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Repetitive Transcranial Magnetic Stimulation (rTMS) for the Treatment of Depression & Other Neuropsychiatric Symptoms After Traumatic Brain Injury (TBI)

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1. Abstract

Background: Traumatic brain injury (TBI) is frequently complicated by depression and other neuropsychiatric symptoms (NPS), such as post traumatic stress disorder (PTSD), sleep disturbance, cognitive deficits and behavioral problems. Untreated depression & comorbid psychiatric symptoms can lead to reduced productivity and poor global outcome. There are no Food and Drug Administration (FDA) approved drugs for the treatment of TBI-related NPS symptoms/syndromes. There have been only two controlled medication trials for the treatment of TBI-associated depression, and neither provided strong evidence that antidepressants are superior to placebo. A major limitation of these previous studies was their focus on a limited subset of depressive symptoms and use of agents with narrow therapeutic profiles. We propose to address these limitations by use of a novel non-invasive technique, repetitive transcranial magnetic stimulation (rTMS) that has the potential to induce widespread neuromodulation, and assessment of a broad range of neuropsychiatric symptoms that are frequently comorbid in post-TBI depression.

Objective/Hypothesis: The overarching goal of the proposed proof of concept study is to determine the effectiveness of low frequency right (LFR) rTMS for the treatment of post-TBI depression and co-morbid neuropsychiatric symptoms.
Specific Aim 1: To determine the effectiveness of LFR rTMS for the treatment of: (a) post-TBI depression and (b) suicidal ideation. We hypothesize that LFR rTMS will be superior to sham treatment in: (a) reducing symptoms of depression and (b) reducing suicidal thoughts.

Specific Aim 2: To determine the effectiveness of LFR rTMS for the treatment of neuropsychiatric symptoms that are commonly seen as co-morbid phenomena in patients with post-TBI depression: (a) post traumatic stress disorder (PTSD) (b) sleep disturbance and (c) cognitive deficits. We hypothesize that LFR rTMS will be superior to sham treatment in reducing symptoms of PTSD, sleep disturbance and cognitive deficits, more specifically, memory, attention and executive function deficits. In addition, effectiveness of rTMS for the treatment of other behavioral symptoms (e.g. apathy, aggression) will be assessed.

Exploratory Analysis: A subset of subjects will be assessed using diffusion tensor imaging (DTI) to determine white matter integrity pre- and post-treatment in an effort to better understand neuro-anatomical correlates of NPS symptoms,symptom improvement, and the potential for LFR rTMS to influence white matter integrity.

Study Design: The study design will include a double-blind placebo-controlled trial of 30 TBI patients of mild & moderate severities. Subjects will be randomized to either active LFR rTMS (N=15) or sham treatment (N=15). All subjects will receive 20 LFR rTMS or sham treatments over 4 weeks, and will be followed thereafter for 3 months. Well-validated psychiatric instruments and cognitive assessments will be

used to compare the effectiveness of LFR rTMS versus sham treatment cross-sectionally at each of the visits and over time.

Relevance: If the proposed rTMS treatment is found to be efficacious, it can be transferred to clinical practice for soldiers with TBI-associated depression and other psychiatric symptoms. rTMS has minimal long-term side effects and is not known to negatively interact with pharmacotherapies. rTMS has the potential to have a broad impact on multiple areas of life functioning and, thus, has the potential to lead to improved instrumental life activities, employability, community re-integration and overall quality of life. Soldiers & civilians with increased emotional stability and improved cognitive skills can more effectively manage stress which, in turn, can dramatically reduce the likelihood of developing disorders associated with chronic stress.

2. Objectives

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SPECIFIC AIMS & HYPOTHESES

Aim 1: To determine the effectiveness of LFR rTMS for the treatment of: (a) post-TBI depression and (b) suicidal ideation. We hypothesize that LFR rTMS will be superior to sham treatment in: (a) reducing symptoms of depression and (b) reducing suicidal thoughts**.**

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3. Background

TBI is often called "the silent epidemic" because emotional, behavioral and cognitive symptoms (collectively referred to here as comorbid neuropsychiatric symptoms), which are the major cause of disability, are not immediately apparent[1]. Neuropsychiatric problems occur at increased rates and last longer in persons with TBI compared with those in the general population[2,3]. Comorbidity is high with about 40% of patient with TBI suffering from two or more psychiatric disorders in the first year after injury[4], and about 48% having at least one major mental illness 30 years post injury[3]. Corrigan et al[5] reported that about 40% of persons with TBI will have at least 1 'unmet need' in the first year after TBI, the two most common being cognitive deficits (34%) and emotional problems (28%). The entire spectrum of TBI severity, from mild to severe, is associated with high rates of psychiatric morbidity[6]. Data collected for the PI's NIH funded Career Development Award (K23 MH066894*)* are consistent with published data indicating high rates of neuropsychiatric disturbance in patients with TBI. The broad aim of that research was to determine clinical risk factors for the development of depression after TBI. First-time head injured adult subjects with all severities of TBI who were hospitalized for evaluation were recruited from two trauma centers: the Trauma Unit at Johns Hopkins Hospital and the Brain Injury Unit at Kernan Hospital, University of Maryland. Subjects were interviewed using the Structured Clinical Interview for DSM IV disorders (SCID IV) to determine Axis I psychiatric disorders. As seen in Table 1, 85% of subjects had at least 1 major mental illness. Comorbidity was high in this sample with at least 60% of subjects meeting criteria for 2 or more psychiatric disorders. Depression was the most common psychiatric illness (52%), and of these, 30% had a new onset mood disorder.

