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Protocol Title	**Brain Targets for Alcoholic Craving in Veterans with mTBI (Aim III)**
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1.0 Background

The clinical conditions of Alcohol Use Disorder, mild Traumatic Brain Injury, and Post-Traumatic Stress Disorder:

Mild traumatic brain injury (mTBI), post-traumatic stress disorder (PTSD) and alcohol use disorder (AUD) are high priority disorders for the Department of Veterans Affairs (VA), in part, because these disorders rarely occur in isolation. The co-occurrence compounds brain impairment and negatively impacts symptom presentation and rehabilitation effectiveness.

mTBI is the signature injury of the military conflicts in Iraq and Afghanistan with over 200,000 newly diagnosed mTBIs attributable to Operation Enduring Freedom, Operation Iraqi Freedom, Operation New Dawn (OEF/OIF/OND)[2]. Between 16-20% of these Veterans were exposed to mTBI events[1,2] causing brief loss or alteration of consciousness as well as cognitive, somatic, or emotional symptoms[3].

Exposure to physically and emotionally traumatic combat-related events often leads to co-occurrence of mTBI with mental health disorders including PTSD. Prevalence estimates[4] indicate that 26-44% of OEF/OIF/OND Veterans with mTBI have co-occurring PTSD[1,5]. Furthermore, the symptoms and diagnoses of these disorders are difficult to dissociate[1]. Hallmark PTSD symptoms include intrusive thoughts, hyper-vigilance, withdrawal and responses to trauma-related cues[6]. Recent evidence suggests that mTBI exacerbates PTSD symptoms and prolongs recovery[7].

AUD rates, in the general U.S. population, reach as high as 9%[8] with 17% engaging in binge drinking (i.e., > 4 or 5 drinks per sitting)[9]. Hazardous drinking rates, as defined by the Alcohol Use Disorder Identification Test (Audit), in OEF/OIF/OND Veterans are estimated at 36%[10] with AUD rates even higher for Veterans with mTBI alone[11] and when co-occurring with PTSD (mTBI+PTSD)[4,12]. mTBI also increases AUD risk for active duty military personnel[13].

There are three main reasons why improving function in Veterans with mTBI+PTSD+AUD is important to the VA. First, the three disorders commonly co-occur. Recent reports indicate that 54% of a sample of OEF/OIF/OND Veterans with PTSD and TBI (N=346) currently use alcohol[4]. Secondly, co-occurrence minimizes rehabilitation effectiveness. Substance abuse and mental health disorders pose additional barriers for community reintegration[14]. A third reason for improving function is that co-occurring chronic disorders come at high economic costs to our nation and the VA health care system[15].

Alcohol Craving:

Substance use disorders, including AUD, are defined by the American Psychiatric Association as: "compulsive engagement or impaired control over behavior, evidence of both tolerance and withdrawal, relapse despite continued harm, impairments in social and occupational functioning, and irritability or intense cravings when a particular substance is not directly available[6]." Studying alcohol craving, or the urge to drink, is important because it influences relapse[16,17], which occurs even among people who have completed behavioral rehabilitation treatment. Reports indicate that people who relapse following treatment had significantly higher self-reported alcohol craving compared to people who did not relapse[16].

The majority of alcohol craving research has focused on the general US population with little to no research involving Veterans with mTBI+PTSD+AUD. Thus, the study of co-occurring AUD with mTBI and PTSD is in its infancy. We have previously demonstrated that alcohol craving levels are elevated among Veterans with probable AUD and co-occurring mental health disorders with and without mTBI[18]. There are no FDA-approved treatments for co-occurring mTBI+PTSD+AUD, thus developing treatments to reduce alcohol craving among mTBI+PTSD+AUD is very important.

Transcranial Magnetic Stimulation (TMS):

Transcranial Magnetic Stimulation (TMS) Principles

TMS is an intervention that is well suited for the treatment of co-occurring neurological and psychiatric conditions such as AUD+mTBI+PTSD, in part, because the TMS mechanism of action allows for non-invasive modulation of neural activity. The physical principles of TMS have been the subject of many previous publications[19-21]. In brief, TMS generates a magnetic field in a coil that is placed on the scalp[20]. The field from the coil induces an electrical current in the brain tissue beneath the coil, resulting in alterations of neural excitability[20]. Depending on stimulation parameters, rTMS is able to modulate cortical and subcortical function by increasing or decreasing cortical excitability[22]. We have also published a review article on the potential of rTMS for co-occurring mTBI+PTSD+AUD[23].

rTMS as an AUD Treatment

Repetitive TMS has been tested as a treatment for substance use disorders including alcohol use disorder (AUD). To date, there are seven published papers on the use of rTMS as an AUD treatment, five of which are randomized controlled trials (RCTs)[24-28], one case series[29] and one case report[30]. All seven studies assessed alcohol craving as an outcome but report inconsistent efficacy results. The findings of these studies are summarized in Table 1 according to site of stimulation, frequency, intensity, and number of stimulation sessions.

The studies conducted by Mishra are the only RCTs which proved efficacious for reducing alcohol craving[24,28]. These studies involved provision of 10 daily sessions of high frequency (10Hz) rTMS over the right DLPFC[24,28] and left DLPFC[28] at an intensity of 110%MT. The most recent study conducted by Mishra provides evidence that provision of rTMS over the right or left DLPFC improve alcohol craving pre- compared to post-rTMS without a difference between groups[24,28]. The high frequency supra-threshold stimulation most likely facilitated excitability in the DLPFC[31]. There is evidence that high frequency stimulation of the DLPFC can modulate dopamine release in deep-brain structures important for addiction and reward such as the nucleus accumbens[32], striatum[33] and aCC[34]. Though there are some gaps as to the precise mechanism of these effects, the modulation of cortico-striatal dopamine release, presumable an effect of rTMS might explain the modulation in alcohol craving reported by

Mishra. Some consensus can be reached by comparing stimulation intensities between studies that using a higher frequency of 20Hz does not impact alcohol craving levels[25-27,29]. More studies, like the one proposed, need to be conducted for a consensus on appropriate rTMS parameters prior to implementing rTMS as a treatment to reduce alcohol craving for AUD.

Table 1. Summary of studies on rTMS as a treatment among people with Alcohol Use Disorder (AUD)

Citation	Sample Size	Site	Coil	TMS Parameters	#Sessions	Assessment	Immediate Outcomes	Long-Term Outcomes
Mishra 2010	N=45 n=30 active n=15 sham	Right DLPFC	Fig-8	10Hz, 110%MT, 4.9s/train, ITI=30s, 20trains/session, 1000 pulses/session	10 daily	ACQ-NOW, GCI, relapse	• ACQ-NOW and GCI scores improved. Relapse rate was non-significantly reduced. • AE: seizure, scalp pain, transient headache, anxiety	• ACQ-NOW and GCI effects maintained 1mo post-rTMS
De Ridder 2011	N=1	mPFC, intended target dACC	Double Cone Coil	50%MO, 1Hz	3 txt courses: txt1=3wks daily, txt2 (after 3mo)= 1wk daily, txt3 (after 3 wks)= single [~29 total sessions over ~5mo]	sLORETA EEG, fMRI, VAS, BAV, relapse	• VAS craving improved. BAV decreased. • Resting state EEG decreased activity in bilateral posterior insula, pregenual ACC, anterior PCC, and retrosplenial PCC. • Functional connectivity EEG is not changed for gamma but beta activity decreased between the PCC and NAc. • fMRI activation decreased in the PCC, ACC, and NAc. • AE: Not reported.	• 3mo post txt 1: BAV 1.9% • 3wks post txt 2: BAV 1.45% time of relapse • Relapse associated with abnormal gamma band activity in the NAc, ACC, pregenual ACC, and PCC. • fMRI data obtained at relapse similar to pre-rTMS in the NAc, ACC, and PCC.
Höppner 2011	N=19 n=10 active n=9 sham	Left DLPFC	Not reported.	20Hz, 90%MT, 2.5s/train, ITI=42.5s, 20trains/session, 1000 pulses/session	10 sessions over 12 days	OCDS, HDRS, BDI, AB	• No differences in OCDS, BDI or HDRS • AB effect was increased after the rTMS session for alcohol-related pictures. • AE: None observed.	Not Conducted.
Herremans 2012	N=28 sham/active cross-over design	Right DLPFC	Fig-8	20Hz, 110%MT, 1.9s/train, ITI=12s, 40trains/session, 1560 pulses/session	1 session repeated 1wk later in cross-over design	OCDS	• No group differences in OCDS. • AE: None observed.	• No differences in OCDS 1, 2 and 3 days post-rTMS.
Rapinesi 2013	N=3	bilateral DLPFC, preference for left side	H1	20 Hz, 120% MT, 2s/train, ITI=20s, 55 trains/session	20 sessions over 28 days	OCDS, HDRS	• OCDS & HDRS scores improved. • Clinical condition improved allowing for reduction of antidepressant medications. • AE: Not reported.	• 6mo follow-up: depression improved in all 3 subjects; alcohol craving was absent in 2 and minimal in 1 subject.
Herremans 2013	N=29 sham/active cross-over design	Right DLPFC	Fig-8	20Hz, 110%MT, 1.9s/train, ITI=12s, 40trains/session, 1560 pulses/session .	1 session repeated 1wk later in cross-over design	OCDS, Go–NoGo task: Response inhibition, state of activation and consistency in cognitive performance	• Go-NoGo Task: Decrease of response inhibition, no differences between active and sham stimulation. No difference in state of activation between active and sham stimulation. Active stimulation increased consistency in cognitive performance • No differences in OCDS. • AE: mild headache	Not reported.
Mishra 2014	N= 20 n= 10 active right n=10 active left	Right & Left DLPFC	Fig-8	10Hz, 110%MT, 4.9s/train, ITI=30s, 20trains/session, 1000 pulses/session	10 daily	ACQ-NOW,	• Significant improvement in ACQ-NOW scores pre- vs. post-rTMS for both Right & Left DLPFC groups. No difference between groups. • AE: nightmare and insomnia	Not reported.

