PittPRO | Pitt Protocol Review Online

Date: Wednesday, April 22, 2020 9:12:47 AM Print Close

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Basic Study Information

ClinicalTrials.gov ID: NCT03577106

1. * **Title of study:**
A Pilot fMRI Study of TMS in Late-Life Severe Worry

2. * **Short title:**
TINA

3. * **Brief description:**
We propose a study that will test a novel intervention through experimental therapeutic approach. We plan to use fMRI-directed Intermittent Theta Burst Stimulation (iTBS), a high frequency TMS paradigm, 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 iTBS. 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 iTBS (5x/week 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.

4. * **What kind of study is this?**
Single-site study

5. * **Will an external IRB act as the IRB of record for this study?**

○ Yes ● No

6. * **Local principal investigator:**

Carmen Andreescu

7. * **Does the local principal investigator have a financial interest related to this research?**

○ Yes ● No

8. * **Attach the protocol:**

- Sponsor/Multicenter/Investigator-initiated protocol
- Coordinating Center supplement
- Emergency Use Consent/ Protocol/ FDA Form 3926
- Exempt Application form

Document	Category	Date Modified	Document History

There are no items to display

View: Pitt SF: Funding Sources (not integrated with Grants)

Funding Sources

1. * **Indicate all sources of support:**
   Internal funding

Study Team Members

1. * **Identify each person involved in the design, conduct, or reporting of the research (includes PI):**

Name	Roles	Affiliation	Involved in Consent	Qualifications
Howard Aizenstein	Co-investigator	Pitt faculty	yes	Howard J. Aizenstein, M.D., Ph.D., is a Professor of Psychiatry, Bioengineering, and Clinical and Translational Science at the University of Pittsbur... view all
Carmen Andreescu	Principal Investigator	Pitt faculty	yes	Carmen Andreescu, M.D., is an Associate Professor of Psychiatry at the University of Pittsburgh and geriatric psychiatrist who carries out research o... view all
Rachel Berta	Primary Study Coordinator	UPP/UPMC staff	yes	
Kara Buente	Key Personnel / Support Staff	UPP/UPMC staff	yes	
David Devine	Key Personnel / Support Staff	UPP/UPMC staff	yes	
Fabio Ferrarelli	Co-investigator	Pitt faculty	yes	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 M... view all
Deborah Goodnow	Key Personnel / Support Staff		yes	
Helmet Karim	Co-investigator	Pitt faculty	no	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 Bio... view all
Rachel Kaskie	Key Personnel / Support Staff	UPP/UPMC staff	no	
Jeffrey Krystek	Key Personnel / Support Staff	UPP/UPMC staff	no	

Name	Roles	Affiliation	Involved in Consent	Qualifications
Sally Lagattuta	Key Personnel / Support Staff	UPP/UPMC staff	no	
Christine Peng	Key Personnel / Support Staff	UPP/UPMC staff	no	
Gonzalo Quinones	Key Personnel / Support Staff		no	
Mark Stinley	Secondary Study Coordinator	UPP/UPMC staff	yes	
Erica Tamburo	Key Personnel / Support Staff	UPP/UPMC staff	no	
Jaclyn Toboz	Key Personnel / Support Staff		no	
Kristine Wilckens	Co-investigator	Pitt faculty	no	Kristine Wilckens, Ph.D., Assistant Professor in Psychiatry at the University of Pittsburgh. She received her doctorate in cognitive psychology from ... view all
Dana Williams	Key Personnel / Support Staff	UPP/UPMC staff	yes	
MARY YOUNG	Key Personnel / Support Staff		yes	

2. External team member information: (Address all study team members in item 1. above and leave this section blank)

Name	Description
There are no items to display	

3. Have you, Carmen Andreescu, verified that all members of the research team have the appropriate expertise, credentials, training, and if applicable, child clearances and/or hospital privileges to perform those research procedures that are their responsibility as outlined in the IRB application?

* ● **Yes** ○ No

Study Scope

Check all that apply

1. * Will this study actively recruit any of the following populations?

