Study Protocol

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

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Scientific Background

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.

Study Objectives

In this pilot proposal we intend 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.

Study Design & Methods

This is an experimental, cross-sectional study. The estimated total enrollment for this study is 40 participants. The primary endpoint of this study would be the participant reaching 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.

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). 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.

A physician investigator who is also a co-investigator will review the consent form with the participant. This will occur either in person, via phone call, or via videoconference. 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. A Physician Investigator of the study will then obtain consent. 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.

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.

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, sleep onset, wake times, and how these may change during the TMS intervention.

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.

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 send a copy of the Penn State Worry Questionnaire either via a link using Pitt RedCap or mail (including a postage-paid envelope) for the participant to complete and return.

Eligibility Criteria

Participants must have completed Dr. Andreescu's study R01MH108509/STUDY19050150 and have a Penn State Worry Questionnaire score of 55 or above. Participants must be 50 years or older.
Participants must not meet any of the following 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.

Statistical Considerations

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 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 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 same atlas used for localizing the WMH volumes is also used for generating tract-specific DTI measures. The DTI data is first preprocessed 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 an 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.