Abbreviations: AB= Attentional Blink paradigm, ACQ-NOW= Alcohol Craving Questionnaire, AE= adverse effects, BAV= Blood Alcohol Volume, BDI= Beck Depression Inventory, dACC= dorsal anterior cingulate cortex, DLPFC= dorsolateral prefrontal cortex, Fig-8= Figure-of-eight TMS coil, GCI= General Craving Index, HDRS= Hamilton Depression Rating Scale, ITI= inter-train interval, sLORETA EEG= standardized low resolution brain electromagnetic tomography electroencephalography, mPFC= medial prefrontal cortex, PCC= posterior cingulate cortex, min= minutes, MO= machine output, MT= motor threshold, NAc= nucleus accumbens, OCDS= Obsessive Compulsive Drinking Scale, txt= treatment, VAS= Visual Analog Scale of alcohol craving, wks= weeks

rTMS as a TBI Treatment

The existing literature regarding use of rTMS as a TBI treatment for the primary brain injury as well as neurological and psychiatric sequelae is in its infancy. To date, there are seven published case studies[35-41] and one non-randomized pilot study on rTMS as a TBI treatment[42]. The case studies are diverse in that rTMS was customized to treat a specified neurological sequelae ranging from overall neurobehavioral function[35], to a particular deficit[39]. The studies also range in TBI severity from severe to mild. Most recently, Koski and colleagues (2014) published a pilot study on a sample of 15 mTBI participants [42]. This study did not include a placebo control group, but it provides preliminary evidence that high frequency rTMS provided over the left DLPFC may improve symptoms associated with mTBI[42]. Each study is summarized in Table 2 including collective contributions or impacts of research findings.

Safety

One adverse event was reported in the eight TBI studies, but it should be noted that some of these studies did not explicitly address safety. For the TBI population, seizure is the greatest potential risk associated with rTMS. Pape and colleagues (2014) reported the first rTMS related seizure for a patient who had remained in a state of disordered consciousness for nine years following a severe TBI[41]. This patient was subsequently treated with 1000 mg levetiracetam and it was reported that the patient safely tolerated a revised rTMS protocol while remaining on levetiracetam (750 mg BID). The study conducted by Kreuzer included a subject with a history of a single seizure after injury, but no seizure activity was reported during the provision of rTMS[40]. In this case, the patient was maintained on anti-seizure medications during the rTMS intervention, and no subsequent seizures occurred during the study[40]. In the pilot study conducted by Koski, two of 15 participants withdrew because they found the rTMS intervention intolerable. Other side effects are listed in Table 2 and, importantly, no seizures were reported in this study[42].

Co-occurring Conditions

Primary injures due to TBI result in contusions, diffuse axonal injuries, hematomas and hemorrhages, but the location and extent of these lesions are heterogeneous[43]. Neurosensory and neurocognitive impairments can occur after the primary injury. For example, two studies reported using TMS to treat auditory impairments due to TBI. Kreuzer and colleagues (2013) reported use of rTMS as a treatment for tinnitus[40], and Cosentino and colleagues (2010) reported use of rTMS as a treatment for musical hallucinations[36]. While aspects of the temporal cortex were sites of the primary lesions, Cosentino stimulated the right posterior temporal cortex to reduce musical hallucinations[36] and Kreuzer stimulated the auditory cortex to reduce tinnitus symptoms[40].

Depression co-occurred for two of the TBI patients who received rTMS studied in this collective literature. The study reported by Kreuzer describes a patient with a TBI and co-occurring tinnitus, depression, and a history of alcohol and benzodiazepine abuse[40]. Fitzgerald and colleagues demonstrated that depression could be reduced in a TBI patient[38]. These studies signify advancement in neuromodulation because the large-scale, double-blind randomized controlled trials on rTMS as a treatment for depression have routinely screened out patients who incurred TBI or have other co-occurring conditions such as substance use disorders. Most recently, George and colleagues (2014) assessed rTMS as a treatment among suicidal inpatients with PTSD, TBI or both[44]. This randomized, placebo-controlled pilot trial of high frequency (10Hz) rTMS applied to the left prefrontal cortex demonstrated that both placebo and active rTMS significantly improved suicidal ideation scores without a treatment effect[44]. However, no PTSD or TBI-specific outcomes were reported.

Summary and Implications for Future Work

The main limitation for this body of literature is the limited data. Seven TBI case studies and one pilot study in mTBI using rTMS as a treatment have been published to date. Each of these studies used different sites of stimulation and rTMS parameters. In addition, the rTMS paradigm for each of the TBI case studies was designed to address different sequelae. Therefore, there is insufficient evidence to determine the optimal stimulation site and TMS parameters for TBI patients. Larger-scale studies that rigorously test and optimize rTMS treatment parameters for the TBI population are needed. Given the heterogeneity of injuries within the TBI population, it may be beneficial to determine if rTMS can be optimized and tailored to each TBI patient or injury. Four reports reviewed above used neuroimaging-guided neuronavigation to identify the exact site of stimulation[35,37,39,41]. Integration of advanced neuroimaging approaches with rTMS provision, to determine ideal site of stimulation and investigate neural mechanisms of recovery, will be vital to developing rTMS as a TBI treatment.

Table 2. Summary of case reports on rTMS as a treatment among people with TBI

Citation	Case Description	Lesion	Site	Coil	TMS Parameters	#Sessions	Assessment	Immediate Outcomes	Long-term Outcomes
Pape 2009	26yo male, motor vehicle accident, severe TBI, 287 d post-injury, No co-occurring conditions reported.	Hemorrhage in lateral and 4th ventricles and right temporal lobe, diffuse traumatic subarachnoid hemorrhage and encephalomalacia.	Right DLPFC	Fig-8	2Hz paired pulse, 110%MT, IPI=100ms, ITI=5s, 300 paired pulse trains, 600 pulses/ session	30 total: 5d/wk for 6wk	DOCS, BAEP, EEG, SSEP	• Functional: Improved from VS to MCS, improved DOCS from baseline to 15th TMS session but decline at last TMS session, left BAEP wave I-V and V latency improvement. • AE: None occurred.	• 6wks post-rTMS, slight improvement in DOCS from baseline but interpretation confounded by medical issue.
Cosentino 2010	63yo male, road accident, TBI severity unknown, 10mo post-injury, co-occurring deafness.	Cranial trauma and contusion on the right temporal pole.	Right PTC	Focal Coil	1Hz, 90%MT 1200 pulses/session	10 total: 5d/wk over 2 wks	musical hallucination intensity scale, PET	• Functional: After 5 sessions, hallucinations decrease in duration and intensity. • At endpoint, hallucinations completely disappeared. • AE: None occurred.	• Less intense hallucinations recurring 4mo post-rTMS. • 5mo post-rTMS PET showed right PTC no longer hyperactive; hypoactivity in the right temporal lobe remained.
Pachalska 2011	26yo male, skiing accident, severe TBI, ≥3 yrs post-TBI, co-occurring anosognosia, executive dysfunction, and frontal syndrome.	Gliotic posttraumatic changes in right hemisphere with dilation of right lateral ventricle.	Left and Right Frontal and Temporal Cortex	Not Reported	1Hz left and 5Hz right, 25 repetitions	20 total	neuropschological battery, Go-NoGo task, Frontal Behavioral Inventory, EEG ERP	• Small improvements in behavioral changes after exam 2 and large improvements in exam 3. • 5 sessions produced clinically significant changes in neuropsychological parameters.	Not Conducted
Fitzgerald 2011	41yo female, motor vehicle accident, mild TBI, 14 years post-TBI, co-occurring depression.	Not Reported	Bilateral DLPFC	Fig-8	110%MT bilateral Right DLPFC: 1Hz, single train of 900 pulses Left DLPFC: 10Hz, 30 trains of 5s, ISI= 25s	20 once daily sessions, 5d/wk over 4 wks	MADRS, IDS-CR, IDS-SR, neuropsychological battery	• Functional: improvement in MDRS, IDS-CR, IDS-SR, mild improvement in information processing and verbal fluency. • AE: None occurred.	Not Conducted
Bonnì 2013	20yo, cause of injury not reported, severe TBI, 2 yrs post-TBI, no co-occurring conditions reported.	Cortical Lesion in Right Temporal Cortex, few small cortico-subcortical lesions in periventricular white matter.	Left PPC	Fig-8	Continuous Theta Burst: 50Hz, 80%MT, 3 pulse bursts, IPI=20ms, burst duration=40s, 600 pulses/session	2 sessions daily, over 2 wks	BIT-C, BIT-B, EEG, MEP, resting state fMRI	• Functional: Non significant improvement in BIT-C and –B scores pre- vs. post-rTMS, decreased excitability of PPC-M1 connection in left hemisphere with MEPs, bilateral increase in connectivity to site of stimulation with fMRI. • AE: None reported.	• Non-significant improvements in BIT remained 2 wks post-TMS.

