychiatry at the University of Pittsburgh, and is an expert in the use of Transcranial Magnetic Stimulation (TMS) as an experimental and therapeutic tool in psychiatry. Prior to joining the WPIC faculty, he completed extensive training and collaborations within one of the leading TMS laboratories in the world, Dr. Giulio Tononi's laboratory at the University of Wisconsin, Madison. Dr. Ferrarelli has conducted numerous experiments examining the neural and cognitive effects of TMS protocols in both healthy and psychiatric populations (e.g., schizophrenia), with a focus on manipulating brain function in order to test experimental hypotheses relevant to human cognition. He will be responsible for overseeing the implementation, piloting, and troubleshooting the TMS protocols and supervising the research assistant in relevant TMS methods and collaborating with Dr. Andreescu and the other investigators to conduct ongoing supervision of data collection and data quality checking.

Helmet Karim, Ph.D., is a postdoctoral scholar on an NIMH T32 Training grant at the University of Pittsburgh. He received his doctorate degree in Bioengineering at the University of Pittsburgh. He has analyzed neuroimaging data related to prediction of treatment response in depression.

Kristine Wilckens, Ph.D., Assistant Professor in Psychiatry at the University of Pittsburgh. She received her doctorate in cognitive psychology from University of Pittsburgh and is affiliated with the Center for Sleep and Circadian Science in the Department of Psychiatry of the School of Medicine. Since 2004 she has conducted cognitive psychology research in human memory and executive function and since 2008 has conducted neuroimaging studies at University of Pittsburgh including a large study investigating sleep, cognition, and resting state MRI in young and older adults under the mentorship of Mark Wheeler, PhD and Kirk Erickson, PhD at the University of Pittsburgh. In May 2016, following completion of an NIH-funded T32 postdoctoral fellowship in Geriatric Mental Health under the mentorship of Daniel Buysse, MD and Martica Hall, PhD, she was awarded a Career Development Award through the National Institute on Aging. Through the K01, she is conducting a study on slow-wave sleep and executive network function in older adults. She was awarded an administrative supplement to augment her K01 in 2017 with aims to examine effects of slow-wave sleep on memory consolidation and memory resting-state network connectivity in mild cognitive impairment.

[\[reviewer notes-\]](#)

7.2 Indicate all sources of support for this research study.

*

Selections

Internal: Department funds

If **Federal** support, provide the sponsor information:

Federal sponsor Grant Title Grant number Awardee institution Federal grant application

For projects not supported by a federal grant, upload the research plan that was submitted for funding:

<u>Name</u>	<u>Modified Date</u>
Pilot_TMS_Worry_RRC.docx	3/8/2018 11:46 AM

If **Industry** support, provide the sponsor information and level of support:

If **Foundation** support, provide the sponsor information:

If **Other** support, provide the support information and level of support:

[\[reviewer notes-\]](#)

7.3

Is this study funded in part or whole by a PHS Agency?

* No

Does any investigator* involved in this study (select all that apply):

Name

- A. Have equity in a publicly-traded entity** that either sponsors** this research or owns the technology being evaluated or developed that exceeds a **5% ownership interest** or a current value of **\$10,000**?
- B. Have equity in a non-publicly-traded entity** that either sponsors this research or owns the technology being evaluated or developed?
- C. Receive salary, consulting fees, honoraria, royalties or other remuneration** from an entity that either sponsors this research or owns the technology being evaluated or developed that is expected to exceed **\$10,000** during the past or next 12 months?
- D. Have rights as either the author or inventor of intellectual property** being evaluated or developed in this research that is the subject of an issued patent or has been optioned or licensed to an entity?
- E. Have an officer or management position**** with a Licensed Start-up Company** overseen by the COI Committee that either sponsors this research or owns the technology being evaluated or developed?
- F. Receive compensation of any amount** when the value of the compensation would be affected by the outcome of this research, such as compensation that is explicitly greater for a favorable outcome than for an unfavorable outcome or compensation in the form of an equity interest in the entity that either sponsors this research or owns the technology being evaluated or developed?
- None of the above options apply and there are no other financial conflicts of interest in the conduct of this research.**

***Investigator** means the PI, co-investigators, and any other member of the study team, regardless of title, who participates in the design, conduct, or reporting of this research, as well as his/her spouse, registered domestic partner, dependents, or other members of his/her household. **The PI is responsible for ensuring that s/he and all other relevant members of the study team review the above questions describing Significant Financial Interests.**

**through the provision of funds, drugs, devices, or other support for this research

****Such as serving on the Board of Directors or Board of Managers or a position that carries a fiduciary responsibility to the company (e.g., CEO, CFO, CTO, or CMO).

[\[reviewer notes-\]](#)

Supporting Documentation Section

References and Other Attachments

Additional documents:

Name	Modified Date	Version
9413 Andreescu - Approval Letter .pdf	4/3/2018 9:46 AM	0.01
In Person Suicide Risk Assessment Protocol.doc	5/3/2018 11:47 AM	0.01
phone suicide assessment flowchart.pptx	5/3/2018 11:48 AM	0.01
References.docx	5/14/2018 2:58 PM	0.03

Please use the Add button to the left to upload additional documents if needed.

[\[reviewer notes-\]](#)

ClinicalTrials.gov is a registry and results database of publicly and privately supported clinical studies of human participants conducted around the world.

"[Applicable clinical trials](#)" are required by **federal law** to be registered in [ClinicalTrials.gov](#).

Applicable Clinical Trials (ACTs) are studies that meet the following criteria:

- The study is an interventional study AND
- The study intervention is a drug, biologic, medical device, radiation or genetic AND
- The Study is not Phase 0 or 1 AND
- The study has at least one site in the United States or is conducted under an investigational new drug application or investigational device exemption

NIH Policy

Effective January 18, 2017, revised [NIH Policy](#) requires that all [clinical trials](#) funded in whole or in part by the NIH be registered and results information posted on ClinicalTrials.gov.

As defined by the NIH, a [clinical trial](#) is:

A research study in which one or more human subjects are prospectively assigned to one or more interventions (which may include placebo or other control) to evaluate the effects of those interventions on health related biomedical or behavioral outcomes.

The NIH Policy extends beyond the Food and Drug Administration Amendment Act (FDAAA 801) requirements in that it requires registration and results reporting of:

- clinical trials of behavioral, surgical and other types of health and medical interventions
- phase 1 studies of drugs and biological products
- small feasibility studies of device products

Failure to submit all required registration and results information requested on ClinicalTrials.gov can jeopardize University grant funding, the future funding of the grantee and subject the University of Pittsburgh to future monetary penalties.

In addition, to promote transparency of the clinical trials process, the [International Committee of Medical Journal Editors \(ICMJE\)](#) has established a policy requiring the entry of clinical trials in a public registry, such as [ClinicalTrials.gov](#), prior to subject enrollment as a condition of consideration for publication of the trial results.

*** Based on the above information, will this study be registered in ClinicalTrials.gov?**

Yes

Who will serve as the Responsible Party? UPMC/Pitt Investigator or IND/IDE Pitt Sponsor

Why are you registering your study? (Check all that apply)

It is an **ACT** (*Registration must be no later than 21 days after the enrollment of the first participant*)

If you are not yet registered and need to establish an account for the PI or other research staff that may need to access the record, please send an email to the University of Pittsburgh PRS administrator at ctgov@pitt.edu with the following information for each individual:

- Full name
- Telephone number
- Pitt or UPMC email address

If you have any questions or concerns, please email us at ctgov@pitt.edu.

To find out additional information about how to register your study go to:
<https://www.clinicaltrials.gov/ct2/manage-recs/how-register>