Table 1: Percentages of psychiatric diagnoses in the first year after TBI

Psychiatric Diagnoses	Percentages (N=103)
Any Psych Dx	85.4%
2 or more Axis 1 Psych Dx	60.1%
Any Depression	52.4%
Any alcohol or substance abuse/dependence	36.9%
Pathological crying/laughter	33 %
Any Anxiety d/o	31.1%
New onset mood disorder	30%
Personality change	15.5 %
PTSD	8.7%
Apathy	8.7%

TBI Depression

As seen in Table 1, of all the psychiatric sequelae seen after TBI, depression is the most common diagnosis. A review of the published literature[7] reveals that the prevalence of depression following TBI ranges between 6%-77% with most studies[8,9] reporting a prevalence of 25-50%. This rate is significantly higher than the general population, which has a lifetime prevalence of major depressive disorder of approximately 21%[10]. Depression following TBI (hereafter referred to as "TBI depression") is characterized by persistent sadness, anhedonia, feelings of worthlessness, hopelessness, loss of interest in work and family activities, poor motivation, decreased social contact and suicidal thoughts[11]. Wood et al[12], in a study of 105 patients with TBI of all severities, found suicidal ideation in 33%, compared to 1.4% of normal healthy controls. Untreated depression is associated with suicide attempts, occasionally completed suicide, reduced work productivity, decreased psychosocial functioning, and poor global outcome both in the acute and chronic TBI period[13,14]. Persistent postconcussive symptoms are more common in those with mild TBI and comorbid depression compared to mild TBI without depression and depression without history of TBI[15]. In addition to the negative impact of TBI depression on patients themselves, high levels of anxiety and depression are reported in family members involved in the care of TBI patients and comorbid mood disturbances[16,17]. Thus TBI depression has an adverse impact on individuals, their families, and the community at large through lost productivity. TBI depression has been found to be associated with a host of factors including pre-injury factors, including presence of prior psychiatric history and pre-TBI psychosocial dysfunction; injury-related factors such as lesions to strategic brain regions such as the fronto-temporal basal ganglia, and post-injury factors , particularly poor psychosocial functioning[11,18,19]. A pilot study by Rao et al[20] to determine the neuroanatomical correlates of post-TBI depression revealed that it was not the severity of injury but dysfunction of the fronto-temporal-basal ganglia regions that was associated with the development of major depression.

Post-TBI Depression & Comorbid Neuropsychiatric Symptoms/Syndromes

Post traumatic stress disorder (PTSD): PTSD can occur independently of depression after TBI or co-morbidly. Risk factors for PTSD following TBI include past psychiatric history[21]; female gender[22] and past history of acute stress disorder[23]. Other correlates of PTSD include poor quality of life, impairment in physical health, and reduced interpersonal/social functioning.[24,25] Thus TBI depression and co-morbid PTSD are associated with significant impairment in physical and emotional health, underscoring the importance of accurate diagnosis and treatment.

Sleep Disturbances: Rao et al[26] have noted that the presence of sleep disturbance in the early TBI period predicts the development of new onset major depression and new onset anxiety disorder in the chronic TBI period. Results from the PI's NIH funded study on TBI depression (K23 MH066894*)* reveal that sleep problems in the post-TBI period are generally greater than those occuring pre-injury[26] (Table 2). Correlates of sleep disturbance in the acute TBI period included generalized anxiety disorder secondary to a general

medical condition (TBI), and major depression secondary to a general medical condition (TBI) in the three month post-TBI period (Table 3). Regression analysis, using the overall sleep score (Sleep Problem Index 2) as the dependent variable and several psychosocial factors as independent variables (Table 4), revealed that sleep disturbance in the early TBI period was associated with the development of depression (all sub-types inclusive) within the 1-year follow-up period, new-onset major depression at 6 and 12 months post TBI, impaired psychosocial functioning at 6 months post TBI, poorer performance on a test of executive function (letter fluency test) and increased dependency on others for instrumental activities of daily living at 6 months post-TBI.