- [ ] Adults with impaired decision-making capacity
- [ ] Children (under the applicable law of the jurisdiction in which the research will be conducted (<18 years for PA))
- [ ] Children who are Wards of the State
- [ ] Employees of the University of Pittsburgh/UPMC
- [ ] Medical Students of University of Pittsburgh as primary research group
- [ ] Students of the University of Pittsburgh
- [ ] Neonates of uncertain viability
- [ ] Non-viable neonates
- [ ] Non-English speakers
- [ ] Nursing home patients in the state of Pennsylvania
- [ ] Pregnant women
- [ ] Prisoners
- [x] N/A

2. * Will any Waivers be requested?

- [ ] Waiver/Alteration of Consent
- [x] Waiver to Document Consent
- [ ] Waiver/Alteration of HIPAA
- [ ] Exception from consent for emergency research
- [ ] N/A

3. * Will this study involve any of the following?

- [ ] Specimens
- [ ] Honest Broker to provide data/specimens
- [ ] Return of Results to Subjects or Others
- [ ] Fetal tissue
- [x] N/A

4. * Will Protected Health Information be collected?

- [x] Pitt medical records
- [x] UPMC medical records
- [x] Other Institutions' medical records
- [ ] N/A

5. * Other Requests?

- [ ] Deception (if not Exempt, also requires Waiver/Alteration of Consent)
- [ ] Emergency Use / Single Patient Expanded Access (using FDA Form 3926)

- ☐ Placebo Arm
- ☑ Withdraw from usual care
- ☐ N/A

6. * **Determining Scientific Review:**
WPIC SRC - Western Psychiatric Institute and Clinic Scientific Review Committee.

7. * **Has this study (or substantially similar study) been previously disapproved by the Pitt IRB or, to your knowledge, by any other IRB?**
○ Yes ● **No**

Review the HRPO policy, if participating in research at the VA Pittsburgh Healthcare System or using funding from the VA

8. * **Does the study use an approved drug or biologic, use an unapproved drug or biologic, or use a food or dietary supplement to prevent, diagnose, cure, treat, or mitigate a disease or condition?**
○ Yes ● **No**

9. * **Does the study evaluate the safety or effectiveness of a device (includes in-vitro laboratory assays)?**
● **Yes** ○ No

10. * **Is this application being submitted to convert an approved study from OSIRIS to PittPRO?** (Tip Sheet)

● **Yes** ○ No

Download the OSIRIS Transition Continuing Review form, complete and upload below. If you need to attach any additional documents (e.g., data and safety monitoring reports), upload in the Local Supporting Documents page and note the Renewal on the form.

OSIRIS Transition Continuing Review form:
TINA OSIRIS Transition Continuing Review form(0.06)

* **OSIRIS ID**
PRO18020214

11. * **Does your research protocol involve the evaluation or use of procedures that emit ionizing radiation? (If yes, upload the HUSC form in the Local Supporting Documents section)**
○ Yes ● **No**

Research Sites

1. **Choose all sites that apply:**
University of Pittsburgh
UPMC
Clinical and Translational Research Center

*** Select the University of Pittsburgh sites where research will be conducted:**
Main Campus – Pittsburgh

List university owned off-campus research sites if applicable:

*** Select the UPMC sites where research will be conducted:**
Presbyterian
Western Psychiatric Institute & Clinic

*** Select the CTRC sites where research will be conducted:**
Neuroscience Clinical and Translational Research Center (N-CTRC)

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 TBS and rTMS protocols. The system includes a variety of coils which are designed to provide relatively focused stimulation and are specifically designed to deliver demanding stimulation protocols. 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.

View: Pitt SF: Devices

Devices

1. * **List each device in the study that will be evaluated for safety or effectiveness:**

	Device	Purpose	Type	Attachments
View	Transcranial Magnetic Stimulation System	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.	AbbreviatedIDE	

2. **If applicable, identify each investigational device exemption (IDE) number:**

IDE Number	IDE Holder	Other Holder
There are no items to display		

3. **Attach files:** (attachments may include justification of risk determination, FDA correspondence and if the holder of the IDE is a University of Pittsburgh based, sponsor-investigator, attach both the FDA acknowledgement letter and approval letter)

Document	Category	Date Modified	Document History
There are no items to display			

4. * **Describe your plan to manage devices so that they will be used only on subjects and be used only by authorized investigators:**

The device will be operated as per current safety guidelines. 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 or 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].

