PROTOCOL TITLE: Noninvasive modulation of motivational brain regions in healthy volunteers.

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REGULATORY FRAMEWORK:

Please indicate all that apply:

☐	DOD (Department of Defense)
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Is this a clinical trial under ICH-GCP E6? ☒ Yes ☐ No

If yes, please confirm that the research team is familiar with and agrees to comply with the investigator requirements cited in ICH-GCP E6. ☐ Yes ☐ No

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1. Objectives

1.1. Describe the purpose, specific aims, or objectives.

The *purpose* of the proposed research is to develop a novel, precise, and individualized approach to modulate motivational neurocircuits in order to ameliorate apathy in traumatic brain injury (TBI). Recent work by the PI and collaborators suggests that damage to ventromedial prefrontal cortex (vmPFC) or dorsal anterior cingulate cortex (dACC) can cause elevated apathy in patients with TBI. Additionally, the PI and collaborators at the Center for Brain Recovery and Repair (CBRR) recently found that heightened connectivity between these structures may provide a compensatory response, reducing apathy in the wake of a TBI. We are currently conducting a related study using task-evoked fMRI to determine the specific neural computations that may be encoded in vmPFC-dACC circuits during motivated decision making in patients with TBI (#19-053), and the present protocol represents a separate but related line of research designed to use precise fMRI-guided transcranial magnetic stimulation (TMS) to stimulate vmPFC-dACC circuits and modulate motivated behavior in healthy controls (HCs). The *purpose* for this project is clear: fMRI-guided TMS could represent a viable approach for treating apathy in TBI, but achieving this goal requires a better understanding of the effectiveness of fMRI-guided TMS approaches for engaging those circuits. We will achieve our overall objective through the following *specific aims*:

i) To measure individualized patterns of vmPFC and dACC activation and connectivity during task-evoked fMRI.
ii) To use these activation patterns to guide brain stimulation using TMS.
iii) To measure TMS-induced changes in brain activation and connectivity using fMRI.

1.2. State the hypotheses to be tested.

i) dACC TMS will modulate motivated decision making.
ii) dACC TMS will increase post-TMS recruitment of the brain networks underlying motivated behavior.

2. Background

2.1. Describe the relevant prior experience and gaps in current knowledge.

TBI is a common and impairing acquired neurological disorder caused by a concussive event to the head. Psychiatric disorders associated with impaired decision making–namely, compulsivity, depression, and impulsivity–are common symptoms post-injury in TBI. Despite the critical importance of diagnosing and characterizing psychiatric problems in TBI, very little is known about the neuropathologies underlying psychiatric symptoms in this patient group.

Reinforcement learning (RL)–i.e. the process of learning the reward value of stimuli and actions–represents a fundamental cross-species construct underlying motivated decision making. Further, aberrant RL and reward processing more broadly have been strongly implicated in symptoms of compulsivity, depression, and impulsivity in the field of computational psychiatry[28-30]. Despite extensive evidence that brain injuries can lead to maladaptive motivated decision making[31,32], the specific RL aberrations that might underlie this phenomenon, and their association with psychiatric sequelae remain unclear. Therefore, extant work has failed to provide insight into the computational mechanisms underlying maladaptive decision making in patients with TBI, and such work will be critical to build a better understanding of the neuropathologies that underlie psychiatric sequelae in TBI. This gap in current knowledge is being targeted by our related protocol #19-053.

However, even if we have a better understanding of the RL neural mechanisms that cause aberrant motivated behavior and psychiatric sequelae in TBI, how to translate this into an actionable target for clinical intervention remains unclear. Psychological interventions including Cognitive-Behavioral Therapy (CBT) and Motivational Interviewing (MI) have been investigated for treating symptoms of TBI. Early trials suggest that CBT fails to show a beneficial effect on its own[8], but when delivered alongside MI–an approach designed to reduce patient apathy–a modest reduction is observed[9]. However, the potential benefit of both CBT and MI is limited in TBI, as they both rely heavily on high-level cognitive abilities–e.g. selective attention, executive control, and metacognition/insight–that are commonly impaired in this clinical population[10]. In addition to psychotherapies, two categories of pharmacotherapy have been investigated to reduce psychiatric sequelae in TBI: selective serotonin reuptake inhibitors (SSRIs) and dopamine agonists. A randomized controlled trial of SSRIs for TBI failed to demonstrate reductions in patient neuropsychiatric symptoms after a 10-week intervention[11]. Multiple pilot studies (*N*s=10-11) of dopamine agonists for TBI have been conducted, demonstrating preliminary support that they may reduce apathy[12,13]. Yet, a recent meta-analysis suggested a high degree of unreliability in the literature on dopamine agonism in TBI[14]. Dopamine agonists also carry the risk of significant side effects including *increased* apathy[15] or maladaptive impulsivity[16]. Unreliability and maladaptive side effects of dopaminergic medications are likely driven by their lack of circuit-specificity[17]: They modulate dopaminergic tone throughout the brain, rather than within a dedicated neural circuit underlying a specific symptom profile. *Therefore, a more effective approach to treating apathy in TBI may involve both i) avoiding therapies that rely on high-level cognition, and ii) establishing circuit-specific approaches for ameliorating patient apathy.* Precise fMRI-guided TMS represents one possible approach. The current project aims to test the efficacy of fMRI-guided TMS to RL neural circuits anchored in dACC on motivated decision making in HCs. Ultimately, the hope is that this approach might represent a first step towards a potential clinical intervention for TBI patients with clinical apathy.

2.2. Describe any relevant preliminary data.

The PI has previously published on how damage to ventromedial prefrontal cortex (vmPFC) can cause significant apathy in patients with traumatic brain injury[32]. Additionally, the study team recently leveraged extant data available in the center to demonstrate that *enhanced* connectivity between vmPFC and dorsal anterior cingulate cortex (dACC) represents a potential compensatory mechanism for reducing apathy in the wake of a mild TBI injury[63]. This dACC target, and enhanced dACC-vmPFC connectivity, will represent the critical targets for TMS neuromodulation in the current study.

2.3. Provide the scientific or scholarly background for, rationale for, and significance of the research based on the existing literature and how will it add to existing knowledge.