Citation	Case Description	Lesion	Site	Coil	Parameters	#Sessions	Assessment	Immediate Outcomes	Long-term Outcomes
Kreuzer 2013	53yo, fall, mod-severe TBI, ~4yrs post-TBI, co-occurring tinnitus & history of alcohol & benzodiazepine abuse	Left-sided frontotemporal epi- and subdural hematoma	Left primary auditory cortex	Fig-8	1Hz, 110%MT, 2,000 pulses/session	10 sessions per course, 5 courses over 3 yrs (4th course only had 5 sessions)	TQ	• Functional: non-significant improvement in TQ scores. • AE: None occurred.	• No time specified but anecdotal reports of tinnitus reduction, alcohol and benzodiazepine abstinence and return to work.
Koski 2014	N=15 with mTBI, time since injury 6 mo to 28 yrs, 60% had elevated depression symptoms	Not Reported.	Left DLPFC	Fig-8	10Hz, 110%MT with intensity increased gradually, 20s train, ITI=25s	20 once daily sessions, 5d/wk over 4 wks	PCS, neuropsychological battery, fMRI with working memory tasks	• Functional: significant improvement in PCS scores pre- vs. post-rTMS, significant improvement in Stroop task performance and category fluency, significantly increased activation in DLPFC with working memory tasks, and significantly greater deactivation in ACC pre- vs. post-rTMS. • AE: 2 people withdrew because intervention was not tolerable, headache, vertigo, anxiety, increased sleep disturbance.	• 3 mo follow-up PCS scores improved for 2/8 completers.
Pape 2014	Patient#1: 54yo male, 188d post-TBI, severe TBI GCS 6 at time of injury. Patient#2: 32yo male, 9 years post-TBI, severe TBI GCS 6 at time of injury.	Patient#1: DAI of splenium, dorsolateral midbrain and upper pons Patient#2: multicystic encephalomalacia of right hemisphere and basal ganglia, hypoattenuation in the anterior frontal lobe and dilation of third and lateral ventricles.	Patient#1: Right DLPFC Patient#2: Left DLPFC	Fig-8	2Hz paired pulse, 110%MT, IPI=100ms, ITI=5s, 300 paired pulse trains, 600 pulses/ session	30 sessions	Structural MRI, EEG	• No change in structural MRI, no change remarkable change in EEG for Participant #1. • AE: Patient#2 had an electrographic seizure without clinical accompaniment 40min after the 21st rTMS session, change in skin condition; Patient#1 change in sleep duration, infection at IV site, and change in skin condition	Not conducted.

Abbreviations: ACC= anterior cingulate cortex, AE= adverse effects, BAEP= Brainstem Auditory Evoked Potential, BIT= Behavioral Inattention Test, BIT-C=Behavioral Inattention Test-Conventional, BIT-B= Behavioral Inattention Test-Behavioral behavioral, d= days, DAI= diffuse axonal injury, DLPFC= dorsolateral prefrontal cortex, DOCS= Disorders of Consciousness Scale, EEG= electroencephalogram, IDS= Inventory of Depressive Symptomology scale, IDS-CR= Inventory of Depressive Symptomology Clinician Rated scale, IDS-SR= Inventory of Depressive Symptomology Self Rated scale, MADRS= Montgomery-Åsberg Depression Rating Scale, MEP= motor evoked potential, mod= moderate, mo= month, MT= motor threshold, PCS= Post-Concussion Scale, PET= positron emission tomography, PPC= posterior parietal cortex, PTC= posterior temporal cortex, SSEP= somatosensory evoked potential, TQ= tinnitus questionnaire, yo = year old, yrs= years.

rTMS as a PTSD Treatment

The potential of rTMS as a neuromodulatory treatment for PTSD has been investigated via a series of case studies, pilot studies and double-blind RCTs. Table 3 summarizes the efficacy studies according to rTMS parameters examining rTMS treatment for PTSD. Efficacy studies are those with statistically significant improvement in outcomes attributed to a rTMS protocol. Studies with questionable or unclear statistical measures were not included. A majority of these studies were also reviewed recently (2014) by Karsen and colleagues[45] including a meta-analysis on three of these studies [45].

Co-occurring Conditions

As PTSD and depression symptoms commonly co-occur, some of the PTSD studies summarized in Table 3 also included patients with co-occurring depression. Study findings reported by Boggio (2010) indicate that depressive symptoms improved only for the active left DLPFC group, while anxiety symptoms improved only for the active right DLPFC group[46]. The depression findings are consistent with the FDA-approved rTMS protocol for drug resistant depression[47]. A double-blind RCT conducted by Cohen and colleagues also found right DLPFC rTMS efficacious for PTSD and anxiety symptoms, but found no change in depressive symptoms[48]. Furthermore, an open-label RCT conducted by Rosenberg and colleagues found that veterans with co-occurring PTSD and depression who received stimulation to the left DLPFC had significantly reduced depression ($p < 0.001$) and PTSD ($p = 0.02$) symptoms[49]. Most recently, Isserles demonstrated in a double-blind RCT that rTMS to the medial PFC using an H-coil significantly reduced PTSD ($p < 0.001$) and depression symptoms ($p < 0.05$) [50]. The evidence summarized suggests that the hemisphere of the DLPFC upon which rTMS is applied may, in part, determine the effects on PTSD and anxiety *versus* depression. All studies in which rTMS was administered over the left DLPFC found that depression and PTSD outcomes improved[46,49,51]. Additionally, Watts[52] found that 1Hz rTMS applied to the right DLPFC improved PTSD and depression symptoms. Furthermore, Isserles[50] found that 20Hz rTMS applied to the mPFC using an H-coil improved both PTSD and depression symptoms. One neurophysiological explanation for this finding is that through the use of the H-coil, rTMS effects occurred at the site of stimulation, the mPFC, as well as the underlying deeper brain structure, the aCC[53]. This is important because the mPFC suppresses hypothalamic-pituitary-adrenal (HPA) axis[54] and the amygdala[55] to regulate stress responses. Evidence from rodents indicates that chronic stress decreases dendritic arborization among mPFC and aCC pyramidal neurons[56]. Therefore, excitation of glutamatergic mPFC pyramidal neurons using high frequency rTMS may ameliorate mPFC/aCC dysfunction and restore proper suppression of the HPA axis and amygdala.

In addition to the importance of site of stimulation, the meta-analysis conducted by Karsen points out that there is a trend ($p= 0.061$) for a positive correlation between effect size and number of rTMS pulses[45]. That is, as the number of rTMS pulses administered in three selected PTSD studies increases, effect size also increased. The study by Isserles administered 20Hz rTMS with a total of approximately 20,000 pulses over the 12 treatment sessions, which is on the high end of rTMS studies for PTSD treatment[50].

Of particular relevance, the open-label trial conducted by Rosenberg and colleagues included 20 veterans with PTSD, depression and a history of alcohol use disorder[49]. Per the exclusion criteria, all subjects had abstained from alcohol within three months of rTMS provision[49]. Although these investigators did not collect alcohol or addiction-related outcomes, the findings indicate that 10 sessions of rTMS provided over the left DLPFC at 1Hz and 5Hz improved PTSD and depression symptoms[49]. The study reported no serious adverse events, which used rTMS among a population with three co-occurring conditions (i.e., PTSD, depression and AUD).

Summary and Implications for Future Work

For the three conditions included in this review, the amount of evidence for rTMS as a treatment for people with PTSD is greater than for people with TBI or AUD. The reported evidence is derived not only from case reports, but also from rigorous double-blind RCTs. Collectively, the evidence suggests that high frequency, supra-threshold intensity rTMS applied to the DLPFC may hold promise for the treatment of PTSD. This evidence also illustrates how rTMS may be beneficial for the treatment of co-occurring conditions. The studies that examine the co-occurrence of PTSD with other mental health conditions measured a myriad of symptoms to understand the potential of rTMS to treat co-occurring conditions. These studies provide an excellent foundation towards developing rTMS as a treatment for co-occurring conditions.

TABLE 3. SUMMARY OF STUDIES ON rTMS AS A TREATMENT AMONG PEOPLE WITH PTSD

Citation	Sample Size	Site	Coil	TMS Parameters	#Sessions	Assessment	Immediate Outcomes	Long-Term Outcomes
McCann 1998	N=2	Right frontal	Not reported.	1Hz, 80%MT, 20min/session	Case 1= 17 Case 2= 30	Described symptoms, Modified PTSD Symptom Scale, PET	Improvement in PTSD symptom frequency, decrease in cerebral metabolism AE: Not reported	Cases 1 & 2: at 1mo, symptoms returned to baseline
Grisaru 1998	N=10	Bilateral Motor Cortex	Angular coil	0.3Hz, 100%MT, 30 pulses/session, IPI= 1min, 15 on each side	single	CGI, IES, SCL-90	Improvement in CGI, IES Avoidance, & SCL-90 Anxiety & Somatization subscales at 24h AE: headache, intrusive thoughts	IES Avoidance improvement at 1 week; SCL-90 Anxiety at 28 days
Rosenberg 2002	N=12	Left DLFC	Fig-8	1Hz or 5Hz, 90%MT, 600 pulses/session	10 sessions, 5 d/wk over 2wks	POMS, HAM-D, MISS, USC-REMT	Improvement in HAM-D & POMS for 1Hz & 5Hz groups but no difference between 1Hz and 5Hz groups, better antidepressant response rate on HAM-D for 5Hz *vs.* 1Hz group AE: tension headache	HAM-D, POMS improvements 1mo & 2mo post-TMS
Cohen 2004	N=48 n=6, sham n=8, 1Hz n=10, 10Hz	Right DLPFC	Circular	1Hz and 10Hz, 80%MT, ITI(1Hz) = 55s, ITI(10Hz)=58s	20min/d over 2wks	PCL, Treatment Outcomes PTSD Scale, CAPS, HAM-A, HAM-D	After 10d of 10Hz improvement in PCL, Treatment Outcomes PTSD scale, HAM-A but no change in HAM-D AE: headaches, neck pain, muscle contraction, exacerbation of dizziness,	14d post-TMS improvement in CAPS for the 10Hz group

