COVER PAGE

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NCT04019054

Transcranial Magnetic Stimulation (TMS) in Conjunction with Exposure Therapy for the Treatment of Spider Phobia

Project Summary:
Spider phobia is an exceedingly common phobia throughout the world. The current standard treatment involves exposure therapy, which consists of a series of brief exposures of an individual to the thing they fear, in this case spiders. This study aims to examine the use of a neuromodulatory technology, transcranial magnetic stimulation (TMS), as a possible treatment option for spider phobia. TMS uses low-intensity electromagnetic energy to stimulate the brain, introducing energy into critical hubs of brain networks to "reset" their function and alleviate symptoms with very few side-effects.

This study will consist of four separate visits. After screening subjects for spider phobia, baseline testing of subjective distress measures and physiologic stress data (heart rate variability and sweat response) during a prolonged spider exposure test will be collected. Subjects will then be placed into one of two groups: one receiving exposure therapy and intermittent Theta Burst Stimulation (iTBS) TMS (active study group), and another receiving exposure therapy with iTBS to a circuit not involved in a phobic reaction (control study group). Subjects will undergo their first treatment session during the first visit following the baseline data collection; the second and third treatments will occur the following two days. The fourth visit will occur one week after the third and consist of the same testing as the first visit; the same data will be collected. Changes from pre- to post-treatment in both subjective and physiologic data will be compared between the treatment and sham groups to examine effects of TMS on spider phobia.

Background and significance

Transcranial Magnetic Stimulation (TMS) is a groundbreaking approach to treatment of neuropsychiatric disorders. TMS uses low-intensity electromagnetic energy to stimulate the brain, introducing energy into critical hubs of brain networks to "reset" their function and alleviate symptoms with very few side-effects.(Leuchter, Hunter, Krantz, & Cook, 2015) Repetitive TMS (rTMS), a specific protocol for using TMS, currently is indicated for the treatment of Major Depressive Disorder (MDD) and Obsessive Compulsive Disorder (OCD) and is more effective than medication for drug treatment resistant illness.(Demitrack & Thase, 2009) There also is evidence that rTMS is effective for the treatment of Generalized Anxiety Disorder (GAD) with fewer side-effects and potentially greater efficacy than medications alone.(Diefenbach, Assaf, Goethe, Gueorguieva, & Tolin, 2016; Dilkov, Hawken, Kaludiev, & Milev, 2017) Intermittent theta-burst stimulation (iTBS), another treatment protocol using TMS, has been shown to have similar benefits and utility as rTMS.(Bulteau et al., 2017; Chung, Hoy, & Fitzgerald, 2015; Mutz, Edgcumbe, Brunoni, & Fu, 2018) Some evidence has demonstrated that rTMS and iTBS may have clinical benefit in the treatment of phobias warranting further study.(Baeken et al., 2010; Deppermann et al., 2016; Guhn et al., 2012; Notzon et al., 2015; Paes, 2013)

Treatment of specific phobias, a disproportionate conditioned fear to a specific stimulus, typically involves exposure therapy, an extinction-based behavioral technique employed in the context of cognitive behavioral therapy (CBT).(Loerinc et al., 2015; Pachana, Woodward, & Byrne, 2007; Wolitzky-Taylor, Horowitz, Powers, & Telch, 2008) It involves exposing an individual to his or her feared stimulus in an effort to generate new non-fear associations with that stimulus. Treatment benefit with exposure therapy is observed in 70-75% of individuals compared to placebo.(Wolitzky-Taylor et al., 2008) However, not only do 25-30% of individuals not respond to exposure therapy, but few studies examining exposure therapy report long-term outcomes.(Wolitzky-Taylor et al., 2008) And these phobias are estimate to affect up to 15% of the world's population.(Eaton, Bienvenu, & Miloyan, 2018; Wolitzky-Taylor et al., 2008) In the cases where therapy fails or a patient would prefer medication, a low-dose benzodiazepine can be used, though it is not considered first-line.(Pachana et al., 2007; Wolitzky-Taylor et al., 2008) This project is designed to examine the feasibility of combining exposure therapy and iTBS treatment for phobia, and gather preliminary data to address the question of whether this combination might lead to greater or more rapid symptom resolution than exposure alone. Should our hypothesis prove true, further study may yield a new effective treatment for phobias. This would not only impact the treatment of phobias, but provide the first evidence for the usefulness of iTBS in an integrated treatment approach for phobia.