Click **Continue** as this page was intentionally left blank.

Recruitment Methods

*** Will you be recruiting individuals for participation in this study?**
● **Yes** ○ No

1. *** Describe who will be recruiting individuals for participation for this study:**
Members of Dr. Andreescu's team will contact those who have participated in the parent protocol ("FINA" STUDY19050150) and have consented for contact for future studies (via the FINA consent form).

2. *** Select all methods to be used for recruitment:**
Directly approaching potential subjects (in-person)
Pitt+Me
Telephone scripts

3. *** Provide details on your recruitment methods:**
Recruitment will take place either over the phone or in-person. In-person this could occur at any of the visits associated with STUDY19050150 once it is determined that the participant has a qualifying PSWQ score.

The Pitt+Me Registry connects community members and UPMC patients with researchers at the University of Pittsburgh and UPMC. Registry Participants will receive a periodic newsletter that describes research study findings and details of research process and a list of research studies based on their health interests and/or medical condition(s). Names will be given to the research coordinator and s/he will follow up with the registry participants within one week of notification.

4. *** Describe all compensation/incentives offered to participants and timing of these offers:**
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 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 an additional $10 for travel reimbursement if they are required to come in for an additional visit as detailed in the consent document.

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

This will result in a total payment of up to $370.

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.

5. **Recruitment materials:** (attach all material to be seen or heard by subjects, including advertisements and scripts)

	Document	Category	Date Modified	Document History
View	TINA_Pitt+Me_online_ad(0.01)	Recruitment Materials	1/13/2020	History

Study Aims

1. * **Describe the purpose, specific aims, or objectives and state the hypotheses to be tested:**
We propose a pilot study that will test the use of fMRI-directed TMS for the treatment of severe, uncontrollable worry in older adults.

The following is a list of specific aims and hypotheses to be tested:
AIM 1: Test target engagement (parietal cortex) activation following TBS.
H 1: TBS will be associated with a relative decrease in BOLD signal in the parietal cortex, during a worry-induction fMRI task.
H 2: TBS will be associated with a relative decrease in worry-rest rSPG-dACC functional connectivity.

2. * **Describe the relevant prior experience and gaps in current knowledge including preliminary data. Provide for the scientific or scholarly background for, rationale for, and significance of the research based on existing literature and how it will add to existing knowledge:**
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 TBS. Based on our preliminary results, the most accessible and relevant target is the parietal cortex – 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 parietal cortex cerebrovascular flow increased in association with

worry severity, we propose to use inhibitory TBS [high 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 the parietal cortex and 2) the relative decrease in rSPG-dACC functional connectivity.

The reasons why this research is significant is as follows:

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 the rSPG. 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 dACC and 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.

Study Design

1. **Total number of subjects to be enrolled at this site (enter -1 for chart reviews, banking, registries):**
   40

2. **Describe and explain the study design:**
   This is an experimental, cross-sectional study.

3. **Describe the primary and secondary study endpoints:**
   The primary endpoint of this study would be the participant would be study completion.

   The secondary endpoints include the removal of a participant from the study for the following reasons:

   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.

4. **Provide a description of the following study timelines:**

   Duration of an individual subject's active participation:
   up to 5 weeks
   Duration anticipated to enroll all subjects:
   We anticipate it will take 2 years to complete enrollment of all subjects.
   Estimated date for the investigator to complete this study (complete primary analyses):
   8/25/2021

5. **List the inclusion criteria:**
   Participants must have completed Dr. Andreescu's study R01MH108509/STUDY19050150.

   Penn State Worry Questionnaire score of 55 or above.

6. **List the exclusion criteria:**
   1) Any form of psychosis or Bipolar Disorder, dementia, or a history of substance abuse within the last six months

   2) Use of antidepressants within the last five to fourteen days (adequate washout interval to be determined by the PI based on each specific antidepressant). For fluoxetine, the washout interval will be six weeks. However, for participants who are prescribed low dose psychotropics for pain, sleep disturbances, and/or medical

conditions (e.g. amitriptyline for peripheral neuropathy, low dose trazodone as a sleep aid), these will be allowed in most circumstances. We will include participants on certain dosages of the most commonly prescribed antidepressants (for medical reasons) as follows: amitriptyline up to 50 mg/d, doxepin up to 50 mg/d, trazodone up to 100 mg/d, and imipramine up to 50 mg/d. We will review other cases individually and the PI will decide if the participants are eligible for the study and if they may continue the current medication.