							manic episode, mild rage attack, ear discomfort	
Osuch 2009	N=9, sham and active cross-over design	Right DLPFC	Fig-8	1Hz, 100%MT, 1,800 pulses/session, 30min session	20 sessions, 3-5 sessions/wk	CAPS, HAM-D, IES, serum, urine	No statistically significant changes AE: None, procedure was well-tolerated	Not conducted
Boggio 2010	N=30, n=10 sham, n=10 right active, n=10 left active	Left DLPFC & Right DLPFC	Fig-8	20Hz, 80%MT, 2s/train, 40 trains/session, ITI= 28s, 1,600 pulses/session	10 sessions, 5 d/wk over 2wks	PCL, Treatment Outcome PTSD Scale, HAM-A, HAM-D, neuropsychological tests	Improved PCL scores pre *vs.* post-rTMS for both active rTMS groups. PCL scores for active right were higher than the active left rTMS group. HAM-D scores improved for left rTMS group. HAM-A scores improved for right rTMS group. AE: mild headache, neck pain, sleepiness, dizziness	PCL and Treatment Outcome PTSC Scale scores were significantly improved for both active rTMS groups 12 wks post-rTMS
Watts 2012	N=20, n=10 active, n=10 sham	Right DLPFC	Fig-8	1 Hz, 90%MT, ITI= 40s, 20min/session, 4,0000 pulses/session	10 sessions	CAPS, PCL, BDI	Improvement in CAPS, PCL & BDI after 10 TMS sessions AE: Not reported	CAPS scores remained improved 1 & 2 mo post-active TMS
Nakama 2013	N=1	Left DLPFC	Fig-8	10Hz, 120%MT, 4s/train, ITI= 26s, 3000 pulses/session	22 sessions over 6 wks	Symptom description, BDI, PCL-M	Improvement in suicidal ideation, PTSD and depression symptoms AE: Not reported	Symptom improvement 3 wks post-TMS
Isserles 2013	N=30 n=9 EXP+TMS	mPFC	H	20Hz, 120%MT, 2s/train, ITI= 20s, 42	12 sessions, 3x/week for 4 weeks	CAPS, PSS-SR, HAM-D, BDI, HR, SC	Improvement in PSS-SR, HAM-D, BDI, & CAPS for EX-TMS group only. HR decreased for EXP-TMS	2 week and 2 mo follow-up showed maintenance

	n=8 NOEXP+TMS n=9 EXP+SHAM n=4 withdrawals			trains/session, 1,680 pulses/session, each session had 4min exposure treatment and 15.5min TMS			group & correlated with CAPS score AE: headaches, anxiety, tonic-clonic generalized seizure	of CAPS scores for EXP-TMS group

Abbreviations: AE= adverse effects, BDI= Beck Depression Inventory, CGI= Clinical Global Impression Scale, d=days, EXP= auditory exposure to traumatic stimulus, HAM-A= Hamilton Anxiety scale, HAM-D= Hamilton Depression scale, HR= heart rate, IES= Impact of Event Scale, IPI= inter-pulse interval, ITI= inter-train interval, MISS= Mississippi Scale of Combat Severity, MO= machine output, MT= motor threshold, NOEXP= no exposure to traumatic stimulus, PCL= PTSD Checklist, PCL-M= PTSD Checklist-Military, POMS= Profile of Mood States, PSS-SR= PTSD Symptom Scale-Self Report version, SC= skin conductance, SCL-90= Symptom Check List, USC-REMT= University of Southern California Repeatable Episodic Memory, wk= week

Rationale for Chosen Treatment Parameters

In Summary, high frequency stimulation over the left DLPFC has been efficacious for reducing alcohol craving[28,57], improving mTBI symptoms[42], and PTSD symptoms[46,51]. Because we seek to improve alcohol craving as our primary outcome, we will use the parameters demonstrated by Mishra as efficacious for reducing alcohol craving[24]. These studies involved provision of 10 daily sessions (every week day for two weeks) of high frequency (10Hz) rTMS over the left DLPFC[28] at an intensity of 110%MT.

2.0 Testable Hypothesis or Research Question

The aim of this protocol is to examine safety, feasibility, and the behavioral and neural effects of an rTMS intervention for Veterans with AUD and co-occurring mTBI and/or PTSD. Behavioral and neural effects of rTMS will be examined after the first rTMS session and after the last rTMS session.

We hypothesize that the rTMS intervention will be 1) safe, 2) feasible and 3) efficacious. Specifically, we hypothesize that there will be no adverse events related to the rTMS intervention. We hypothesize that all participants enrolled will successfully complete all rTMS sessions. We hypothesize that participants treated with active rTMS, relative to placebo rTMS, will have reduced alcohol craving severity levels. Finally, we hypothesize that participants treated with active rTMS relative to placebo rTMS will have reduced brain activation in response to alcohol cues and improved functional connectivity after the last rTMS session.

3.0 Study Design and Methods

Study Design:

This is a prospective, pilot, double-blind randomized controlled trial of the intervention rTMS. Participants that completed Aims I (IRB# 13-077, 985219) and II (IRB# 16-042, 1035381) of Brain Targets for Alcoholic Craving in Veterans with mTBI or Alcohol Craving Treatment Development for Individuals with Co-occurring mTBI, PTSD and AUD (Aim I-Phase I) (IRB# 15-036, 985221) will be eligible to complete this Aim III protocol. There will be 2 groups of Veterans with AUD and co-occurring mTBI and/or PTSD those given 1) active rTMS and those given 2) placebo rTMS.

Study population:

Targeted enrollment for this study is 40 Veterans: n=20 active rTMS and n=20 placebo rTMS. Veterans that previously participated in Brain Targets for Alcohol Craving in Veterans with mTBI (Aim I and Aim II) or Alcohol Craving Treatment Development for Individuals with Co-occurring mTBI, PTSD and AUD (Aim I-Phase I) will be invited to participate. We will screen a total of up to 94 Veterans for participation in the current study. Only Veterans that indicated on the informed consent form of these studies that they wish to be contacted regarding future research will be invited to participate. The contact information for these Veterans is stored as a part of the IRB-approved TBI Data Repository (IRB# 14-003, 985344). These Veterans will be sent an informational letter, study flyer and MRI brochure along with an opt-out card and return-address envelope. The informational letter will instruct the Veteran to return the opt-out card if they do not wish to be contacted about research participation for this study. One week later, Veterans that did not send in an opt-out card will be contacted via phone to see if they are interested in completing the study. No more than two voice messages and three phone calls will be made.

Inclusion criteria: English Speaking Veterans ages 22 through 65 meeting AUDIT-C criteria for AUD (≥4 for men and ≥3 for women) and tobacco dependent. Pass MRI screening using the Center for Translational Imaging (CTI) Safety Form. Participants must also have Clinical Institute of Withdrawal

Assessment in Alcohol Withdrawal (CIWA-Ar) scores of ≤ 10. Veteran participants must also have previously met study criteria for a mTBI per the Symptom Attribution and Classification Algorithm, which is in keeping with the American Congress of Rehabilitation Medicine, and the VA/DoD criteria for mTBI. Veterans may or may not have also previously met study criteria for PTSD per the Clinician-Administered PTSD Scale for DSM-V.

Exclusion criteria:

- history of moderate to severe TBI;
- history of mild TBI within the last 3 months
- documented and verified history of psychotic spectrum disorders (i.e., schizophrenia, bipolar);
- receipt of anti-epileptic medications to control active seizures or evidence of documented seizure within past six months;
- receipt of tricyclic anti-depressants, antipsychotic agents, or other drugs that lower the seizure threshold;
- current use of opiates, cocaine, amphetamines, barbiturates, or benzodiazepine; marijuana/cannabis dependence as determined by the SCID-IV;
- currently prescribed any anti-craving/addiction medications (i.e., naltrexone, varenicline, bupropion, disulfiram, acamprosate);
- meet questionable validity or malingering criteria on the Minnesota Multiphasic Personality Inventory-2-RF (MMPI-2-RF; F: T score ≥ 107; F(p): T score ≥ 85; TRIN: T score ≥ 80; VRIN: T score ≥ 80) or the Letter Memory Test (LMT; total score ≤ 92%), as determined in IRB#13-077;
- pregnant or nursing;
- have congestive heart failure;
- have cardiac pacemaker or defibrillator, cochlear implant, nerve stimulator, intracranial metal clips, implanted medical pump, or increased intracranial pressure;
- history of surgery on blood vessels in brain and/or valves of the heart;
- history of brain hemorrhage, neurovascular conditions and neurodegenerative disorders;
- history of claustrophobia, metal in eye/face, or shrapnel/bullet remnants in brain.
- actively suicidal as evidenced by plan to harm or recent attempt communicated on the BDI-II or electronic medical record within the past 6 months.

Safety of participants based on medical history will be evaluated on a case by case basis when determining eligibility by the PI in consultation with study physicians.

Current use of above listed substances and prescriptions is defined as a positive result on urine screen and/or documentation of use or prescription one month prior to screening.

Women and minorities will be included in the study as long as they meet the inclusion/exclusion criteria. Participants will not be excluded from the study based on their gender or ethnic background.