OVERVIEW

The experiment will consist of four days. Day 1 will include informed consent, questionnaires, a behavioral approach test with a spider, a series of short exposures with a spider, and the first TMS treatment (for a total of approximately 75-90 minutes). Day 2 will occur one to two days after Day 1 and will consist of a second series of short exposures with a spider and the second TMS treatment (30 minutes). Day 3 will occur one to two days after Day 2 and will also consist of a series of short exposures and a TMS treatment (30 minutes). Day 4 will occur five to seven days after Day 3 and will consist of post-study questionnaires and an identical behavioral approach test as is conducted on the first visit (30 minutes). Participants will be randomized to either an active TMS treatment group (using an iTBS stimulation protocol over the participant's ventro-medial prefrontal cortex, an area involved in phobic response) or a control TMS treatment group (using the same iTBS stimulation protocol over the central sulcus and between hemispheres, a site not associated with memory or fear response).

Prospective participants will be undergraduate students recruited through the UCLA Psychology Department Subject Pool (i.e., SONA). At this time, this small pilot study is not equipped to recruit from the population at-large, and therefore is currently limited to recruitment through SONA. All prospective participants will be screened with the 31-question Spider Phobia Questionnaire (SPQ) to ensure eligibility for participation, with a minimum total score equal to or greater than 17 required for participation.(Klorman, Weerts, Hastings, Melamed, & Lang, 1974) Participants will be enrolled for the study only if they are able to complete all four visits of the experiment. Exclusion criteria will include:

1) Subject is mentally or legally incapacitated, unable to give informed consent.

2) Subjects with psychosis (psychotic depression, schizophrenia, or schizoaffective diagnoses (lifetime)); bipolar disorder (lifetime); dementia (lifetime); delirium within the past 6 months; eating disorder within the past year; obsessive-compulsive disorder (lifetime); post-traumatic stress disorder within the past year; acute risk for suicide or self-injurious behavior. Patients with diagnostic uncertainty or ambiguity (e.g. rule-out pseudodementia of depression) will be excluded.
3) Subjects with a HamD suicidality item score of '3' or '4,' corresponding to "suicidal ideas or gestures" or "attempts at suicide," will be excluded.
4) Subjects with exposure to ECT within the past 6 months, previous TMS treatment for any condition, or VNS treatment
(lifetime).
5) Past history of skull fracture; cranial surgery entering the calvarium; space occupying intracranial lesion; stroke, CVA, or
TIAs; cerebral aneurysm; Parkinson's or Huntington's disease; or Multiple Sclerosis.
6) Any history of intracranial implant including cochlear implant, implanted electrodes/stimulators, aneursym clips or coils, stents, bullet fragments; implanted cardiac pacemaker, defibrillator, vagus nerve stimulator, deep brain stimulator; or other implanted devices or objects contraindicated by product labeling.
7) Neurological conditions including epilepsy, cerebrovascular disease, dementia, increased intracranial pressure, history of repetitive or severe head trauma, or with primary or secondary tumors in the CNS.
8) current pregnancy or breast feeding.
9) Infection or loss of integrity of skin over the forehead, where the device will be positioned.
10) Increased risk of seizure as indicated by: a) history (or family history) of seizure or epilepsy; b) history of stroke, head injury, or unexplained seizures; c) concurrent medication use such as tricyclic antidepressants, neuroleptic medications, or other drugs that are known to lower the seizure threshold; d) secondary conditions that may significantly alter electrolyte balance or lower seizure threshold; e) no quantifiable motor threshold such that TMS dosage cannot be accurately determined.
11) Known bee, insect, or arachnid allergy
12) Other medical contraindications to any of the study procedures.