Dopamine agonists have demonstrated limited efficacy for ameliorating apathy in TBI, but they have significant side effects because they are circuit-general (e.g. modulate dopaminergic tone across the brain). Conventional repetitive TMS (rTMS) can induce circuit-specific changes, but its rate limiting factor is the method used to determine the target region of interest (ROI). In contrast, task fMRI-guided rTMS has the potential to enable localization of a circuit relevant to a specific symptom, and selective enhancement of excitability in that circuit. The *rationale* for this approach is that, while fMRI-guided rTMS is an established method for making causal brain-behavior inferences[19,57,58], its therapeutic potential for circuit-specific neuromodulation has not been fully realized.

3. Study Design

3.1. Describe the study design (e.g., observational; randomized placebo-controlled clinical trial, etc.)

This is a brain stimulation / HC arm of an existing protocol (#19-053). The current protocol describes a clinical trial where we will focus on the causal effect on decision-making of rTMS targeting dACC using a fully randomized, within-subjects, sham- controlled experimental design.

4. Inclusion and Exclusion Criteria

4.1. Describe how individuals will be screened for eligibility.

- Participants will be phone-screened to determine their eligibility, and the phone screen and script are provided in **Appendices 1**–**2**.

4.2. Describe the criteria that define who will be included or excluded in your final study sample.

- The protocol will recruit male and female adults (18-55 years old) of any ethnic background. All recruited participants will be capable of providing informed consent.
- Participants will have 12 or more years of education and the ability to provide informed consent independently.
- Exclusion criteria will be: any condition that would prevent the subject from being able to complete the protocol, prior history of neurological disease or any history of seizures (including prior history of TBI; i.e., any loss of consciousness ≥1 minute), not fluent in English, any contraindications to MRI or TMS (**Appendices 3-4**), history of substance abuse (excluding moderate alcohol or marijuana usage), a medical diagnosis of psychosis or mania, or stable doses of antipsychotics or mood stabilizers taken for less than two months.
- Participants who are found to have falsely represented any factors which should exclude them from the study, or who are unable to follow the study protocols for study session attendance may be withdrawn prematurely form the study.
- To reduce the possible spread of COVID-19, during the SARS-CoV-2 pandemic any participants who answer "yes" to any of the items in Question 34 of the Phone Screen (**Appendix 1**) will be excluded from the study at this time.

4.3. *Indicate specifically whether you will include each of the following special populations: (You may not include members of the above populations as subjects in your research unless you indicate this in your inclusion criteria.)*

The study will not recruit from the following special populations: adults unable to consent, individuals who are not yet adults, pregnant women, or prisoners.

4.4. *Indicate if you excluding any particular populations (e.g., women, children, persons not fluent in English, a particular racial or ethnic group, etc.) and provide justification.*

Individuals not fluent in English will have difficulty performing the behavioral assays used in the current protocol, and will find it difficult to understand the study protocols to the point where they are capable of providing truly informed consent. Accordingly, proficiency in the English language is a requirement for the current protocol.

5. Number of Subjects

5.1. If this is a multicenter study, indicate the total number of subjects to be accrued across all sites.

N/A – This is a local single-site protocol.

5.2. Indicate the number of subjects to be recruited at this site.

42 HC participants will be recruited.

5.3. Provide sample size justification

Prior studies using fMRI-guided TMS to modulate task-related neural computations have observed effect sizes of approximately $d \approx 1.02$[67-69], requiring a sample of $N=17$ per stimulus condition. Therefore, even if a high attrition rate of 20% is factored into the current study protocol, the protocol will achieve an adequate sample size to detect true differences as a function of stimulation condition.

6. Study Timelines

6.1. Describe:

Participants recruited for the study will be invited to complete three experimental sessions as soon as it is convenient for them to come in. The three experimental sessions will include one MRI scan (1-2 hours per scan). The first session will include all questionnaires and assessments (maximum time: 170 minutes, see Table 1). The second and third sessions will include rTMS administration including motor thresholding (≈20-40 minutes), neuronavigation (≈10-20 minutes) and rTMS delivery (≈3-20 minutes, depending on the specific pulse sequence). The total rTMS session will last ≈1-1.5 hours, and will be immediately followed by an MRIscan (total session time: 3-4 hours for day 1, 4-5 hours for day 2). It is expected that data collection targets will be reached by September, 2022.

7. Study Endpoints

7.1. Describe the primary and secondary study endpoints.

The study will end when $N=42$ HC have completed the protocol.

7.2. Describe any primary or secondary safety endpoints.

N/A – The study is minimal risk and no safety endpoints are necessary.

7.3. Describe any exploratory endpoints.

N/A – The study design does not include any exploratory endpoints.

8. Research Setting

8.1. Describe the sites or locations where your research team will conduct the research.

The study will be conducted in Domenici Hall on the UNM North Campus, at the Mind Research Network (MRN) also located in Domenici Hall, and in the Department of Psychology at Logan Hall on the main campus.

8.2. Identify where your research team will identify and recruit potential subjects.

All participants will be recruited from the community and from study 19-053: Reward-guided decision making in patients with moderate-to-severe traumatic brain injury (msTBI), whowere contacted via the following strategies:

i) Participants who have participated in previous studies at the CBRR and consented to be contacted for future research opportunities.

ii) Fliers posted in the community and online (**Appendices 5-7**), and word of mouth.

8.3. Identify where research procedures will be performed including any laboratory analytics

Analytic procedures will be conducted at the MRN, CBRR, and Logan Hall.

8.4. Describe the composition and involvement of any community advisory board

N/A – There is no community advisory board.

8.5. For research conducted outside of UNM HSC and its affiliates describe:

There will be no research conducted outside UNM / HSC / MRN.

9. Resources Available

9.1. Describe the qualifications of the PI and study staff (e.g., training, experience, oversight) as required to perform the research. When applicable describe their knowledge of the local study sites, culture, and society.

The PI has extensive experience studying affective and reward processes in HC and patients with TBI[32,38–40]. The PI also has experience with fMRI: The PI has experience running the MRI scanner and preparing a diverse range of subjects to be scanned, been first author on two peer-reviewed manuscripts using fMRI[41,70], and has completed both a week-long fMRI course at the Harvard-MIT Martinos Center for Biomedical Imaging, and a three-day fMRI course at the MRN. The PI has also published several papers using TMS[64-66], containing a total of 95 safely-completed TMS sessions, and recently completed an extensive hands-on refresher course on the safe and efficient administration of TMS protocols in Mark George's world-class brain stimulation laboratory in the Department of Psychiatry at the Medical University of South Carolina (**Appendix 8**).Therefore, the PI is well qualified to lead the current research protocol.