All participants are required to remain abstinent from drinking alcohol during study participation.

Screening: A partial HIPAA waiver and waiver of informed consent for screening purposes will provide regulatory approval to screen candidates to determine study eligibility prior to obtaining informed consent. A week after potential participants were mailed an informational letter, they will be contacted via phone to determine interest and complete a phone screening. The telephone conversation will begin

with a description of the study and the time commitment required to complete the study. The phone screening will include administering the CTI Safety form, and the Alcohol Use Disorder Identification Test, consumption questions (AUDIT-C). A list of prescribed and over-the counter medications and the length of time the participant has been on each medication will also be collected over the telephone. Current medications will be cross-referenced with study eligibility criteria and the EMR to identify any antiepileptics, and any medications known to lower seizure threshold. The electronic medical record (EMR) will also be reviewed for study eligibility criteria. If review findings indicate possible contraindications to rTMS or MRI related to a metal implant, then the model and manufacturer of the implant will be obtained to determine whether or not it is safe to expose the implant to a strong magnet. Manufacturer recommendations regarding safety will be followed. If potential participants meet all eligibility criteria, they will be scheduled for the first research visit. They will be mailed a copy of the informed consent form to review, a map of Northwestern University's Chicago campus, and an appointment reminder of the appointment date and time.

VISIT 1: Visit 1 will occur at Hines VA and will take approximately 1 and a half hours.

Informed Consent: Authorized clinical researchers will meet with the eligible participant in a private room to review the consent form and all research procedures, risks, confidentiality measures and study contact information. All participants will be able to make their own decisions regarding research participation. They will be encouraged to have a family member or friend in the room during the discussion of the study. The participant will not be openly encouraged to participate in the research or told that there is any expected benefit from the experimental interventions during participation. Research participants will have access to research staff to assist with any questions or concerns until understanding is achieved to the judgement of the individual asking the question. If a participant refuses participation, no further contact will be made. If signed informed consent forms are completed, a note will be made in the Hines VA EMR, and the original consent will be kept in a locked cabinet in a locked research office behind swipe-access doors in Bldg. 1, Room B-351 or B-318 of Hines VA. Copies of the signed consent forms will be provided to the Hines VA IRB Office. Additionally, a copy will be provided to the participant.

Drug and Alcohol Screening: Abstinence from alcohol and illicit substances will be requested for each visit and will be confirmed with a breathalyzer and urine drug screen. On Visit 1, the urine drug screen will be completed by Hines VA clinical laboratory using a manual requisition with the participant's unique subject ID number. All subsequent urine drug screens will be conducted using a urine test kit by research staff. No results from the urine drug screen will be entered into the Veteran participant's medical record. These results will be for research purposes only. An acute cannabis intoxication scale[58] will also be completed that includes the following 4 items: (1) increased resting heart rate (>100 beats/minute), (2) congestion of the conjunctival blood vessels (red eyes), (3) slowed speech, and (4) giddiness. Any participant testing positive for alcohol, drugs, or cannabis intoxication will be asked to re-schedule research procedures, and safe transportation will be arranged (e.g., taxi) or participants will be escorted to the ER or mental health intake as appropriate (see 4.0 Risks).

All female participants will complete a pregnancy test during visit 1. If a pregnancy test is positive, then participation in the study will stop. This pregnancy screening will be repeated again at midpoint of the study and may occur at least one time randomly during continued study participation.

Baseline Behavioral Self-Report Assessments: Participants will complete the assessments listed on Table 4 in a private room with trained research staff.

All participants will also complete a baseline 20min electroencephalogram (EEG). This will be conducted so that if a seizure occurs, and EEGs are ordered by the participants treating physician, there will be a pre-rTMS baseline for comparison. The 20min baseline EEGs will be evaluated by the study team epileptologist, Dr. Vijaya Patil, will complete a clinical read of all baseline EEGs. If Dr. Patil is out of the office, then the Hines VA neurologist covering for her will complete the read. The baseline EEGs will be

evaluated, and confirmation of no epileptiform activity will be determined prior to Visit 2 (i.e., initiation of rTMS).

The following behavioral measures will then be completed with the participant in person due to the sensitive nature, need for clinical evaluation, and necessity for study eligibility determination: The Clinical Institute of Withdrawal Assessment in Alcohol Withdrawal (CIWA-Ar), the Beck Depression Inventory-II (BDI-II), and the Structured Clinical Interview for DSM-5 Diagnoses (SCID-5), Module E, AUD section only. These assessments will be conducted by trained research staff and the CIWA-Ar and BDI-II will be reviewed by a physician (see Safety Monitoring, below).

VISIT 2: Visit 2 will occur at Northwestern University's Center for Translational Imaging (CTI), 710 N. Fairbanks Ct, Chicago, IL and will take approximately 1 hour.

Northwestern Specific Procedures:

All participants will also sign a Northwestern IRB approved consent form, as Visits 2 and 12 will be completed at Northwestern. Copies of the Northwestern signed consent forms and original VA consent forms will be mailed via chain of mail custody to the Clinical Research Coordinator at the Hines VA. Consent documents will be stored in locked file cabinet, behind a locked door at the Hines VA Bldg. 1, Room B-351 or B-318. A copy of the signed Northwestern consent form will be provided to NU through the Study Tracker system.

Drug and alcohol screening will be completed as described above. Per CTI policy, all participants will re-complete the CTI Safety Screening form.

MRI Scan:

The MRI will last **approximately 45 minutes**.

Participants will be asked to change into a hospital gown or surgical scrubs and remove any metal, such as earrings. An MRI technician will give the participant instructions outside the MRI scanner about the scanning. Next the participant will be asked to lie still on the MRI patient table and the participant's head will be placed in a specially-designed head holder and their head will be cushioned by a firm foam pillow. The table will then slide into the enclosed space of the MRI scanner. Participants will be given ear plugs to dampen the MRI noise.

A Siemens 3 Tesla Prisma MRI scanner with a 64-channel head coil will be used. Participants will be provided with headphones to reduce scanner noise and asked to keep still during scanning procedures. A 3D structural T1-weighted image (MPRAGE) will be acquired using conventional acquisition parameters[31], diffusion tensor imaging, resting state functional connectivity and functional MRI paradigm described below. For the functional activation protocol, participants will undergo a series of single-shot gradient echo planar imaging sensitive to blood oxygen level dependent (BOLD) contrast sequences using conventional acquisition parameters[31] . Total scan time will be approximately 45 minutes.

The functional MRI paradigm is a visual alcohol cue presentation protocol modified from Vollstadt-Klein and colleagues[17] includes blocks of visual alcohol cues, neutral cues and a fixation cross. A visual analog craving scale will be presented after each visual block. Severity of craving will be rated by the participant in the scanner using four buttons. The alcohol cues will be taken from a validated picture series[18] and neutral cues will be taken from the International Affective Picture System[32]. Visual cues will be presented with Presentation software (Neurobehavioral Systems, Inc.).

The alcohol fMRI imaging protocol is a blocked design incorporating visual alcohol cues, neutral cues, rest and a visual analog craving scale. This protocol design was modified from Vollstädt-Klein *et al.* 2011, *Biological Psychiatry,* 69(11):1060-6. Twenty-eight blocks will be included: 7 blocks of visual

alcohol cues, 7 blocks of visual neutral cues and 14 blocks of rest and visual analog craving scale after each visual block. Each visual block consists of five visual stimuli presented for four seconds each. The alcohol visual stimuli will be taken from a validated picture series[18] and neutral visual stimuli will match each alcohol visual stimuli by hue and will be taken from the International Affective Picture System[32]. The entire length of alcohol fMRI scan time will be approximately 12 minutes.

A de-identified copy of the TI/MPRAGE/structural scan will be made available to the Veteran's physician on a CD/DVD with a viewing program upon request. The veteran will sign a medical release form and the CD/DVD will be mailed to the veterans' physician using a Courier mailing service.

VISIT 3: Visit 3 will occur at Hines VA and will take approximately 2 hours.

Drug and alcohol screening will occur as described above.

The following behavioral measure will be completed prior to rTMS treatment (see Table 4): The Clinical Institute of Withdrawal Assessment in Alcohol Withdrawal (CIWA-Ar), demographics, Penn Alcohol Craving Scale (PACS), Obsessive Compulsive Drinking Scale (OCDS), Alcohol Craving Questionnaire (ACQ-NOW), Alcohol Urge Questionnaire (AUQ), Timeline Followback calendar for alcohol use (TLFB), Beck Anxiety Inventory (BAI), Buss Perry Scale, PTSD Checklist for DSM-5 (PCL-5), and Neurobehavioral Symptom Inventory (NSI). The TLFB of alcohol use calendar will be completed for the past 90 days for Visit 3. These assessments will be conducted by trained research staff and the CIWA-Ar will be reviewed by a physician (see Safety Monitoring, below).