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

4) 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).

5) 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.

7. Will children or any gender, racial or ethnic subgroups be explicitly excluded from participation?

● **Yes** ○ No

*** Identify the subgroups and provide a justification:**

Children less than 18 years of age will not be studied.

The justification for this exclusionary criteria is this research study is investigating anxiety in older adults.

8. Describe the power analysis used and cite your method of statistical analysis. If a power analysis is not possible, thoroughly justify the sample size required for the study, including appropriate literature citation (alternatively provide page reference in attached protocol):

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

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 (parietal cortex). 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 WHM 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 dlPFC. 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 dlPFC 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 dlPFC 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 dlPFC 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).

Research Activities

1. * **Provide a detailed description of all research activities (including screening and follow-up procedures) 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.**

Screening Procedures
We plan to recruit up to forty participants with moderate and severe worry (e.g. Penn State Worry Questionnaire of 55 or higher) from the current R01 MH108509 with the goal of thirty participants completing the study. The Penn State Worry Questionnaire 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 safety 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.

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
As an optional component of the study, participants will be asked to complete a sleep diary and possibly wear an actigraphy monitor, depending on availability of the actiwatch, for at least 4 days 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. Since the sleep and activity monitoring occurs in conjunction with the TMS intervention, this may require the participant to come in for an additional visit at least 4 days prior to the beginning of the TMS intervention to collect the actiwatch and sleep diary. In this circumstance, the participant would be reimbursed an additional $10 for travel.

TMS
Transcranial Magnetic Stimulation Protocol. Theta Burst Stimulation (TBS) will be targeted to the Inferior Parietal Cortex based on neural navigation software. TBS will be delivered for about 5-6 minutes, five days a week for two weeks, for a total of ten

sessions. Accounting for set-up time and possible technical issues, participants will be informed that visits may last up to 45 minutes, but on average will take about 20 minutes.

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:
In most cases, participants will be required to be medication free at the time of scanning (e.g., antianxiety and antidepressant medications). However, participants will be allowed to continue taking low doses of psychoactive medications when used to treat medical conditions, pain, and sleep disturbances. The dose range for the most common antidepressants that are prescribed for medical reasons are as follows: amitriptyline up to 50 mg/d, doxepin up to 50 mg/d, trazodone up to 100 mg/d, and imipramine up to 50 mg/d. As for other medications, each case will be reviewed individually and the PI will decide if the participants are eligible for the study and if they may continue the current medication.

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.

Follow-up Procedures
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 below.

2. **Upload a copy of all materials used to collect data about subjects: (Attach all surveys, interview/focus group scripts, and data collection forms except for case report forms, SCID or KSADS):**

	Document	Category	Date Modified	Document History
View	08_1-month follow-up call template.docx(0.01)	Data Collection	2/8/2019	History
View	07_TINA Worry Medication Taper Documentation.docx(0.01)	Data Collection	2/8/2019	History
View	09_Sleep Diary.pdf(0.01)	Data Collection	2/8/2019	History
View	01_MADRS.pdf(0.01)	Data Collection	2/8/2019	History
View	02_HARS.pdf(0.01)	Data Collection	2/8/2019	History
View	03_PSWQ_1to5.pdf(0.01)	Data Collection	2/8/2019	History

3. * **Will blood samples be obtained for research purposes?**

○ Yes ● **No**

Consent Process

Enter N/A in response to the following questions if a Waiver of Consent is requested for all research activities or if no subjects are being enrolled.

1. * **Indicate where the consent process will take place and at what point consent will be obtained:**
The consent process will be completed in private suites and offices. Consent will be obtained after performing certain screening procedures, but prior to performing any of the research interventions/interactions.

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.