All study personnel will have been trained and certified in safe MRI practices at MRN, and will have received required training sessions in order to gain access to the UNM Noninvasive Neurostimulation Lab (PI: Dr. Davin Quinn).

Dr. Campbell oversees all projects being conducted at the Clinical Neuropsychology Research Core within the CBRR, and is well qualifiedto advise the PI while the current project is being carried out. Finally, the entire study team (including all research assistants) have completed the required CITI training modules, and have experience collecting behavioral and neuroimaging data from human participants.

9.2. When applicable, describe which licensed physicians/providers will be responsible for medical decision-making and ordering and evaluation of necessary diagnostics and therapeutics.

Within 24 hours, the Beck Depression Inventory (BDI) will be examined for endorsement of suicidal ideation. If the participant endorses suicidal ideation (scoring 2 or 3 on item #9 of the BDI) the PI will be immediately notified. The participant will then be contacted over the phone by a senior member of the research team. This protocol will be done in consultation with attending psychiatrists at the UNM Psychiatric Center.

This phone screen protocol consists of multiple steps to protect participant confidentiality:

1) The experimenter will verify via person-to-person contact with the participant that this is a "*good time to talk discreetly*" prior to raising the reason for the call about the depression rating score for suicidality.
2) If the participant endorses thoughts of suicidality they will be notified of number of local counseling and psychiatric resources, including 24-hour hotlines and free or low-cost counseling services.
3) If the participant endorses imminent suicidal ideation, the PI will call 911 to inform emergency responders of the participant's location and imminent suicide plans.

Additionally, all research MRI scans at MRN will be read for incidental findings by a radiologist.

9.3. Describe other resources available to conduct the research: For example, as appropriate:

A waiting area with a dedicated front desk staff member will greet the participants when they arrive at the CBRR. For administering the pre-MRI behavioral practice tests, five private testing rooms are available for participant visits at the CBRR. The MRI scanning facility is in close proximity to the CBRR testing facilities in the MRN portion of Domenici Hall. The scanning facility provides MRI-compatible scrubs for each participant.

With respect to equipment, a PC laptop will be available for running pre-MRI behavioral practice tasks at the CBRR. At the MRN, MRI scans will be carried out on a 3T Siemens MRI scanner using a 32-channel head coil. TMS will be conducted at the Psychiatric Neuromodulation Laboratory on the 2nd floor of the Center for Psychiatric Research, in Domenici Hall on the UNM Campus.

10. Prior Approvals

The UNM Main Campus Office of the Institutional Review Board has reviewed the protocol and agreed to defer review of the application to the UNM-HSC

Human Research Protections Office. The current protocol represents the HC arm of a separate protocol that has been approved by the HRPO (#19-053).

11. Multi-Site Research

N/A – The current protocol is a single-site study.

12. Study Procedures

The study will be conducted in three 3-6 hour sessions which can be arranged to accommodate participants' schedules. The three sessions will take place with no less than 24 hours, and no more than two weeks apart between each study visit. Approximately 24 hours prior to the scheduled date, the participants will receive an email and a phone call including important information for them to be aware of prior to coming in for thestudy (**Appendix 9**). An IRB-approved member of the research team will greet participants, and will go through the study consent procedures.

SARS-CoV-2 related note: For the duration of the SARS-CoV-2 pandemic, consent procedures will be completed remotely via a HIPAA-compliant Zoom account or phone call, with participants receiving the document via email. They will then sign the consent document when they appear in person for their study visit. A note to file will be created for each consent signed in this way. Additionally, for the duration of the visit the participant and experimenter will remain physically-distanced as much as possible, will both be wearing face coverings, and the experimenter will also be wearing a laboratory coat to reduce the risk of SARS-CoV-2 spread through droplets. During the TMS protocol, an acrylic divider will be used whenever possible to separate the participant and experimenter. MRI scans will be completed using HRRC approved protocols for scanning during the SARS-CoV-2 pandemic.

Table 1. Assessments

Order	Measure	Time (max minutes)
1	Consent + MRI Screen + Demographics	30
2	Rivermead Post Head Injury Questionnaire	10
3	Apathy Evaluation Scale (AES)	5
4	Apathy Motivation Index (AMI)	5
5	Neurobehavioral Symptom Inventory	5
6	NIH-Toolbox Cognition Battery	45
7	Frontal Systems Behavior Scale	10
8	Barratt Impulsivity Scale	5
9	Padua Inventory-Revised	5
10	Meta-Cognitions Questionnaire	5

11	Toronto Alexithymia Scale	5
12	The Next Big Five Inventory	5
13	Beck Anxiety Inventory	5
14	Beck Depression Inventory	5
15	Posttraumatic Stress Disorder checklist	5
16	Substance & Alcohol Use Questionnaires	10
17	Practice of fMRI Task ('Bandit Task')	5
18	Practice of fMRI Task #2 ('Apples Task')	5
ALL	**Total**	**170 minutes**

- **Demographics:** The Demographics spreadsheet includes background information on ethnicity, education, alcohol, and medications. It is attached in **Appendix 10**.

- **Rivermead Post Head Injury Questionnaire:** Is a semi-structured, gold standard interview used to assess each participants' TBI history in depth. This is primarily to provide evidence that HC participants in this study have quantifiably fewer / less severe TBI histories than patients in Study #19-053. It is attached in **Appendix 11.**

- **Apathy Evaluation Scale (AES):** Is an 18-item self-report measure used to assess apathy symptoms in individuals with neurological disorders such as TBI. It is attached in **Appendix 12.**

- **Apathy Motivation Index (AMI):** Is an 18-item self-report measure used to assess apathy symptoms in individuals with neurological disorders similar to the AES, but also assays a dimension known as "social-motivational apathy". It is attached in **Appendix 13**.

- **Neurobehavioral Symptom Inventory (NSI):** The NSI is a 22-item self-report questionnaire designed to probe the specific set of sequelae experienced by patients with TBI. Patients rate the degree to which they have experienced a set of common symptoms on a scale of 0-4, depending on how severely they have disturbed the patient in the past two weeks. It is attached in **Appendix 14**.