Table 4. Study Assessments

Assessment	Description	Time Point Assessed
CTI Safety Screening Form	MRI safety	Screening, Visit 2 and Visit 12
Alcohol Use Disorder Identification Test, consumption Questions (AUDIT-C)	Alcohol use in past year	Screening
Clinical Institute of Withdrawal Assessment in Alcohol Withdrawal (CIWA-Ar)	Alcohol withdrawal	Visit 1 and 3
Demographics	Date of birth, age, gender, race, ethnicity,	Visit 3
Penn Alcohol Craving Scale (PACS)[59]	Alcohol craving in past 2 weeks	Visit 3 and Visit 12
Obsessive Compulsive Drinking Scale (OCDS)[60]	Alcohol craving	Visit 3 and Visit 12
Alcohol Craving Questionnaire (ACQ-NOW)[61]	Alcohol craving	Visit 3 and Visit 12

Alcohol Urge Questionnaire (AUQ)[62]	Alcohol craving	Visit 3 and Visit 12
Time Line Follow Back calendar (TLFB)	Alcohol use	Visit 3 and Visit 12
Structured Clinical Interview for DSM-5 Diagnoses (SCID-5), Module E, AUD section only	AUD diagnosis and severity	Visit 1
Acute cannabis intoxication scale[58]	Cannabis intoxication	Visits 2-12
Beck Depression Inventory-II (BDI-II)	Depression symptoms	Visits 1, 7 and 12
Beck Anxiety Inventory (BAI)	Anxiety symptoms	Visits 3 and 12
Buss Perry Scale	Aggression symptoms	Visits 3 and 12
PTSD Checklist for DSM-5 (PCL-5)	PTSD symptoms	Visits 3, 7 and 12
Neurobehavioral Symptom Inventory (NSI)	mTBI symptoms	Visits 3 and 12

Motor Threshold & Brain Mapping Site of Stimulation: Stimulation intensity that will be used for rTMS treatment will be determined by collecting each participant's motor threshold (MT) for the finger representation of the motor cortex. The consensus in the literature is that rTMS can be safely provided at 110% of resting motor threshold (MT)[63].

In order to determine motor threshold, a structural brain image of the participant is needed. All participants previously completed an MRI scan in order to obtain a structural brain image also referred to as the participant's 3D-MPRAGE T1 volume. This T1 image will be loaded into the Localite TMS Neural Navigator system which is a Magventure compatible and portable neuronavigational system. Based on the T1 image, the left motor cortex will be initially targeted to determine MT. Single pulse TMS will be applied to the optimal scalp location ('hot spot') to activate the abductor pollicis brevis (APB) (i.e., thumb muscle) on the right hand to determine the RMT, or the lowest stimulus intensity necessary to produce MEPs of peak-to-peak amplitude ≥50μV in 5 of 10 subsequent trials. MEPs will be recorded using surface electrodes. Data will be stored on the computer for offline analysis. The Magventure C-B60 coil will be used to deliver single TMS pulses for MT determination. All participants, regardless of group randomization will receive MT testing and thus will receive some stimulation. We will use each subject's MT, an indicator of cortical excitability, as the benchmark for determining rTMS intensity for each subject (as described later, rTMS intensity will be 110% of each subject's MT).

rTMS Session#1:

Half of the participants will be randomly assigned to the active rTMS and half to the placebo rTMS group. Each session will take approximately 1 hour to complete.

TMS pulses will be applied to the left DLPFC at 10Hz rate, 4.9 seconds per train, with inter-train interval of 30 seconds, and a total of 20 trains per session[28]. These parameters fall within established rTMS safety parameters[63]. Each patient will receive approximately 1000 pulses per day. rTMS will be delivered with the Magventure MagProX100 with MagOption stimulator and Magpro Cool Coil B65 A/P.

The Magpro Cool Coil B65 A/P can be switched to active or placebo (A/P). Participants randomized to active rTMS will receive stimulation at the left DLPFC at 110% resting MT. The left DLPFC will be marked in the TMS Localite Navigation system for each participant. The navigation system will provide target guidance and will help the researcher to position the coil very precisely in reference to the participant's brain. The neuronavigation system will be used for every rTMS session to ensure reproducibility and consistency at the stimulation site.

Participants randomized to placebo rTMS will not receive any rTMS stimulation. The placebo coil will be connected to a placebo noise generator. Similar to the active rTMS participants, the placebo participants as well as the researchers providing rTMS will wear headphones that are connected to the placebo noise generator so that they hear the sound of active TMS in order to maintain blinding. The sensation from the placebo coil will be identical to the sensation produced by the active rTMS coil. rTMS will always be provided with a nurse present in order to observe the participant for seizure activity.

Additionally, to monitor for discomfort or pain, participants will be asked, after rTMS session, to rate their pain. They will characterize the sensation by describing it as painful, tingling, sharp, piercing, tugging, pinching and/or intolerable and rate the degree of the sensation on a 0-100 scale (0 being no sensation and 100 being significant).

The rTMS Treatment Day Safety Monitoring Plan/Log will also be filled out. Each item on this log specifies as to whether it will be completed before, during or after the rTMS session. The adverse event log will also be completed as necessary.

All investigators and research team members who will be providing the experimental treatment will undergo training on the use of the Magventure device and provision of Active and Placebo rTMS with the Magventure device. Magventure representatives have come to Hines VA Hospital and Northwestern University to hold training sessions on the Magventure stimulator and coils. Drs. Herrold and Pape have attended these training sessions with other research staff. Drs. Herrold and Pape will train other investigators and research team members. Anyone who is trained to use the Magventure system will be required to sign an Investigator Agreement stating that they have received training. Training will be mandatory for any research team member who provides the experimental treatment. Once trained, Drs. Herrold and Pape will observe the research team member providing rTMS treatment at least three times to ensure that the research team member is properly and safely administering the treatment.

VISITS 4-11, rTMS Sessions #2-9:

Procedures for rTMS Session #1 will be repeated.

- **VISIT 7 (post-rTMS Session #5) Mid-point Safety Assessments:** The BDI-II and PCL-5 will be repeated after the first week of rTMS at the end of rTMS Session #5.

VISIT 12, Endpoint: Visit 12 will occur at Northwestern University's CTI at 710 N Fairbanks Ct, Chicago, IL for all participants.

All participants will also complete a CTI Safety Form, which is required by CTI for each participant to complete in person prior to the MRI.

rTMS Session #10: Procedures for rTMS Session #1 will be repeated.

MRI Scan: Procedures detailed above for the MRI scan in Visit 2 will be completed for all participants.

Endpoint Behavioral Assessments: Participants will complete the assessments listed on Table 4 in a private room with trained research staff. The Time Line Follow Back of alcohol use calendar will be completed for the past 2 weeks between Visit 3 and Visit 12.

Follow-up Assessments: Follow-up phone interviews will be conducted at one day, one week and one-month post-rTMS to assess alcohol craving (PACS, OCDS, ACQ-NOW, AUQ), mTBI (NSI) and PTSD (PCL-5) symptoms.

4.0 Risks

Known and Unknown Potential Risks:

Repetitive Transcranial Magnetic Stimulation (rTMS): The biggest concern for magnetic stimulation is seizure induction. Other known side effects of rTMS include headache, dizziness, tinnitus, nausea, neck pain or scalp burns (Rossi et al, 2009)[63]. Alcohol use and alcohol withdrawal may introduce an unknown seizure risk as both of these circumstances lower the seizure threshold[63], which is why participants must meet minimum scores on the CIWA to assess alcohol withdrawal and those with a positive breathalyzer result will not be stimulated and rTMS will be re-scheduled and CIWA will be re-assessed at the re-scheduled session.

Additional Known risks of TMS are:

- Possible electrocution during TMS due to insufficient insulation of the coil. The coils will be inspected before and after each TMS session to ensure that the coil does not have any cracks or loss of integrity.
- Over-heating of the coil which may lead to scalp burns or damage to underlying tissue. The TMS device has a sensor that alerts the researcher when the coil is beginning to overheat so the coil can be replaced. The researchers will switch the coils halfway through each stimulation session to prevent overheating.
- Physical discomfort, facial numbness, headache or dental pain. Mechanical vibrations that occur within the coil while a TMS pulse is being generated, for example, may result in discomfort or headache to the participant. The participant will be advised to take acetaminophen (i.e., Tylenol) on their own before each TMS session to reduce any potential discomfort. At the end of the session they will be advised when they could take another dose of Tylenol if they are experiencing any discomfort.
- Device failure due to overheating, electrical short-circuiting or mechanical breakdown from force on the device. All precautions will be taken to prevent device breakdown that may affect the welfare of the participant. The TMS device will be inspected routinely and safety guidelines from the manufacturer will be followed.
- Contamination transferred from one participant to another following treatment. The device will be disinfected after every use to prevent spread of germs between participants.
- Mania, depression, anxiety and suicidality, although rare and usually associated with depression or bipolar depression. Repeat measures are collected to monitor for emergence of new mental health conditions and worsening of existing conditions. If new conditions emerge or existing conditions worsen, then the participant will be withdrawn and the psychologists on the study team will evaluate the participant to make recommendations for treatment.

Alcohol and other Mental Health Behavioral Assessments: The participant may experience some distress in speaking about his/her alcohol use severity and alcohol craving. The participant will be asked to notify study staff if these questions or questionnaires make them feel uncomfortable in order to make sure that the participant has timely access to mental health resources or information for organizations they can contact for support (e.g., Alcoholics Anonymous). However, it has been demonstrated that craving assessments are a safe and effective way of monitoring people that may have substance use disorders in veteran,[14,16] alcohol-dependent [14] and in PTSD populations [45].

Participants will be questioned about PTSD symptoms and suicidal ideation (BDI-II) routinely during study participation. Safety management of adverse responses to these measures is outlined below.

Neuroimaging: There are no known risks associated with the MRI procedures, although some participants experience mild discomfort from trying to keep still during the MRI, and some participants feel anxious or claustrophobic in the scanner. This is minimized by having the researchers in constant communication (via headphones) with the participant.

Unknown TMS Risks: There may be other unknown and/or unanticipated side effects that could occur. An adverse events (AE) log and daily study monitor log will be used to monitor the occurrence of any AE including unanticipated events. A response plan to unanticipated AE will be developed should this occur.