Cognitive Deficits: Several studies have shown an association between depressive symptoms and cognitive deficits after TBI[27-29]. In a study of 74 TBI patients, Rapoport et al[30] noted that subjects with major depression following TBI (28%), when compared to those without depression, had significantly lower scores on tests of working memory, processing speed, verbal memory and executive functioning. Executive functioning impairments were also found to be related to depression in a very recent study of mild to moderate TBI in the early phases of recovery[31]. These associations suggest that cognitive impairments are a common comorbidity of post-TBI depression. Research suggests that self-appraisal of post-TBI abilities, which can be negatively affected by cognitive impairments, is strongly associated with the presence of depression after TBI and may potentially explain the relationship between cognitive impairment and depression[32].

Table 2. Comparison of Sleep Scores Pre- and Post-TBI

Sleep Variable	Pre-TBI	3 months Post-TBI	F, P variables
Sleep Disurbance	17.5 (15.9)[1]	27.7 (24.1)	6, p=0.018
Snoring	18.4 (30.2)	14.5 (26.9)	0.72, p=0.4
SOB/HA[2]	0.39 (2.8)	14.1 (27.5)	0.72, p=0.4
Sleep Adequacy	26.7(28.2)	38.6 (31.1)	5.5, p=0.023
Daytime Sleepiness	17.3 (17.5)	31.8 (26.9)	10.8, p=0.002
SPI 1[3]	14.4 (14.0)	28 (22.3)	16.8, p=<0.001
SPI 2[4]	17.2 (12.7)	29.3 (20.5)	13.2, p=0.001

[1]Mean (SD); [2]Shortness of breadth/headache; [3-4] Sleep problem Index & overall Sleep score

Table 3. Association Between Participant Characteristics and Sleep Domains/Summary Scores

	Sleep disturbance	*Snoring*	*SOB/HA[1]*	*Sleep Adequacy*	*Daytime Sleepness*	*SPI 1[2]*	*SPI 2[3]*
Age	0.01 (0.2)[4]	0.42 (0.2)*	-0.04 (0.22)	-0.05 (0.3)	0.47 (0.2)*	0.12 (0.2)	0.11 (0.2)
Female	4.91 (6.6)	-3.67 (7.4)	15.63 (7.3)*	4.06 (8.8)	8.25 (7.4)	8.56 (6.1)	7.12 (5.6)
MDGMC[5]	21.12 (9.2)*	6.96 (10.8)	10.68 (11.0)	11.49 (12.8)	18.42 (10.6)	17.86 (8.8)*	18.69 (7.9)*
GADGMC[6]	27.42 (9.4)**	12.72 (16.2)	8.94 (16.8)	21 (16.9)	38.86(14.4)**	25.62 (9.8)*	26.35(8.7)**
GMHR[7]	-5.28 (3.4)	-2.6 (3.9)	-0.87 (4.0)	-0.22 (4.7)	-5.85 (3.9)	-3.7 (3.3)	-3.65 (3.0)
Body Injury	-5.21 (6.5)	-1.15 (7.4)	5.63 (7.5)	-9.3 (8.7)	-5.41 (7.4)	-2.79 (6.2)	-5.35 (5.6)
GCS[8]	-0.69 (1.0)	-0.17 (1.1)	-0.08 (1.1)	0.7 (1.3)	-0.05 (1.1)	-0.68 (0.9)	-0.45 (0.8)

*[1]Shortness of Breath/ Headache; [2-3] Sleep Problem Index overall sleep score;[4] Beta (SE); [5]Major Depressive-like Episode due to General medical disorder; [6] Generalized Anxiety Disorder due to General Medical Condition; [7] General Medical Health Rating; [8]Glasgow Coma Scale. *p<0.05; **p<0.01.*

Table 4. Predictors of Sleep Disturbance

	Beta (SE)	*p*-value	Adj. R2
Any Depression 1yr post-TBI	24.8 (5.5)	<0.01	0.17
New-onset Depression 6m post-TBI	22.2 (9.9)	0.03	.0.04
New-onset Depression 12m post TBI	50.7 (10)	<0.01	0.20
Letterfluency 1yr post-TBI	1.3 (0.63)	0.05	0.07
Psychosocial function 1yr post- TBI	55.3 (19.8)	<0.01	0.11
IADL Dependence 6m post-TBI	1.6 (0.75)	0.04	0.06

***Behavioral Issues*: Post-**TBI Depression is often associated with other comorbid symptoms, such as anxiety, apathy, anger/aggression, impulsivity and disinhibition. These symptomscan be an integral component of a depressive syndrome, a consequence of brain injury, or both[33]. In a study of 67 individuals with first-time TBI seen within three months of injury, Rao et al[33] noted rates of aggression (predominantly verbal) to be about 28%. When participants with and without TBI aggression were compared (Table 5), participants with aggression had a higher prevalence of new-onset major depression (p=0.02). No group differences were observed for any other Axis 1 psychiatric diagnoses. Participants with aggression were also more likely to have poorer social functioning (p= 0.04) and increased dependence on others for personal and instrumental activities of daily living (p=0.03). Importantly, there were no differences between those with and without aggression on pre-TBI or post-TBI history of alcohol or substance abuse, pre or post-TBI legal problems, pre- or post-TBI history of adult behavior problems and childhood behavior problems. These findings underscore the point that TBI aggression is related specifically to post-TBI depression.