- **NIH-Toolbox Cognition Battery (NIH-TB):** The NIH-TB is a comprehensive set of standardized cognitive assessments developed by the NIH to evaluate a range of cognitive functions–including attention, episodic memory, executive function, language, processing speed, and working

memory[20]. These tasks will be administered on an iPad, with a member of the research team supervising the participants' progress and answering any questions they might have. The NIH-TB is not a pen and paper task, and was not programmed by the PI, and is therefore not appended here. However, for reference the NIH has posted a series of demonstration videos on YouTube: https://www.youtube.com/channel/UC-WnVlfVYm5i5xULhBCjOkQ

- **Frontal Systems Behavior Scale (FrSBe):** Is a self- or family-report questionnaire comprising 46 items that are highly sensitive to behavioral syndromes that present in patients with frontal brain injury. In particular, the FrSBe provides measures of apathy, disinhibition, and executive dysfunction. We will be using the self-report version in the current protocol.

- **Barratt Impulsivity Scale (BIS):** The BIS is a 30-item self-report questionnaire that is designed to measure several dimensions of impulsivity. Items are rated in terms of frequency (from 1=rarely/never to 4=almost always/always). Principal component analyses of the items on the BIS has suggested that it is comprised of three distinct factors: motor impulsivity (e.g. "I am restless at the theatre or lectures"), non-planning impulsivity (e.g. "I buy things on impulse"), and attentional impulsivity (e.g. "I am self-controlled")[25]. The BIS provides a dimensional measure of each of these factors that is useful for capturing levels of impulsivity in both the subclinical and clinical range. All BIS items are attached in **Appendix 15**.
- **Padua Inventory-Revised (PI-R):** The PI-R is a 39-item self-report instrument that is ideally suited for measuring OC traits in the subclinical and clinical range[26]. Similar to the BOCS, the PI-R breaks down into five factors, including contamination obsessions (e.g. "I feel my hands are dirty when I touch money"), dressing/grooming compulsions (e.g. "I feel obliged to follow a particular order in dressing, undressing, and washing myself"), checking compulsions (e.g. "I have to do things several times before I think they are properly done"), obsession thoughts of harm to self/others (e.g. "I imagine catastrophic consequences as a result of absent-mindedness or minor errors which I make"), and obsessional impulses to harm self/others (e.g. "When I look down from a bridge or a very high window, I feel an impulse to throw myself into space"). Items are rated with respect to intensity, from 1 = "not at all" to 5 = "very much". Scoring details and the items from the PI-R are attached in **Appendix 16**.

- **Meta Cognitions Questionnaire (MCQ):** The MCQ a 30-item self- report instrument that is designed to measure one's beliefs about their degree of access to and control over worry and intrusive thoughts[27]. Anosognosia–i.e. reduced awareness of one's own psychopathology– is often occurs in TBI, it will be critical to evaluate patients' degree of conscious access to their mental states through the MCQ. The MCQ can be broken down into positive beliefs

(e.g. "worrying helps me avoid problems in the future"), negative beliefs (e.g. "my worrying is dangerous for me"), cognitive confidence (e.g. "I have little confidence in my memory for words or names"), need for control (e.g. "I should be in control of my thoughts at all times"), and cognitive self-consciousness (e.g. "I think a lot about my thoughts"). The MCQ-30 is attached in **Appendix 17**.

- **Toronto Alexithymia Scale (TAS):** The TAS is a self-report questionnaire designed to assess one's ability to identify and describe their own emotions[28]. Participants rate 20 items on a 5-point Likert with respect to agreement (I.e. 1-Strongly Agree to 5- Strongly Disagree). TAS data reliably loads onto three factors: difficulty identifying feelings (e.g. "I am often confused about which emotion I am feeling"), difficulty describing feelings (e.g. "It is difficult for me to find the right words for my feelings"), and externally-oriented thinking (e.g. "I prefer to analyze problems rather than just describe them"). The TAS is attached in **Appendix 18**.

- **The Next Big Five Inventory (BFI-2):** This is a recent revision of the classic big five personality inventory[29], in which participants rate 60 items related to their personality with respect to their level of agreement (1 = disagree strongly to 5 = agree strongly). The BFI-2, like the original BFI, is designed to classify participants based on their personality in five dimensions: openness, conscientiousness, extraversion, agreeableness, and neuroticism. The BIF-2 is attached in **Appendix 19**.

- **Beck Anxiety Inventory (BAI):** The BAI is a 21-item self-report questionnaire of a variety of somatic (e.g. "hot/cold sweats") and affective (e.g. "fear of worst happening") anxious manifestations. Ratings are with respect to frequency of symptoms over the past month, ranging from 0 = "not at all" to 3 = "severely"[30]. The BAI is attached in **Appendix 20**.

- **Beck Depression Inventory (BDI):** The BDI is a 21-item self-report questionnaire of a variety of symptoms of depression, such as boredom ("I am dissatisfied or bored with everything") and rumination about the future ("I feel the future is hopeless and that things cannot improve")[31]. The BDI is attached in **Appendix 21**.

- **Posttraumatic Stress Disorder Checklist, DSM 5 (PCL-5):** The PCL5 is a 20-item self-report inventory of PTSD symptoms (e.g. "disturbing memories of experience," "feeling distant or cut off from other people," etc.), which are rated based on how frequently the participant has experienced those symptoms in the past month[32]. The PCL-5 is attached in **Appendix 22**.

- **Substance Use Questionnaire (SUQ):** The SUQ is a brief self-report inventory dealing with the consumption of alcohol, and both legal and illegal drugs. The SUQ is attached in **Appendix 23**.