Confidentiality: Loss of confidentiality is a potential risk. This research study involves collection of self-report alcohol craving and alcohol use severity. Participant's response to self-report questionnaires will be documented. All hard copies of questionnaires and behavioral assessments as well as urine screens and breathalyzer screens will include a unique participant identification number and the date the assessment was completed.

Precautions Taken to Minimize Risks:

rTMS Safety Monitoring: The rTMS Safety Sheet (DSMS) contains a customized severity indicator scale. Additionally, an Adverse Events Tracking Log has been developed for this project. Both are integrated into the safety monitoring of this study. All serious and non-serious adverse events will be tracked on the Adverse Event Tracking Log.

For each safety variable specified on the DSMS, change from baseline is rated according to severity and for each severity rating there is a specified medical response to be followed. The ratings are on a scale of 1 to 5 with a higher number indicating more deleterious change. This scale rates changes from baseline in vital signs (temperature, blood pressure, heart rate, oxygen saturation levels), fatigue, tinnitus, sleep, dizziness, nausea, vomiting, confusion, seizure, syncope (fainting), headache, neck pain, skin integrity of the scalp, substance use, suicidal ideation, and PTSD symptoms. This scale will be completed at baseline and then weekly thereafter.

Participants will be clinically monitored for seizure by a trained RN. Should a seizure occur, the following response plan would be utilized:

1) RN will evaluate the participant and determine if the Hines Rapid Response Team (RRT) is to be contacted. RN will remain with participant.Other research team member to call 911 for RRT at Hines or for Emergency services at Northwestern.
2) When the Rapid Response Team arrives, they will take over and assume responsibility for carrying out approved seizure response procedures.
    a. For participants treated at Hines VA ED, the PI will contact the participant within a week and encourage them to follow-up with their Primary Care Physician (it is Hines VA policy that patients treated in the ED follow up with their Primary Care Physician within 2 weeks).
    b. For participants treated at Northwestern Memorial Hospital, the PI will contact the participants Primary Care Physician within 24 hours and inform them of the seizure and that they were seen at Northwestern Memorial Hospital ED in order to facilitate a follow up and a neurology consult will be encouraged.
3) As outlined below, any seizure will result in stopping treatment and withdrawal from study.

All females will complete a pregnancy test at Visit 1 and before the 5th rTMS session on Visit 7. If a pregnancy test is positive, then treatment will stop. All participants will complete the same urine drug screen during the 2nd screening phase, but this drug screening will be repeated at least one time

randomly during study participation. Persons with a positive urine opiate screen without an opiate prescription will be withdrawn. If they test positive for barbiturates, cocaine and amphetamine then they will also be withdrawn.

To insure participant medications remain stable during study participation, medication lists will be reviewed once per week with the participant to monitor for any changes in medication.

Participants will complete the BDI-II during the 2nd screening phase; item #9 specifically assesses suicidal ideation, plan, and intent on an increasing point value scale (0-3). To monitor for changes in suicidality, item 9 from the BDI II will be administered every week in accordance with our data safety monitoring sheet. Item 9. Suicidal Thoughts or Wishes is as follows:

Score	Responses
0	I don't have any thoughts of killing myself.
1	I have thoughts of killing myself, but I would not carry them out.
2	I would like to kill myself.
3	I would kill myself if I had the chance.

Participants positively endorsing 2 or higher (more than transient ideation with possible plan and/or intent) will be queried about their response prior to proceeding with screening. The assessor will be trained in risk assessment which will include review of frequency and severity of suicidal ideation, discussion of past and present planning behaviors, and current intent to act on ideation and/or planning.

Northwestern Specific: For any participant at NMH/NU who continues to endorse active ideation with plan and/or intent, 911 will be called and asked to escort the patient to the NMH emergency department for further evaluation and assistance.

Hines VA Specific: For any participant at Hines VA who continues to endorse active ideation with plan and/or intent, an attempt to complete a safety plan will be conducted by assessor at Hines VA. This safety plan, and the local documentation template, standard clinical practice within the VA will be utilized. All 6 steps of the safety plan will be completed utilizing a safety planning worksheet and entered in the medical chart as follows:

1. Recognition of signs that lead to suicidal thoughts
2. Using Internal Coping Strategies
3. Social contacts who may distract from the crisis
    a. Identify by name and document contact number
4. Family or friends who may offer help
    a. Identify by name and document contact number
5. Contact professionals
    a. Identify by name and contact information
    b. Hines providers working with patient and suicide coordinators (automatically listed in safety plan template)
    c. Hines 24-hour contact (automatically listed in safety plan template)
    d. National Hotline (automatically listed in safety plan template)
6. Making the environment safe
    a. Identify steps to limit access to means to harm self
    b. Give a copy of the completed "Suicide Safety Plan" to the patient

If the participant is in imminent danger (i.e., severe intent, refusal to complete safety plan) they will be escorted by Hines police and research team member to the Mental Health Service Line Intake at Hines VA for further evaluation. Similarly, the safety assessment procedure will be utilized for positive endorsement on the suicide symptom question in the SCID-5 Depression Module.

All Sites: Any participant taking a new mental health medication or altered dose for mental health reasons, during study participation, will be withdrawn from the study because of possible study confound.

To monitor for sleep disruption, we will record the number of hours the participant slept in the nights prior to treatment on the DSMS and compare this to the baseline report. If a pattern of sleep disruption is seen according to the DSMS categories, we will consult with a Hines VA epileptologist to determine if study participation should continue. Sleep disruption/deprivation is associated with a lower seizure threshold which may put the subject at a heightened seizure risk when receiving iTBS.

rTMS will be performed by a trained research team member in a clinical setting at either Hines VA Hospital or Northwestern. If an AE occurs, then the research team member will contact Dr. Herrold.

Each rTMS session will be video recorded for safety purposes. In the event a subject would have a seizure or other adverse reaction during the provision of rTMS, the videotape would allow investigators to determine temporally when the reaction occurred in relation to rTMS initiation and may help with determining other factors necessary for adverse event reporting. A separate consent for video recording will be obtained at the time of informed consent.

Rules for Stopping/Pausing rTMS:

To minimize the risks of rTMS, the following rules will apply for pausing, stopping or rescheduling rTMS:

Rules for Pausing treatment to Evaluate Need to Change rTMS Treatment Protocol: 1) Skin break-down on scalp at site of TMS 2) Constant headaches that do not resolve with acetaminophen 3) Suicidality item (Item 9) on BDI II is 2 or higher
Rules for Stopping rTMS Treatment: 1) Shock (of any etiology), 2) Any Seizure 3) Any participant starting a new mental health medication or altering a dose for mental health reasons during study participation 4) Participants with a positive urine opiate, barbiturates, cocaine and amphetamine screen. 5) Positive breathalyzer for breath alcohol concentration above 0%
Rules for Rescheduling Treatment Session (1) Subject reports sleep disruption and epileptologists determine that rTMS should not be provided during scheduled visit, but could be provided after sufficient sleep is achieved.

Other rTMS Safety Precautions:

While the risk of inducing a seizure in a person with AUD+mTBI+PTSD is not known, it is possible that multiple sessions of rTMS would evoke one or more seizures. In the event of a seizure, a seizure response plan will be followed. Research team members will all be trained on how to respond to a seizure. If a seizure occurs, rTMS will be stopped or paused based on the rules above. In order to minimize the risk of harm from seizure should one occur during rTMS, a nurse or physician will be in the room during each rTMS session. In the event of a seizure, the nurse or physician will follow established emergency procedures for Hines VA and Northwestern.

Published reports have shown that TMS has caused syncope [177-180]. The risk of causing syncope with or without convulsions in persons with mild TBI, AUD or PTSD is not known. A nurse will be

present at every TMS session. Study team members will be trained to monitor for signs of syncope. The nurse will ask the patient to report any sensations of dizziness, blurred vision, nausea or faintness. Blood pressure will be measured during and after each TMS session as low blood pressure is often a precursor to syncope; therefore, patients will be told to be hydrated for TMS sessions and will have water available to them before and after each TMS session. If the blood pressure decreases or if syncope occurs or appears imminent, the patient will immediately be placed in a supine position with elevated legs and without restraints to prevent and/or mitigate convulsive syncope and other adverse events associated with syncope. Study physicians will be contacted to medically evaluate the patient. The study physicians will determine whether further evaluation and/or testing is required based on the symptoms/event.

Participants may experience mild headaches or localized pain as a result of rTMS.
To prevent hearing loss, all participants will wear noise canceling headphones connected to the sham noise generator that will be set to a sound level that is within the normal hearing range to prevent any hearing damage. This mechanism also insures double-blinding.

The Magventure MagProX100 with MagOption stimulator or one of the coils may malfunction which may result in harm to the patient. To prevent equipment malfunction, the equipment will be inspected before and after each rTMS session. Manufacturer guidelines will be followed according to maintenance and useful life of the device. Should any equipment appear broken or have loss of integrity, the equipment will not be used until it is inspected by the biomedical engineering department at Hines VA Hospital or Northwestern Memorial Hospital and the Magventure service representatives.

The stimulating coil will be used on multiple participants. To prevent the spread of contamination from one participant to the next, the coil will be disinfected and sanitized after every rTMS session.

Psychological: The participant may experience some distress in speaking about his/her alcohol use severity and alcohol craving. However, it has been demonstrated that craving assessments are a safe and effective way of monitoring substance use disorders in Veterans [14,16,46], alcohol-dependent individuals [14,47,48] and individuals with PTSD[45]. Therefore, assessments conducted regarding alcohol craving and alcohol use severity are considered minimal risk. However, if the participant volunteers information that s/he intends to hurt him/herself or others, it will be followed up immediately by calling 911 so that the Veteran can be transported to the Northwestern Memorial Hospital Emergency Room.