2. * **Describe the steps that will be taken to minimize coercion and undue influence, including assurance that there is sufficient time for subjects to make an informed decision:**
A physician investigator who is also a co-investigator will review the consent form with the participant. This will occur either in person or via phone call. 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. 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. Participants will be able to ask the physician investigator clarifying questions either in person, or via phone call, 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. 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. 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. Participants will sign the consent form prior to beginning any screening procedures (excluding the phone screen), clinical assessments, sleep and activity monitoring, TMS, or MRI scan as these require completed written informed consent.

If the physician investigator conducts the consent process via phone call, he or she will sign the consent form retroactively once available to do so.

3. **For studies that involve multiple visits, describe the process to ensure ongoing consent:**
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. * **Steps to be taken to ensure the subjects' understanding:**
During the consent process, 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.

5. * **Are you requesting an exception to the IRB policy related to the informed consent process:**
○ Yes ● **No**

View: Pitt SF: Consent Forms

Consent Forms

1. **Consent Forms:**

	Document	Category	Date Modified	Document History
View	andreescu consent 3.11.20 for approval.docx(0.09)	Consent Form	3/11/2020	History

Refer to the following templates and instructional documents:

- Guidance - Consent Wording
- Template - Consent Document - Short Form
- HRP-090 - SOP - Informed Consent Process for Research
- HRP-091 - SOP - Written Documentation of Consent

View: Pitt SF: Waiver to Document Informed Consent

Waiver to Document Informed Consent

This waiver to document informed consent can be requested 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, such as with phone screening).

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:**

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.

2. * **Select the regulatory criteria applicable to your request:**

- ○ 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.
- ● 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
- ○ 45 CFR 46.117(c)(3) If the subjects or legally authorized representatives are members of a distinct cultural group or community in which signing forms is not the norm.

* **Address why the specific research procedures for which you are requesting a waiver of the requirement to obtain a signed consent form presents 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.

* **Justify why the research 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.

3. * **Upload Scripts:**

	Document	Category	Date Modified	Document History
View	Phone_screen_TMS_worry 7.29.19(0.02)	Waiver Script	7/29/2019	History

Medical Records

1. You are required to submit this study to the Research Informatics Office, Health Record Research Request (R3). Per UPMC Policy HS-RS0005, all research projects that access or involve UPMC electronic protected health information (e-PHI) must be submitted to R3, with the exception of clinical trials that are contracted through the UPMC Office of Sponsored Programs and Research Support (OSPARS).

   Complete the R3 intake form available at http://rio.pitt.edu/services. An R3 representative will conduct a review. You will be notified once your R3 review is complete or if anything further is needed.

*** Describe the protected health information that will be collected from the covered entity and/or the research derived information that will be placed into 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 safety 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. *** Describe what protected health information will be obtained from a non-UPMC/Pitt covered entity for research purposes and 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.

Electronic Data Management

1. * **Will only anonymous data be collected (select NO if identifiers will be recorded at anytime during the conduct of the study)?**
   ○ Yes ● No

Select all identifiers to be collected during any phase of the research including screening:

Name:	☑	**Internet Protocol (IP) Address:**	☐
E-mail address:	☑	**Web Universal Resource Locators (URLs):**	☐
Social security #:	☐	**Social security # (for Vincent payment only):**	☑
Phone/Fax #:	☑	**Full face photo images or comparable images:**	☐
Account #:	☐	**Health plan beneficiary #:**	☐
Medical record #:	☑	**Device identifiers/serial numbers:**	☑
Certificate/license #:	☐	**Vehicle identifiers/serial #/license plate #:**	☑
		Biometric identifiers, finger and voice prints:	☐

* **a: Will you be collecting any of the following location data: geographic subdivisions smaller than a State such as street address, city, county, precinct, zip, geocodes, etc.?** ● Yes ○ No

* **b: Will you be collecting any date information such as birth date, death, admission, discharge, date of surgery/service?** ● Yes ○ No

c: List any other unique identifying numbers, characteristics or codes related to an individual that are to be collected:

d: Will you be collecting any data subject to the General Data Protection Regulation (GDPR)? ○ Yes ○ No

* **e: Provide a justification for recording Social Security numbers including why it's required, where it's stored, how it's protected and who will have access:**

We collect the participant's SSN for the purpose of creating a Vincent account. After creating the Vincent account the Vincent form with the SSN on it is shredded.