- **Alcohol Use Disorder Identification Test (AUDIT):** the AUDIT is a gold standard self-report assay dealing more specifically with the consumption of alcohol and is attached in **Appendix 24.**

- **Bandit Task:** The Bandit task is the gold standard for isolating the neural circuits underlying explore/exploit decision making in humans and nonhuman primates[24–27,55]. During this task, participants select between images with varying probabilities of receiving a reward. After learning the reward values of each picture over a series of trials, at random intervals one of the pictures is swapped for a novel picture with a randomly assigned reward value that may be higher or lower than the remaining familiar pictures. This process is repeated for a series of trials, and participants are told that if they score high enough on a randomly selected trial, they will earn a bonus $20. In actuality, the $20 will be awarded to all participants as part of the standard compensation rate at the end of the experiment. Therefore, this process will motivate participants to accumulate points on the task, but will be evenly compensated no matter how they do on the task. A random set of pictures will be randomly selected from the International Affective Picture System (IAPS[56]) for each participant. The task was programmed by the PI, and a sample trial image is provided in **Appendix 25**. A brief practice version of the Bandit task will be performed with a research team member prior to the MRI portion on day 1, 2 or 3 of the protocol (≈3 minutes).

- **Apples Task:** The Apples task is an effort-based decision-making task that will be performed during MRI data collection on all days of the protocol. Participants will begin by practicing effortful grips requiring a certain percentage of their maximum voluntary contraction on a dynamometer (%MVC; **Appendix 26**). After experiencing the effort required to execute various %MVC grips, participants will be asked to make a series of reward-effort tradeoff decisions (**Appendix 26**). Each trial will randomly sample the parameter space between 20 and 100%MVC and one to thirteen apples. Participants will be told that at the end of the session the experimenter will select a random set of 10 responses they said 'yes' to during the MRI, but in reality (similar to the Bandit task) all subjects will receive a $20 bonus for completing the task. This will ensure participants are motivated, without placing a burden on them in terms of their physical effort requirement. A brief practice version of the task will be performed with a research team member prior to the MRI portion on day 1 of the protocol (≈5 minutes).

- **TMS Protocol:** On day 2 and 3 of the protocol, single pulses of TMS will be applied over the scalp area overlying the participants' motor cortex using a

handheld TMS coil (Magventure MagPro; Magventure, Inc., Alpharetta, Georgia, USA). TMS pulses will be delivered through an air-cooled coil in either a figure-eight or double-cone shape, with the latter being particularly useful for targeting deeper structures such as dACC. The first phase of the TMS protocol will involve a standardized motor-thresholding procedure, wherein peripheral responses evoked by single TMS pulses are recorded via an electromyographic recording device (BioPac psychophysiological recording system; BIOPAC Systems, Inc., Goleta, CA). In this phase, the TMS coil's stimulation intensity is titrated to a level that is comfortable yet effective at reliably exciting neuronal populations orthogonal to the coil (50% MEPs ≥50μv; typical duration≈20-40 mins). Then, the repetitive TMS (rTMS) procedure will be administered to a pre-determined cortical target based on the individual's pre-TMS fMRI scan using a Localite Neuronavigation system (TMS Navigator, Localite GmbH, Bonn, Germany; duration≈10-20 mins). The rTMS protocol will involve the delivery of a train of TMS pulses over a cortical target prior to performance of the behavioral tasks during a post-rTMS fMRI scan.

- Our rTMS protocol will involve one of two safe and widely used 'theta-burst' stimulation procedures, which are used to drastically reduce the total amount of time required for rTMS pulse delivery (Huang et al., 2005, *Neuron*). Theta burst rTMS will take the form of either *intermittent* theta burst stimulation (up to 1200 pulses delivered in 50Hz triplets for 2s every 10s with an 8s gap, resulting in a total stimulation duration of 190s) [73] or *continuous* theta burst stimulation (up to 3600 pulses delivered in 50Hz triplets continuously for 40s) [73]. Intermitted theta burst enhances cortical excitability at the target site, whereas continuous theta burst stimulation inhibits cortical excitability. However, priorstudies have observed conflicting beneficial cognitive effects of both excitatory (e.g. Wang et al., 2014, *Science*) and inhibitory (e.g. Tambini et al.,2018, *J Cogn Neurosci*). Therefore, we will evaluate the behavioral and neuralconnectivity data after N=10 subjects using an intermittent theta-burst rTMS protocol, and if the effects are not trending in the hypothesized direction we will plan to reevaluate and potential shift to a continuous theta burst protocol.

- Sham rTMS procedures will be identical, but will involve the delivery of subtle electrical stimulation underneath the TMS coil to mimic the tactile effects of rTMS *without* delivery of verum neuromagnetic stimulation. Both single pulse TMS / motor thresholding and rTMS are extremely safe when used within the safety guidelines for TMS. As an additional precaution, participants will be screened for contraindications to TMS using a gold-standard questionnaire[71] (**Appendix 4**).

- **MRI Scan Protocol:** Participants will complete two MRI sessions. Both scan sessions will take 1-2 hours and will happen on three separate days. To ensure

that there is no metal in their clothing, participants will be asked to remove their masks and change into a clean hospital shirt and pants before entering the MRI room. Participants will be given an MRI-compatible surgical face mask provided by MRN to wear during MRI scanning. Participants will perform 4 functional task MRI runs of the Bandit task and the Apples task, which will take approximately 50 minutes total. Additionally, T1-weighted sequence (≈5 minutes), a diffusion-weighted scan (dMRI; ≈12 minutes), and participants will look at a fixation cross for ≈11 minutes to collect resting state data. Resting state and task MRI runs will be repeated on the second and third sessions post-rTMS delivery, to elucidate the effectiveness of rTMS for engaging the targeted neuronal mechanisms. All task orders will be counterbalanced.

13. Data Analysis

13.1. Describe the data analysis plan, including any statistical procedures.

All data will undergo standard preprocessing (e.g. motion correction, spatial normalization) and quality control prior to statistical modeling. Depending on the specific question of the study, data may be analyzed using the general linear model, independent components analysis, machine learning techniques, or a variety of other standard approaches for neuroimaging data.

13.2. Provide a power analysis

Prior studies using fMRI-guided TMS to modulate task-related neural computations have observed effect sizes of approximately $d \approx 1.02$[67-69], requiring a sample of $N=17$ per group.