Participants will be assigned course credit after participating in the study. Participants will sign up for the study only if they are able to make all four visits of the experiment. If a participant does not attend all three visits, course credit will still be given for the amount of time the participant spent doing the experiment (i.e., 1 credit for 1 hour). At this time, participants will be emailed blank copies of the forms, questionnaires, and screening tools that will be completed during the first visit, and they will be informed that they may complete the forms in advance and bring the completed forms with them to save time, should they desire. They will be asked to not return their forms via email, and to only bring them to the first visit.

DAY 1
On Day 1, participants will first provide informed consent after the nature of the study has been fully explained and the participant has had time to ask questions. After obtaining informed

consent, participants will complete a demographics and eligibility questionnaire (see Section 10.1, Item 1.0) or hand in their already-completed forms, which will be reviewed by the researcher upon completion. Ineligible participants (i.e., participants with bee, insect, or spider allergies, with scores below 17 on the SPQ, who do not speak English, are taking medications that lower the seizure threshold, or other exclusion criteria as listed in section 11.1) will be informed that they do not meet criteria and the research session will be terminated at this time. Participants found to be ineligible will still receive 1 credit for their time. All to-be-administered questionnaires are listed below and uploaded in Section 10.1, Item 1.0 of this IRB submission.

Spider Phobia Questionnaire (SPQ; Klorman et al, 1974)
Demographics & Eligibility Questionnaire
Fear of Spiders Questionnaire (FSQ; Szymanski & O'Donohue, 1995)
PHQ2
PHQ9
Hamilton Rating Scale for Depression (specifically the suicidality item)
GAD7

All participants will complete a BAT with a live tarantula. This phase of the experiment consists of 9 steps, lasting 30 seconds each with a 30 second pause between each step. During the BAT, self-reported and physiological data will be collected at each step. Skin conductance response (SCR) and heart-rate variability (HRV) will be utilized as physiologic measures of fearful arousal using BIOPAC MP150 hardware and AcqKnowledge version 4.2 software (BIOPAC Systems, Inc.).(Appelhans & Luecken, 2006; Choi et al., 2017; Christopoulos, Uy, & Yap, 2016; Laine, Spitler, Mosher, & Gothard, 2009; Thayer, Åhs, Fredrikson, Sollers, & Wager, 2012; Williams et al., 2001) Baseline SCR and HRV will be measured during a 3-minute prior to initiation of a BAT. SCR will be recorded from electrodes attached to the subjects' second and third fingers. Average SCRs and peak SCRs at each step will be measured and compared to individual baselines. HRV will be calculated from R-R intervals in a lead II electrode configuration recording; average HRVs from each step will be compared to individual baselines. The steps are as follows:

1. Stand 5 feet away from tarantula in closed terrarium
2. Stand 1 foot away from tarantula in terrarium with top removed
3. Place both hands on the side of terrarium with top removed
4. Touch nose against the glass of terrarium while looking at the tarantula
5. Place gloved hand halfway inside terrarium
6. Place gloved hand inside terrarium with all fingertips touching base of terrarium
7. Place bare hand inside terrarium with all fingertips touching base of terrarium
8. Touch the back of the tarantula's leg continuously with a Q-tip
9. Touch the back of the tarantula's leg continuously with the tip of the index finger