* **For ALL identifiable data collected, will you be coding the data by removing the identifiers and assigning a unique study ID/code to protect the identity of the participant?** ● Yes ○ No

* **Will the data be HIPAA de-identified?** ● Yes ○ No

* **Briefly describe your plan to store coded data separately from the identifiable data:**

Participants will be assigned a unique TINA screening identification (ID) number when they complete the phone screen. The TINA screening ID number will help protect and maintain a participant's

identifiable information, since it will not be used on any other assessments, and will not be used in conjunction with a participant's subject identification number. On our password-protected server, there is a password-protected table accessible only by staff members that links the participant's TINA screening ID to their subject identification number. Otherwise, data is kept separately from identifiers. We have separate files that contain the phone screen, consent form, and medical record information such as surgical reports needed for MR clearances. These files do not contain any research data or subject ID numbers.

2. * **Will sensitive data be collected (e.g., protected health information, mental health, medications, drug/alcohol use, illegal behaviors)?**

● **Yes** ○ No

3. * **Select all locations where data will be stored or accessed (including e.g., personal / employer laptop or desktop):**

	Storage Device	Description	Identifiable Data	Sensitive Data	De-Identified/Anonymous Data
View	Server: Pitt Department Managed Server		yes	yes	yes
View	UPMC owned desktop, laptop or other device		yes	yes	yes

4. * **Select all technologies being used to collect data or interact with subjects:**

Wearable device (also select mobile app if it will be used with the device)

5. * **Wearable Device - identify all wearable devices used to collect data during any phase of the research:**

	name	Identifiable
View	Actiwatch	no

Data Safety and Monitoring

1. * **Describe your plan to periodically evaluate the data collected regarding both harms and benefits to determine whether subjects remain safe. The plan might include establishing a data monitoring committee and a plan for reporting data monitoring committee findings to the IRB and the sponsor:**
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.

2. * **Describe your plan for sharing data and/or specimens:**
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.

We may share identifiable information with authorized representatives of UPMC (including the Research Conduct and Compliance Office) for the purpose of oversight of the research study or for services they provide to the research team. Additionally, identifiable information (which may include identifiable medical information) may be shared with authorized representatives of the UPMC hospitals or other affiliated health care providers (such as MRRC technicians) for the purpose

of (1) fulfilling orders, made by the investigator, for hospital and health care services (e.g., laboratory tests, diagnostic procedures) associated with research study participation; (2) addressing correct payment for tests and procedures ordered by the investigator; and/or (3) for internal hospital operations (i.e. quality assurance).

3. **If any research data is collected, stored, or shared in a paper format, address what precautions will be used to maintain the confidentiality of the data:**
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.

View: Pitt SF: Risk and Benefits

Risk and Benefits

1. * Enter all reasonably foreseeable risks, discomforts, hazards, or inconveniences to the subjects related to subjects' participation in the research:

View

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. Involuntary clenching of jaw and/or rattling of teeth due to TMS activation of jaw and facial muscles. 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	***No Value Entered***

View

Research Activity	**Actiwatch sleep monitoring device**
Common Risks	***No Value Entered***
Infrequent Risks	**Mild discomfort from wearing watch**
Other Risks	***No Value Entered***

View

Research Activity	**Rating scales, questionnaires, and cognitive assessments**
Common Risks	***No Value Entered***
Infrequent Risks	**Some inconvenience and or anxiety may occur due to time required to complete formal rating scales and questionnaires.**
Other Risks	***No Value Entered***

View

Research Activity	**MRI**
Common Risks	***No Value Entered***
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.**
Other Risks	***No Value Entered***

View

Research Activity	**Temporary discontinuation of short-acting anti-anxiety medications**
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.**
Infrequent Risks	***No Value Entered***
Other Risks	***No Value Entered***

View

Research Activity	**Collection of private information**
Common Risks	***No Value Entered***
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.**
Other Risks	***No Value Entered***

2. * Describe the steps that will be taken to prevent or to minimize 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 have participants wear earplugs that will greatly attenuate the click sound generated from the discharge of the TMS coil. We will also provide the participants the option to place gauze between their teeth to prevent teeth rattling and discomfort caused by TMS activation of jaw muscles. 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.