14. Provisions to Monitor the Data to Ensure the Safety of Subjects

The protocol is minimal risk. As this study fits NIH criteria for a clinical trial– with subjects prospectively assigned to an intervention–an independent Data Safety and Monitoring Board (DSMB) will review the study data on an annual basis with the PI to ensure participant safety (annual reports to the DSMB– **Appendix 28**). The DSMB for this study will be composed of Drs. Christopher Abbott (UNM Psychiatry) and Dr. Vincent Clark (UNM Psychology). Their experience in assuring safety of brain stimulation therapies and seizure monitoring protocols make them ideally suited to serving on this project's DSMB. Continuous, close monitoring of participant safety will include prompt and frequent reporting of safety data (i.e., adverse/serious adverse events) to the DMSB and the University of New Mexico Health Sciences Center Human Research Protections Office. The PI and members of the DSMB are well-versed in the latest scientific literature on noninvasive brain stimulation, and in each meeting will allocate time to discuss any new studies that might inform the safety or conduct of this study. According to best estimates, the rate of adverse/serious adverse events using rTMS safely is approximately 0.1% (Dobek et al., 2015, *Neuropsychiatr Dis Treat*.). Therefore, if a single seizure is reported in the current study, the DSMB will carefully evaluate whether some risk factors were missed

during the consent and TMS contraindications screening (namely: sleep deprivation, a personal or family history of seizures, or neurological disorders such as moderate-to-severe traumatic brain injury, multiple sclerosis, or stroke). If we observe a seizure where no such prior indicators are identified by the DSMB, the study will be suspended while we revise our rTMS protocol, and consider alternative stimulation parameters (e.g. lower rTMS dose), or targets (e.g. other nodes of the brain's value and effort computation circuits).

15. Withdrawal of Subjects

Participants may withdraw from the study at any time without penalty. To protect the integrity of the research study, data collected up to the time of subject withdrawal will remain in the database and managed according to the protocols outlined in Section 16. Alternatively, subjects may submit written notification that they intend to withdraw their authorization for their data to be used in the current study, which is described to participants in the detailed consent statement.

16. Data Management/Confidentiality

- All data are coded with a unique research subject identifier (URSI) number. Electronic data is stored on password protected computers only accessible by the research team, and on the COINS database on a secure HIPAA compliant cloud-based server. For non-computer based forms, the data collection sheets are stored in a locked cabinet in a locked office.
- Paperwork with identifying information–namely, payment receipts and study consent forms–will be stored in a locked filing cabinet in the CBRR while the study is being conducted, and retained there for long-term storage after data collection is complete. The laboratory's door will be kept locked, and located within the Psychology Clinical Neurosciences Center (PCNC) on the second floor of Logan Hall, which is only accessible to approved PCNC staff. These forms will be maintained for a maximum of 7 years after which they will be shredded by a member of the research team.
- Additionally, the CBRR maintains a repository of documents on REDCap (Research Electronic Data Capture)[72] to trace subjects and their documents for use during audits, or for the potential future benefit of the participant. The Research Supervisor and two research staff will have access to this repository. MRN also retains the link between identifiers and URSI indefinitely for the potential future benefit to the research participant. For example, it may become medically advantageous in the future for a former participant to have access to the clinical information that is present in most radiological scans. For example, if a participant is diagnosed with a neurological condition (e.g. multiple sclerosis, glioblastoma, TBI, etc.) it may be clinically beneficial for the participant's physician to have access to a research scan that was performed at an earlier time-point to determine disease course and severity. Both the Phone Screen spreadsheet and Master Key spreadsheet are password

protected and only accessed by the Research Coordinator as per UNM North Campus IRB suggestions.

- All assessments will be administered electronically and tracked using the participant's URSI number, and no personally identifiable information. During data collection and analysis, all electronic data will be stored on COINS, on servers at the Center for Advanced Research Computing (CARC) for advanced fMRI data processing pipelines, and accessed using secured computers in either the PI's office or laboratory at Logan Hall on main campus. The data will be archived via local backups to secured servers maintained by PCNC staff.

- In order to further protect the confidentiality of participant data, NIH-funded projects automatically fall under a Certificate of Confidentiality (CoC). With this certificate, the investigators cannot be forced (for example, by court subpoena) to disclose research information that may identify the participant in any Federal, State, or local civil, criminal, administrative, legislative, or other proceedings. Disclosure will be necessary, however, upon request of DHHS or other federal agencies for audit or program evaluation purposes. The CoC will not prevent the participant or a member of the participant's family from voluntarily releasing information about themselves or their involvement in this research. Note however, that if an insurer or employer learns about the participant's participation, and obtains consent to receive research information, then the investigator may not use the CoC to withhold this information. This means that the participant and the participant's family must also actively protect their own privacy and the confidentiality of their data. Finally, the investigator is not prevented from taking steps, including reporting to authorities, to prevent serious harm of the participant or others.

17. Data and Specimen Banking

To promote open and rigorous science practices, de-identified behavioral data and skull-stripped MRI data (i.e. with any potentially identifiable facial features removed from the brain images) will be hosted for use by external researchers through the COINS Data Exchange System. The data storage and sharing plan is described in the informed consent statement.
Additionally, Participants will be given the option of having their data stored in the MRN Data Repository (see HRRC# 06-387, PI: Roberts).

18. Risks to Subjects

- Contrast-free MRI has not been associated with any known adverse effects and is considered minimal risk by the FDA and OHRP.

- Since the scanner is a powerful magnet, it is possible to move objects containing ferrous metal in the room during the scan. Accordingly, as per MRN policy, all participants will wear MRI-compatible scrubs for the scan, and will complete a safety screening form to reveal any contraindications to MRI (**Appendix 3**) prior to completing study protocols.
- On rare occasions, some participants may experience discomfort due to claustrophobia when inside the MRI scanner. For such events, an emergency squeeze ball will be provided to participants. This ball elicits an alarm in the MRI control room, which will enable the MRI technologist/research team to rapidly extricate participants from the scanner if needed.
- The scanner produces loud 'drum' beating noises that are slightly different across the different scanning protocols. During the consent process, each of these different scanner noises will be played for the participant via headphones, to ensure they are familiar with these sounds prior to entering the scanner environment. Additionally, noise attenuating headphones will be provided for ear protection during the MRI protocols.
- On rare occasions, large or recent tattoos can heat up during an MRI scan and cause skin irritation like a sunburn. All recent tattoos will be cleared with the MRI technician before scan sessions to reduce burn risk.
- The current protocol will follow HRRC-approved MRN MRI policy for pregnancy testing adult females (page 2 of **Appendix 26**). Specifically, all females who have had their first menstrual period must answer "no" to the question on the safety screening form that asks if there is any possibility of being pregnant. If there is any uncertainty, or if the participant requests to take a pregnancy test, a urine pregnancy test will be administered and documented as negative prior to MR imaging. Testing is the responsibility of the PI and/or their designated research team members. All results are confidential and are discussed with the participant alone (regardless of participant age) in compliance with applicable laws and regulations. In the event of an unexpected positive pregnancy test, participant partners, family members, and parents may be told that the participant is not eligible for MR scanning, but no further explanation is given unless requested by the participant.
- Due to the very high sensitivity of MRI in detecting abnormalities, there is a risk of false-positive findings. This may result in anxiety and additional testing, possibly including a recommendation for clinical scans at your cost. The radiology report or other study data will not be put into participant medical record unless they provide it to their physician. If the radiology report becomes part of their personal medical record, it may or may not have an effect on their getting health insurance or life insurance in the future.
- TMS is considered a minimal risk procedure but can produce side effects that are noted here. Most people do not find TMS painful but occasionally strong