Prior to beginning the BAT, all participants will be read the following instructions (from BAT Admin Script): "This part of the experiment consists of 9 steps, each lasting 30 seconds. Instructions for each step will be read aloud before you proceed to the next step. Each step

must be completed before moving on to the next step, and steps much be completed in sequential order. During each step, your heart rate and sweating will be recorded via the electrodes on your chest and finger. After the experimenter reads the instructions for the next step and prior to completing the step, you will also be asked to rate your confidence level to complete the step on a scale from 0 to 100 (0= no confidence, 25= mild confidence, 50= moderate confidence, 75= high confidence, 100 = complete confidence) and your anticipatory distress on a scale from 0 to 100 (0=no distress, 25=mild distress, 50=moderate distress, 75= high distress, 100= severe distress). After completion of each step, you will be asked to rate your maximum level of distress during the step on a scale from 0 to 100. You are entitled to withdraw at any step if you do not wish to continue. Do you have any questions before we begin? The first step of the experiment is to stand 5 feet away from the tarantula while it is in its closed container for 30 seconds. The final step of the experiment is to touch the back of the tarantula's leg with the tip of your index finger continuously for 30 seconds."
Before beginning the BAT and after ensuring comprehension of the above instructions, the experimenter will ask the participant to rate his/her overall confidence and overall anticipatory distress with respect to his/her ability to complete all nine steps (see rating scales in above instructions). Before each subsequent step, the participant will be asked to rate his/her confidence and anticipatory distress regarding his/her ability to complete that particular step. During each step, the experimenter will record the spider's movement on a categorical scale (0 = no movement, 1 = a little movement, 2 = a lot of movement). After each step, the participant will be asked to rate his/her maximum level of distress while completing that particular step. Finally, the experimenter will record the number of steps willingly completed for a given participant.

Next, all participants will engage in a series of exposure practices with a different live tarantula from the one they saw during the BAT. Exposure therapy will consist of a series of 10 identical exposure trials of a 30-second duration with a 30-second pause between trials. Participants will be asked to place an ungloved hand in the terrarium (with all fingertips touching the base of the terrarium) on the opposite end of the terrarium as the tarantula during the trial. Prior to completing the series of exposures, participants will be asked about their feared outcome concerning approaching the tarantula (e.g., being bitten). Participants are entitled to withdraw at any step during exposures and will not be prevented from further continuation in the study.

Following the series of exposures, participants will undergo TMS treatments using an iTBS protocol. Before the first iTBS treatment, the TMS coil will be calibrated to the subject's individual resting motor threshold (RMT), or the minimum stimulus intensity necessary to elicit a motor response in the right abductor pollicis brevis (APB) or first dorsal interosseus (FDI) muscles for ≥ 50% of stimuli applied to the motor cortex. After initial calibration, the TMS coil will be placed over the subject's ventral medial prefrontal cortex (vmPFC; as determined using position Fpz of the international 10-20 EEG electrode system), a TMS target shown to affect phobic response.(Baeken et al., 2010; Guhn et al., 2012, 2014; Suarez-Jimenez et al., 2018) Stimulation intensity of 100% of the individual RMT in bursts of three pulses at a frequency of 50 Hz every 200 ms on top of a 5Hz carrier wave. Pulse delivery is over 2 s and repeated every 10 s, 20 times in succession, for a total of 600 pulses delivered in 3.33 minutes.(Baeken et al., 2010; Bulteau et al.,

2017; Guhn et al., 2014) This specific protocol was selected based on the assumption that it should impact fear circuitry top-down from prefrontal to subcortical networks (particularly the amygdala) as seen in prior work.(Baeken et al., 2010; Bulteau et al., 2017; Guhn et al., 2014) Control iTBS will consist of the same stimulation parameters over the subject's midline central sulcus or vertex (as determined using position Cz, of the international 10-20 EEG electrode system). This placement was chosen for control as its position over the vertex will minimize amount of cortex stimulated and the stimulated area is not associated with the circuitry examined in this experiment.(Duecker & Sack, 2015) It is a commonly-used control site in TMS studies because it is associated with no known effects and has a similar risk profile to other TMS sites. (Foltys et al., 2001; Jung, Bungert, Bowtell, & Jackson, 2016; Rossi et al., 2009; Weiss, Sparing, Fink, Tomasino, & Dafotakis, 2008) It is generally associated with lower rates of scalp discomfort and no clinically-observed behavioral or mood effects.(Jung et al., 2016; Rossi et al., 2009) Some work has demonstrated a possible decrease in activation of the default mode network though this has not been found to be clinically-significant.(Jung et al., 2016)