The participant may also experience distress in speaking about his/her psychological health. We will be using the SCID-V to assess for AUD. We will be using the PCL-5 to assess PTSD symptoms. If research staff feels that the participant is incurring undue distress, they will end research procedures for that day and reschedule the appointment. 911 will be called if any participant expressing thoughts of harming herself or others so that the Veteran can be transported to the emergency room at Northwestern Memorial Hospital.

If participants have a breath alcohol level greater than the local legal limit (0.08) or show clinically significant behavioral signs of intoxication (e.g., inappropriate or aggressive behavior, mood lability or impaired judgment, alcohol on breath, slow, slurred speech, incoordination, and unsteady gait) and verbally or nonverbally demonstrate intent to operate a vehicle, research personnel will attempt to assist in arranging for other transportation. If this cannot be accomplished, the participant will be escorted to the emergency room at Northwestern Memorial Hospital to remain for extended observation. If the participant is unwilling to be held for extended observation, the participant may not be held against his or her will. It will be documented in the research activity and communication log that the participant was informed of any safety concerns and advised not to operate a motor vehicle. If the patient refuses to make other arrangements or to remain for observation until no longer intoxicated, the patient should be informed that police will be contacted consistent with procedures described in IL 10-2007-388005. In accordance with IL 10-2008-001 as referenced above, when calling the police, the patient will not be

described as intoxicated. Instead, the patient could be described as impaired to drive. No information that is protected by Title 38 United States Code (U.S.C.) 7332 (i.e., information related to the condition of sickle cell anemia or HIV, or the condition and treatment of drug and/or alcohol abuse) may be disclosed. Results of the research Breathalyzer test will not be shared with law enforcement and, in accordance with IL10-2008-001; VA personnel will not assist law enforcement in conducting chemical data testing.

Loss of confidentiality: Loss of confidentiality is a potential risk. This research study involves collection of self-report alcohol craving and alcohol use severity. Participant's response to self-report questionnaires will be documented. All hard copies of questionnaires and neuropsychological assessments as well as urine screens and breathalyzer screens will include a unique participant identification number and the date the assessment was completed. Thus, it will be de-identified. The only identifiable information will be the demographics questionnaire and contact information. The demographic questionnaire will be kept in a locked filing cabinet in a locked office of the study PI, Dr. Herrold. The participant name and contact information will be linked to the unique study identification number and saved electronically on a secure VA cross-walk server at Hines VAH. This secure cross-walk file is the only place where the participant name will be linked with the unique participant identification number. The study PI, Dr. Herrold will have control over the research team members who are allowed access to the cross-walk file. Any breach in security will be reported to ACOS/Research, Facility Information Security Officer (ISO) and facility Privacy Officer within one hour. To protect from breach of confidentiality, each participant will be assigned a unique identification number by the study personnel and the only place where this participant identification number will be linked to identifying information (e.g., name, address, phone number, date of birth, social security number) will be on a cross-walk file within secure Hines VAH servers.

All urine samples or data will be marked only with the participant's identification number and date of collection in order to guard against privacy risk. Any hard copies of urine tests or data will not include any participant identifiers and will be kept in the participant's file in a lockable filing cabinet located in the PI's lockable office at Hines VAH. All urine tests or other data entered will be done in an electronic database on the Hines VAH secure data server. No information, including results from urine tests will be entered into the electronic medical record.

All data entry and analysis will be completed and saved on secure Hines VAH data servers. The Hines VAH data servers will be accessed at Hines VA Building 1, Room B351, B313, B317, and B321. The study PI, Dr. Amy Herrold, will access secure data servers remotely with an encrypted, VA-issued lap top computer. Data entry and data analysis will be completed on desktop computers located at Hines VAH, Building 1, Room B317, B321, and B313 or on Dr. Herold's VA-issued and encrypted lap top computer. No identifiable information will be saved on this lap top. However, de-identified information will be saved on the hard drive of this lap top and will be backed up by transferring data to the secured Hines VAH data server via an encrypted memory stick after data from each new subject has been collected. These lap tops, or mobile storage devices, therefore, do not contain the only copy of research information.

All information collected will remain within the VA. Until a schedule for local research records is published, all records including identifiers must be retained. Once a study team member leaves, his/her access to study data will be terminated.

The storage location for hard copies of all research related materials (e.g., consents, questionnaires, neuropsychological assessment forms) will be kept in a locked cabinet in the office of the study PI, Dr. Amy Herrold. Her office is located at Hines VAH in Building 1, Room B351, which is behind secured key-card access doors. All de-identified data and data analyses will be stored on a secured data server.

All imaging data (MRI and fMRI) will be uploaded to the Northwestern University Research Image Processing System (NURIPS), an online collaborative research environment for securely storing,

managing, analyzing and sharing de-identified medical imaging, associated data (e.g. behavioral), and results from advanced customizable processing pipelines. NURIPS is supported by both NUIT and FSM-IT and takes advantage of the NU high performance computing cluster, Quest. NURIPS is a secure environment that supports the latest NU policy and procedures for encryption of data during transit and rest, provides granular project level access controls with varying permissions based on user groups, and allows non-NU collaborators access once they obtain an affiliate NetId. All data are backed up and have restore points that go back for 30 days. Users have access to common data analysis pipelines and the opportunity to create and share their own pipelines.

5.0 Compensation of Research Subjects

All participants will be compensated $225 for completing research procedures in this study. Participants also completing the MRI at Visit 2 will be compensated an additional $65 (total $290 for these participants). They will also be reimbursed for parking at Northwestern. If the participant did not drive to Northwestern then they will also be reimbursed the cost of the 6-hour parking voucher which is $5.75. If the participant withdraws or the PI withdraws the participant from the study, the participant will receive a prorated amount based on how much of the study they completed. The participant will be reimbursed in cash from the agent cashier's office at Hines VA.

6.0 Benefits of participation in the study

It is expected that participants receiving active rTMS will benefit by experience a reduction in alcohol craving. The participants receiving placebo rTMS will not directly benefit from these research procedures, but these data will be disseminated and may impact and benefit future military Veterans and active duty soldiers, as well as other civilians incurring mild traumatic brain injuries, alcohol use disorder and/or post-traumatic stress disorder.

7.0 Alternatives to participation

The alternative to participation is to not participate in the study. Participation is entirely voluntary and the participant may withdrawal at any time for any reason. There are no known safety risks of stopping rTMS among people with AUD, mTBI or PTSD.

8.0 Data Analysis

Safety: Safety indicators will be monitored; frequency of adverse events as well as successfully coordinated and completed rTMS and neuroimaging sessions will be tabulated and compared between the active and sham rTMS groups using a Pearson chi-square test or Fisher's exact test.

rTMS Efficacy: To determine the effect of rTMS on alcohol craving a mixed effects regression model with a random intercept will be used. The dependent variable in the model will be alcohol craving score and the covariates will be rTMS treatment (sham *vs.* active rTMS), time (before and after rTMS) and rTMS treatment by time interaction (if the interaction is significant). Similar analyses will be applied using mTBI and PTSD symptoms as the dependent variables. If power is not sufficient for the mixed effects approach, a non-parametric test will be used to compare mean alcohol craving scores pre- and post-rTMS.

9.0 Confidentiality Plan – see above, Loss of Confidentiality, under Precautions to Minimize Risks

10.0 Monitoring and reporting Serious Adverse Events:

An adverse event (AE) is any undesirable experience associated with rTMS (Active or Placebo) measured as a deleterious change from baseline on the Data Safety Monitoring Scale (DSMS). AEs can be non-serious and serious. A serious AE is when the changes are disabling, life threatening, require hospitalization or requires intervention to prevent impairment. We will measure deleterious changes in (1) neurologic status including cognitive symptoms, (2) somatic and vestibular symptoms, (3) depression and specifically suicidal ideation, plan and intent and (4) PTSD symptoms. AE will be tracked using the AE log.

Amy Herrold will be responsible for training other research staff of the protocol set forth in this IRB application. If unanticipated problem occurs such as deviation to this protocol that involve risks or has the potential to recur, this information will be reported by the investigator to the IRB as well within 2 business days but no longer than 5 business days of the investigator or staff becoming aware of the event.

Finally, any finding of noncompliance, other deficiencies that substantively compromise the effectiveness of the facility's research information protection program, or suspensions or terminations will be reported to the ACOS/ACME/Research, Facility Information Security Officer (ISO) and facility Privacy Officer within 5 days of becoming aware. Any loss of confidentiality falls under immediate reporting requirements and will be reported within the hour of becoming aware.

11.0 Relevance of the study to the VA:

The current study addresses specific research interest areas to the VA including chronic diseases, psychiatric disorders, neurological dysfunction, brain injury and rehabilitation outcomes. Current military conflicts in Iraq and Afghanistan have led to over 200,000 reported cases of mild traumatic brain injury (mTBI). Among Veterans, mTBI commonly co-occurs with chronic, psychiatric conditions including alcohol use disorder (AUD) and post-traumatic stress disorder (PTSD). In particular, AUD negatively affects rehabilitation outcomes in Veterans. Specifically, the completion of this study will provide essential knowledge that can be incorporated into therapeutic strategies targeted to reduce alcohol craving and subsequent relapse in Veterans returning from Iraq and Afghanistan with co-occurring mTBI, PTSD, and AUD.

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