contractions of the scalp muscles can cause discomfort or headache that usually go away promptly with nonprescription medication. The noise of the TMS magnet may affect hearing, so participants will be fitted with earplugs. Like MRI, TMS involves the use of a powerful magnet. Thus TMS will not be performed on people who have pacemakers, implanted pumps or stimulators, or who have metal objects inside their heads. The risk of inducing seizure with rTMS is considered very low at <0.1%. However, certain factors increase the risk of seizure such as sleep deprivation, family history of seizures, polypharmacy, alcohol use, and previous neurological conditions. Participants will be carefully screened for these factors to ensure that risk of seizure is minimized (**Appendix 4**).

- The CBRR and MRN are both located on the UNM North Campus, in close proximity to the UNM-ER. Therefore, participants will have rapid access to an emergency facility should an unforeseen medical emergency occur during testing.
- Participants will be told that they will only win a $20 merchandise card on the primary task of interest (Bandit task) if they perform it well. However, at the end of the task all participants will receive the same compensation regardless of task performance. This protocol is used to ensure high motivation to perform the Bandit task, but may lead some participants to feel deceived at the end of the study. Accordingly, the reason for this procedure–i.e. "to ensure participants are motivated to try their best on the Bandit task"–will be explained clearly during a debrief at the end of the experimental session.

- During the SARS-CoV-2 pandemic, the current study's procedures will be in accordance with the guidelines provided by the State of New Mexico and UNM-HSC Office of Research for maintaining physical distancing and face coverage. While supporting the efforts to reduce the spread and risk of infection, COVID-19 exposure is a potential risk associated with this study.

19. Potential Benefits to Subjects

- Participants will help science and medicine better understand how TBI impacts the brain and decision-making and may help to better diagnose psychiatric problems in TBI patients using brain imaging.

20. Recruitment Methods

HC participants from the community will have been recruited via a flier that will be posted in public buildings, local businesses, and through other advertisement mechanisms such as the Weekly Alibi local newspaper, Craigslist, etc. From the participants' perspective, all study advertisements will appear as either the study flier (**Appendix 5**), or one of the approved online advertisements (**Appendices 6-7**). Electronic links to the study flier will appear as an approved link phrase (Appendix 29) and the approved thumbnail (Appendix 30). In certain instances, targeted advertisement through social media platforms (Facebook, Instagram, or Twitter) may be

used to ensure a demographic match between the current study and linked clinical study 19-053. In particular, if the current sample and 19-053 are unmatched with respect to age or sex, we will use widely-available advertisement filtering algorithms on these platforms to ensure that individuals from particular age or sex groups in the local Albuquerque community are more likely to see our approved recruitment materials. This step will be critical from a scientific perspective, ensuring our final sample will enable a valid comparison between our key outcome measures between the current study and 19-053. HC participants who consented to be contacted for future studies within the COINS system may also be contactedwithin the current protocol.

21. Provisions to Protect the Privacy Interests of Subjects

- Participants will be assigned a unique research subject identifier (URSI) number prior to their arrival on the day of their study participation, which will link their data with their name and other identifying information in the COINS system. After data collection is complete, the linking code will be made inaccessible to the research team.
- Participant behavioral testing rooms at the CBRR are equipped with white noise generators to ensure privacy during testing.
- The MRN has private changing rooms including lockers for participants to store their personal items during the MRI portion of the protocol.

22. Economic Burden to Subjects

Participants will not be charged for any of the experimental study procedures, including MRI scans and TMS sessions. If incidental findings from the study result in the need for further evaluation/treatment, the participant or their insurance company will be responsible for additional clinical evaluation/treatment that may be needed. Also, incidental finding information is disclosed only to the individual participant. However, if a participant chooses to disclose such information also to their personal physician, this may become part of their medical record which may or may not have an effect in the future on getting health or life insurance.

23. Compensation

Participants will be paid $30/hour cards for participation in the current study via Greenphire cash cards that can cashed out at any bank or physical/online store. This rate is in line with standard UNM compensation rates, particularly for patient studies where recruitment can be difficult. Minimum compensation will be $30, and after the first hour compensation will be rounded *up* to the nearest half hour for participants who do not complete the protocol. Participants will also receive $20 for completion of the Bandit Task (explained on page 12).

24. Compensation for Research-Related Injury

No commitment is made by UNM, UNM-HSC, or MRN to provide free medical care or money for injuries to participants in this study. This is clearly stated in the consent form.

25. Consent Process

- Phone screening: The protocol will be described in detail during the phone screening only for participants who meet the study inclusion / exclusion criteria. We request a waiver of consent for the phone screen process. If the participant is unable to communicate effectively, a video call will be made to accommodate them.