DAY 2

As described above, this visit will occur one to two days after Day 1. All participants will return to the laboratory to engage in a second series of exposure practices with the same tarantula from exposures at the first visit. They will undergo 10 identical exposure trials for durations of 30 seconds each, with a 30-second pause between trials. During each exposure trial, they will again be asked to place an ungloved hand in the terrarium (with all fingertips touching the base of the terrarium) on the opposite end of the terrarium as the tarantula during the trial. Prior to completing the series of exposures, participants will be asked about their feared outcome concerning approaching the tarantula (e.g., being bitten). Participants are entitled to withdraw at any step during exposures and will not be prevented from further continuation in the study.

Following the series of exposure practices, participants will undergo a TMS treatment using an iTBS treatment protocol in the same location that they received stimulation on Day 1 (vmPFC vs. vertex).

DAY 3

This visit will be identical to Day 2, and will occur one to two days after Day 2.

DAY 4

This visit will occur five to seven days after Day 3. All participants will complete the Spider Phobia Questionnaire (SPQ; Klorman et al, 1974) and Fear of Spiders Questionnaire (FSQ; Szymanski & O'Donohue, 1995), uploaded in Section 10.1, Item 1.0, to test for change in arachnophobia fear/avoidance symptoms as a function of TMS treatment received. Next, all participants will complete an identical BAT to that completed at their first visit with the same tarantula (see DAY 1 above). Self-report and physiological (i.e., SCR) data will again be collected. After completion of these forms, participants will be debriefed by an un-blinded member of the study team and informed to which group they are assigned. They will be

encouraged to discuss whatever questions or concerns they have regarding the study at that time.

After completion of Day 4, participants will be compensated for their time with one credit per hour of study participation.

Dependent variables (DVs) will be quantitative self-reports and behavioral symptoms of fear and avoidance of spiders both pre- and post-treatment, including SCR (difference between baseline and average level during BAT anticipation period, and number of peaks during BAT), total number of steps completed during the BAT, self-reported distress, anticipatory distress, and maximum distress per BAT step, and total score on the SPQ. BAT measures will be collected for each step and therefore minima, maxima, and means will be compared between the two groups. Primary outcomes examined will be number of steps completed during BAT, self-reported distress during BAT, number of SCR peaks during BAT, SPQ score, and FOS score. All other variables examined will be secondary outcomes. Additionally, for feasibility and tolerability assessment, attendance to TMS treatment sessions and early termination of TMS treatment sessions will be recorded. The primary independent variable examined will be the treatment group (iTBS vs. control iTBS). The sample size will be 40 participants (20 per group). Pre-comparison ANOVA will be performed to limit type 1 error due to multiplicity of comparisons.

Hypotheses will be tested using between-group two-tailed t-tests given that we are testing not only for magnitude of an effect, but also direction of an effect. We expect that comparisons of efficacy will demonstrate increased confidence during BAT approach, decreased endorsed fear of spiders as measured by SPQ and FSQ, and reduced physiologic response to stimulus (reduced HRV and SCR) with active iTBS and exposure when compared to control iTBS and exposure. We expect that comparisons of feasibility and tolerability will show no significant difference between attendance to, early termination of, or subjective tolerability ratings of TMS treatment sessions between treatment groups.