3. **Financial risks - will the subject or insurer be charged for any research required procedures?**

○ Yes ● **No**

4. **Describe the steps that will be taken to protect subjects' privacy:**

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

6. **Describe the potential benefit that individual subjects may experience from taking part in the research or indicate if there is no direct benefit. Do not include benefits to society or others:**
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.

7. Do you anticipate any circumstances under which subjects might be withdrawn from the research without their consent?

● **Yes** ○ No

* **Describe the circumstances and any procedures for orderly termination:**

A participant may be removed from the research study at any time by the investigators if we discover that they do not meet study eligibility requirements, if they are unable to complete study procedures according to schedule, or if the study is not believed to be in their best interest.

8. Describe procedures that will be followed when subjects withdraw from the research, including partial withdrawal from procedures with continued data collection and data already collected:

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.

Withdrawal from Usual Care

Address the following questions since you plan to withdraw subjects from known effective therapy for the purpose of participating in this research study:

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. * **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.

Conflict of Interest

1. * Is this an FDA Covered Clinical Study?

○ Yes ● **No**

*Answer **YES** if it is:*

- *A study of a drug or device in humans to be submitted in a marketing application or reclassification petition that the applicant or FDA relies on to establish that the product is effective (including studies that show equivalence to an effective product); or*
- *A study in which a single investigator makes a significant contribution to the demonstration of safety.*

*Do **NOT** include:*

- *phase I tolerance studies or pharmacokinetic studies;*
- *clinical pharmacology studies (unless they are critical to an efficacy determination);*
- *large open safety studies conducted at multiple sites;*
- *treatment protocols; or*
- *parallel track protocols.*

2. * Does this study involve a Non-Significant Risk Device and you anticipate including the results as part of any type of submission to the FDA for approval of this device?

○ Yes ● **No**

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

○ Yes ● **No**

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

☐ A. Have a financial interest (aggregated value of equity and remuneration during the past or next twelve months) 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. Receive remuneration (during the past or next twelve months) from a non-publicly traded entity that either sponsors this research or owns the technology being evaluated or developed that exceeds $10,000?

☐ C. Have equity in a non-publicly traded entity that either sponsors this research or owns the technology being evaluated or developed?

- [ ] D. Have rights as either the author or inventor of intellectual property being evaluated or developed in this research and for which you are receiving royalties, milestone fees, or other proceeds that have or will exceed $10,000 in any 12-month period (include payments through the University of Pittsburgh, the Veterans Administration Pittsburgh Healthcare System, UPMC, and University of Pittsburgh Physicians)?
- [ ] E. Have an officer or management position with a company 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?
- [x] None of the above options apply and there are no other financial conflicts of interest in the conduct of this research.

5. **Provide the name of the investigator(s) and describe the nature of the Significant Financial Interest(s):**

Ancillary Reviews

1. **Ancillary reviews or notifications selected below are required based on previous answers to questions. If a selection is incorrect, return to the appropriate page and adjust the answers to questions on that page:**

- [ ] Conflict of Interest (**COI**)
- [x] Clinical and Translational Research Center (**CTRC**)
- [x] Data Security
- [ ] Honest Broker
- [ ] UPMC Investigational Drug Service
- [ ] Pitt Medical School Review
- [ ] Office of Investigator-Sponsored IND & IDE Support (**O3IS**)
- [ ] Radioactive Drug Research Committee (**RDRC**)(study involves the evaluation or use of procedures that emit ionizing radiation)
- [ ] RCCO Business **Manager** (required for industry sponsored studies)
- [ ] Religious Directives
- [x] Scientific Review
- [x] Health Record Research Request (**R3**) (required if using UPMC clinical data and authorization for other UPMC data sources for research)
- [x] UPMC Office of Sponsored Programs and Research **Support** (using UPMC facilities and/or UPMC patients during the conduct of the study)

2. **Additional ancillary reviews the PI may choose to include as needed for the research:**

- [ ] Human Stem Cell Oversight (**hSCRO**)
- [ ] Institutional Biosafety Committee (**IBC**)(study involves deliberate transfer of recombinant or synthetic nucleic acid molecules)

View: Pitt SF: Clinical Trials

Good Clinical Practice (GCP) Training

1. * **Regardless of funding source, is this study a clinical trial (**as defined by the NIH**)?**

   ● **Yes** ○ No

ClinicalTrials.gov Information

Visit the University of Pittsburgh Office for ClinicalTrials.gov website or contact ctgov@pitt.edu for further information.