- Phone Consent Process: Due to the SARS-CoV-2 pandemic and in consideration of the safety and health of both participants and staff, the consent process will be completed via a HIPAA compliant Zoom account or phone call. All documents will be sent and completed through email or fax depending on participant preference. Participants unable to provide informed consent independently will be excluded in the current protocol, therefore the consent process will *not* require a legally authorized representative. Prior to the initiation of the protocols, participants will be given sufficient time to consider participation. The study MRI safety screening form and the informed consent statement are attached. Participants will be given time to complete a physical copy of the MRI safety screening form, to confirm their responses to the same items that were covered verbally with a member of the research team during the phone screen. Participants will be given time to go through the informed consent statement, and an IRB-approved member of the research team will verbally describe the most important points of the consent statement prior to beginning the protocol via Zoom or phone call. For participants who indicate that they have been diagnosed with a learning disability including dyslexia, the consent form will be read to participants by a member of the study team. Specifically, the team member will clarify what will happen over the course of the protocol, the minimal potential side effects of the protocol, and the fact that the primary benefit for participating in the proposed research will be financial remuneration and an MRI reading by a radiologist. Most importantly, participants will be told that their completion of the protocols is entirely voluntary, and that they can discontinue their participation at any time. Aftereach point, the team member will ask for verbal consent from the candidate participant. All participants are required to be fluent in English. All participants are required to be cognitively capable of providing their informed consent to complete the protocol. HIPAA authorization is included in the consent form and will be obtained for all participants.

- Note: For the duration of the SARS-CoV-2 pandemic, participants will be asked screening Question #34 (**Appendix 1**) during both the phone screen and at the end of the remote consenting procedure. Any “yes” response to this question during screening or consenting will result in exclusion from the study at this time, with the possibility to re-screen / re-consent for the study after provision of a negative COVID-19 test result and a cessation of associated symptoms for ≥14 days.

26. Documentation of Consent

Signatures will be obtained as documentation of informed consent for all participants.

27. Study Test Results/Incidental Findings

- MRI Reading: All research MRI scans are read for incidental findings by a radiologist. When the scan is read, an e-mail notification is sent to the participant letting them know new results are available. The participant can securely log in to the COINS Homepage to access their MRI radiology report. No sensitive or identifying information is sent via e-mail. If an abnormality that requires follow-up is identified, such as a Doctor Referral recommendation, a hard copy of the report may be mailed to the participant in addition to the e-mail notification. In these cases, the MRN Medical Director may also attempt to contact the participant by phone to explain the information and help answer questions.

28. Sharing Study Progress or Results with Subjects

N/A – Study progress or results will not be shared with participants for this protocol.

29. Inclusion of Vulnerable Populations

N/A – This protocol does not involve selective recruiting any vulnerable populations.

30. Community-Based Participatory Research

N/A – This protocol does not involve community-based participatory research.

31. Research Involving American Indian/Native Populations

N/A – This protocol does not involve selective recruiting of Indian/Native populations.

32. Transnational Research

N/A – This is a protocol for a single-site study.

33. Drugs or Devices

- The following devices will be used in the study: a Magventure MagPro X100 (Magventure, Inc., Alpharette, Georgia, USA). This TMS device is FDA approved for the treatment of treatment-resistant depression. The TMS device used in this study is determined to be a Non-Significant Risk device by the Principal Investigator (Jeremy Hogeveen, PhD). The device is housed at UNM in the Noninvasive Neurostimulation Lab, and access will be limited to study personnel who are trained to use this device safely.

Checklist Section

This section contains checklists to provide information on a variety of topics that require special determinations by the IRB. Please complete all checklists relevant to your research.

I. Waivers or Alterations of Consent, Assent, and HIPAA Authorization

A. Partial Waiver of Consent for Screening/Recruitment

Complete this checklist if you are requesting a partial waiver of consent so that you can review private information to identify potential subjects and/or determine eligibility prior to approaching potential subjects for consent or parental permission.

1. Describe the data source that you need to review (e.g., medical records): N/A
2. Describe the purpose for the review (e.g., screening): N/A
3. Describe who will conducting the reviews (e.g., investigators, research staff): N/A
4. Do all persons who will be conducting the reviews already have permitted access to the data source?

   ☐ Yes

   ☐ No. Explain:

5. Verify that each of the following are true or provide an alternate justification for the underlined regulatory criteria:

   a) <u>The activity involves no more than minimal risk to the subjects</u> because the records review itself is non-invasive and the results of the records review will not be used for any purposes other than those described above.

   ☐ True

   ☐ Other justification:

   b) <u>The waiver or alteration will not adversely affect the rights and welfare of the subjects</u> because eligible subjects will be approached for consent to participate in the research and are free to decline. Further, the information accessed during the records review will not be

   disclosed to anyone without a legitimate purpose (e.g., verification of eligibility).

   ☐ True

   ☐ Other justification:

c) The research could not practicably be carried out without the waiver or alteration because there is no other reasonably efficient and effective way to identify who to approach for possible participation in the research.

☐ True

☐ Other justification:

d) Whenever appropriate, potentially eligible subjects will be presented with information about the research and asked to consider participation. *(Regulatory criteria: Whenever appropriate, the subjects will be provided with additional pertinent information after participation.)*

☐ True

☐ Other justification:

Partial Waiver of HIPAA Authorization for Screening/Recruitment
Complete the following additional questions/attestations if the records you will review to identify potential subjects and/or determine eligibility include Protected Health Information (PHI).

The protected health information will not be reused or disclosed to any other person or entity, except as required by law, for authorized oversight of the research study, or for other research for which the use or disclosure of protected health information for which an opportunity to agree or object is not required by 45 CFR 164.512

6. Will you be recording any PHI when conducting the records review to identify potential subjects and/or determine eligibility?
   ☐ Yes. Describe: ☐ No

7. If you answered "Yes" to question 6 above, please describe when you will destroy identifiers (must be the earliest opportunity consistent with the conduct of the research) or provide justification for why they must be retained: N/A

8. The PHI accessed or recorded for identification/screening purposes will not be reused or disclosed to (shared with) any other person or entity, except as required by law, for authorized oversight of the research study, or for other research for which the use or disclosure of the PHI would be permitted under the Privacy Rule.

   ☐ True

   ☐ False

B. Waiver of Documentation of Consent

Complete this checklist if you intend to obtain consent verbally but will not be obtaining signatures from subjects on a consent form to document consent. Waivers of documentation of consent are commonly requested when using scripts, information sheets, or email or survey introductions to present the elements of consent instead of using a traditional consent form.

1. Are you requesting a waiver of documentation of consent for some or all subjects?

   ☐ All

   ☐ Some. Explain:

2. Provide justification for one of the following:

   a) 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.

   N/A

   b) 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.

   N/A

3. Do you intend to provide subjects with a written statement regarding the research in lieu of a traditional consent form?

   ☐ Yes. Please attach a copy to your submission in Click.

   ☐ No

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