NOTE 2/2/21: the above reported statistical analysis plan was modified given the small sample size, technical limitations, and distributions of the data observed. The number of statistical tests performed was minimized and multi-level mixed-effects models (MLMs) and nonparametric tests were utilized as appropriate based on the sample size of the experiment. Behavioral measures acquired during the BATs (anticipatory distress, maximum distress, mean skin conductance at each step) were examined using MLMs in Stata version 16.1 as functions of BAT step, group assignment, and timepoint (pre or post-treatment). All other analyses were performed in SPSS (version 26.0.0.0). Demographics and experimental parameters were analyzed for between-group differences using 2-sided Mann-Whitney U Tests. Changes in self-reported fear of spiders (SPQ and FOS) were analyzed using a repeated-measures MANOVA (Greenhouse Geisser correction was applied in case of non-sphericity). A pair of chi-square analyses were performed to validate blinding of the study (based on questionnaires completed by subjects and raters), and no significant deviation from 50/50 chance was observed. A p-value of <0.05 was considered significant for all testing.

ADVERSE EVENT MANAGEMENT

Study personnel administering the BAT and exposure treatments will be bachelors-level trained or current UCLA students. These personnel have not been identified at this time, but will be added to the IRB and protocols as they are identified. They will be trained by personnel from Anxiety and Depression Research Center (ADRC; personnel under the supervision of Dr. Michelle Craske) in both how to properly administer the BAT and exposure treatments, as well as how to address any questions, concerns, or unexpected events that arise from these treatments (including acute episodes of psychological distress, escape of spiders, etc.). These personnel have ample experience in training others how to administer these treatments.

Three Chilean Rose Tarantulas (*Grammostola rosea*) will be stored in individual terrariums with weighted lids in a locked room within the ADRC (Life Sciences 5347), under the supervision of Dr. Michelle Craske and her laboratory personnel. All BATs and exposure treatments will take place in a controlled closed room without windows, open vents, or other large openings, to minimize the likelihood of a tarantula escape. At the beginning and end of every study session, study personnel will confirm the presence of the tarantula within the terrarium and confirm complete closure of the terrarium. After termination of testing for the day, study personnel will again confirm of the presence of the spider and the terrarium closure before departing.

In the event that a spider should escape from its terrarium, the participant will be removed from the room and study personnel will immediately re-close the room, search for the tarantula, and transfer it back to the terrarium in a manner safe for both the personnel and the spider when found. This will involve coaxing the spider to a sealable pre-dampened carrier, temporarily sealing it, and opening it inside the spider's terrarium. Though the risk posed by a tarantula bite or hair projection is low and the risk of occurrence is low, study personnel will don gloves, eye protection, and a long-sleeved labcoat (all three of which will be provided) before attempting transfer to minimize this risk. If not found after a thorough search, the room will remain closed, and other laboratory personnel and the PI will be notified, and further action will be taken to locate the spider.

Any injury sustained in the process of a spider escape or containment, such as a spider bite, will be reported as an adverse event. Should such an event emerge, study personnel present at the time of the event will be asked to contact the PI or a study clinician, who will assess the severity of the event. If the PI is not contacted in real-time, personnel will contact the PI within 24 hours of the event, and the PI will then report the adverse event within 24 hours of being informed.

We will employ the following strategy to manage suicidality and other serious adverse events (SAEs). All exposure and TMS procedures will be performed during normal working hours while there is a psychiatrist on duty at the Clinical TMS Service. Should participants become acutely distressed during a study visit, the attending psychiatrist on duty will take any steps necessary to address any clinical issues that emerge. The PI will follow up with all participants by phone