2. * **Was this study registered, or will it be registered, on ClinicalTrials.gov?**

   ● **Yes** ○ No

3. * **Is the University of Pittsburgh or UPMC the Sponsor Organization for this study record?**

   ● **Yes** ○ No

   * **Who will be the Responsible Party for this study record?**

   Principal Investigator of this IRB application

Supporting Documents

1. **Attach any additional supporting documents not previously uploaded. Name the documents as you want them to appear in the approval letter:**

	Document	Category	Date Modified	Document History
View	Summary of Participants Withdrawn since Last Renewal.docx(0.01)	Other	3/14/2019	History
View	References.docx(0.01)	Other	2/12/2019	History
View	phone_suicide_assessment_flowchart.pptx(0.01)	Data Collection	2/12/2019	History
View	In_Person_Suicide_Risk_Assessment_Protocol.doc(0.01)	Data Collection	2/12/2019	History
View	9413 Andreescu - Approval Letter .pdf(0.01)	Other	2/12/2019	History

View: Pitt Create

Add Storage Information

1. * **Select a Storage Type:**
   Server: Pitt Department Managed Server

2. **Description:**

3. * **Will identifiable data be stored in this location?**
   ● **Yes** ○ No

4. * **Will sensitive data be stored in this location?**
   ● **Yes** ○ No

5. **Will de-Identified or anonymous data be stored in this location?**
   ● **Yes** ○ No

6. **Provide additional information as needed:**
   The subjects table will contain date of birth and initials, and links this information with the participant's study ID number that is used in data analysis. Otherwise all other data is linked with the study ID number.

View: Pitt Create

Add Storage Information

1. * **Select a Storage Type:**
   UPMC owned desktop, laptop or other device

2. **Description:**

3. * **Will identifiable data be stored in this location?**
   ● **Yes** ○ No

4. * **Will sensitive data be stored in this location?**
   ● **Yes** ○ No

   Define your encryption methods:

5. **Will de-Identified or anonymous data be stored in this location?**
   ● **Yes** ○ No

6. * **Is anti-virus software installed and up to date on all devices and are the operating systems kept up-to-date on all devices?**
   ● **Yes** ○ No

7. **Provide additional information as needed:**

View: Pitt Risk

Risk

1. * **Research Activity:**
   TMS

2. **Common Risks:**
   Scalp discomfort. Experiencing mild headache during or immediately after the TMS procedure due to TMS activation of superficial scalp muscle. Involuntary clenching of jaw and/or rattling of teeth due to TMS activation of jaw and facial muscles. Possibility to develop a delayed onset headache, which usual resolves with single dose of common analgesics (i.e., acetaminophen, ibuprofen).

3. **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.

4. **Other Risks:**

View: Pitt Risk

Risk

1. * **Research Activity:**
   Actiwatch sleep monitoring device

2. **Common Risks:**

3. **Infrequent Risks:**
   Mild discomfort from wearing watch

4. **Other Risks:**

View: Pitt Risk

Risk

1. * **Research Activity:**
   Rating scales, questionnaires, and cognitive assessments

2. **Common Risks:**

3. **Infrequent Risks:**
   Some inconvenience and or anxiety may occur due to time required to complete formal rating scales and questionnaires.

4. **Other Risks:**

View: Pitt Risk

Risk

1. * **Research Activity:**
   MRI

2. **Common Risks:**

3. **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.

4. **Other Risks:**

View: Pitt Risk

Risk

1. * **Research Activity:**
   Temporary discontinuation of short-acting anti-anxiety medications

2. **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.

3. **Infrequent Risks:**

4. **Other Risks:**

View: Pitt Risk

Risk

1. * **Research Activity:**
   Collection of private information

2. **Common Risks:**

3. **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.

4. **Other Risks:**