12-24 hours after all exposure treatments to ensure that they are not suffering from ongoing distress, and participants will be given contact information for the PI to reach out sooner should they desire. The PI will involve licensed clinicians as appropriate. At the initial study visit, subjects will complete the PHQ2 (reflex to PHQ9), GAD7, and HamD suicidality item and review their responses with a research assistant and clinician. All subjects also will be reminded at each visit about the availability of a clinician should the subject develop any event of concern, including suicidality or adverse events. Should such an event emerge, the subject will be instructed to contact the PI or a study clinician, who will assess the presentation as per their standard clinical protocol. This assessment will categorize the SAE as emergent or nonemergent. For non-emergent events, the clinicians will manage as they see fit. Rapid consultation with the Principal Investigator is available; should the clinician contact the PI, he or she will then be responsible for reporting the event as an SAE. If a consultation with the PI is not pursued in real-time, the clinician will inform the PI of the event within 24 hours of having identified the event. For emergent events, such as the worsening of suicidality or self-injurious behavior, the clinician will instruct the subject to go to the nearest emergency room possible. Should the clinician be concerned about the subject's imminent safety, he or she may contact the individual named by the subject in the consent form as the emergency contact, so that the contact person may help the subject get to an emergency room. If such an action is not feasible, the clinician may petition the subject to be brought involuntarily to the nearest emergency room possible, as provided for under state mental health laws in California where the study is being conducted. Consultation at any time is available by contacting the PI or a study clinician. Should the PI be contacted in real-time, he will then be responsible for initiating the SAE reporting. If the PI is not contacted in real-time, the clinician will contact the PI within 24 hours of the event, and the PI will then complete SAE reporting within 24 hours of being informed. All reports of adverse events will be reviewed by the PI and reported to the UCLA Institutional Review Board in accordance with its policies.

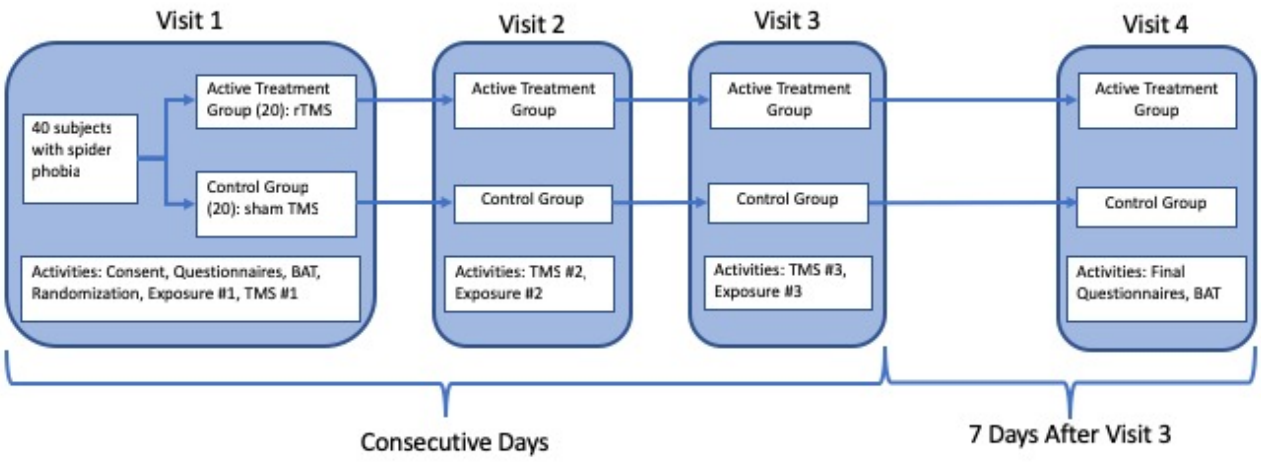

Figure 1: Flow diagram for proposed study

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List of Abbreviations

- rTMS: Repetitive Transcranial Magnetic Stimulation
- iTBS: Intermittent Theta Burst Stimulation
- MDD: Major Depressive Disorder
- OCD: Obsessive Compulsive Disorder
- GAD: Generalized Anxiety Disorder
- CBT: Cognitive Behavioral Therapy
- SPQ: Spider Phobia Questionnaire
- FSQ: Fear of Spiders Questionnaire
- BAT: Behavioral Approach Test
- SCR: Skin Conductance Response
- HRV: Heart-rate Variability
- RMT: Resting Motor Threshold
- APB: Abductor Pollicis Brevis
- FDI: First Dorsal Interosseus
- vmPFC: Ventral Medial Prefrontal Cortex