Other common co-morbid psychiatric symptoms seen following TBI include anxiety, apathy, disinhibition, and impulsivity. Rates of anxiety disorders in post-TBI depression is high, ranging from 40-77%[11,34]. Persons with post-TBI depression and co-morbid anxiety have longer duration of symptoms compared to those with post-TBI depression alone (7.5 months versus 1.5 months). Apathy, defined as lack of motivation, anhedonia and disengagement is a common symptom after TBI. Kant et al[35] noted apathy and depression in 60% and apathy alone in 11% of TBI subjects.

In summary, post-TBI depression is the most common psychiatric sequela of TBI, but it usually does not occur alone. Co-morbidity is high and adds to the distress and disability that is experienced by individuals following TBI.

Table 5: Comparison of TBI subjects with and without Aggression on clinical variables

Variables	Aggression	No Aggression	t	df	p-value
Major Depression Pre-TBI	2 (10.5%)	4 (8.3)	FET		1.00
Major Depression Recurrent Post-TBI	0	1 (2.1)	FET		1.00
New onset Depression post TBI	5 (26.3)	2 (4.2)	FET		0.02
Post-TBI Anxiety Disorder	6 (31.6)	6 (12.5)	0.07	1	0.07
Pre-TBI Alcohol abuse/dependence	9 (47.4)	26 (54.2)	0.62	1	.79
Childhood Behavior Problems	6 (31.6)	13 (27.1)	.71	1	0.77
Adult Behavior Pre-TBI	6 (31.6)	14 (29.2)	.85	1	1.00
Social Functioning Post-TBI	.33 (.15)	.25 (.14)	-2.2	64	.03
Personal & Instrumental activities of daily living Post-TBI	9.6 (8.1)	5.3 (6.6)	-2.3	64	.03

Pathophysiology of TBI & TBI Depression

The pathophysiological consequences of trauma to the brain may be best conceptualized as the result of a combination of direct impact forces (i.e. at the site of impact) and acceleration-deceleration forces[36]. The two most common sites of focal injury include the anterior and inferior frontal regions and the tips of the temporal lobes, as they sit on bony protuberances of the skull and are thus vulnerable to the impact forces[37]. In addition to focal injury secondary to acceleration and deceleration forces, there are also backward/forward and rotational movements of the brain within the skull during TBI, resulting in diffuse axonal injury[38]. Following acute TBI-induced physical injury, a cascade of metabolic events occurs, resulting in more damage. It is unclear how long neurotransmitter imbalances persist following TBI, as decreased levels of acetylcholine, serotonin and dopamine have all been noted, even in the chronic TBI period[39]. Thus, the pathophysiology of TBI includes a combination of mechanical damage, metabolic disturbance, cytotoxic damage and neurotransmitter alterations which can persistfor a prolonged period. In many patients, neuronal changes following TBI are subtle and cannot be identified by routine magnetic resonance imaging (MRI) or computerized tomography (CT) scans. However, Diffusion Tensor Imaging (DTI), which is known to be sensitive to the microscopic anatomical status of axonal structures, may have the potential to detect diffuse microstructural injury[40]. DTI measures the microscopic random translational motion of water molecules[41]. Because freedom of motion is restricted by interactions with other molecules, the structure of axons, and integrity of neuronal membranes, DTI measures can be used as markers of tissue organization at a microscopic level. Therefore, DTI represents a promising approach to quantify microscopic brain damage by measuring both water diffusion (mean diffusivity; MD) and the degree of diffusion directionality, or anisotropy (fractional anisotropy; FA)[42]. In a pilot study to determine whether diffusion tensor imaging (DTI) measures of fractional anisotropy (FA) and mean diffusivity (MD), collected within 1 month of mild TBI (mTBI) could predict incident depression, Rao et al[43] noted a negative association between FA in the left superior and middle temporal gyri and severity of depression (indicating that decreased white matter integrity in these regions is associated with increased depression) and a positive correlation between MD and severity of depression in several fronto-temporal regions (indicating that increases in microstructural abnormalities in these regions are associated with increases depression). One goal of the current study is to determine whether these preliminary findings can be replicated. Because this is a treatment protocol, we also hope to characterize DTI changes associated with successful treatment of TBI depression and comorbid neuropsychiatric disturbances.

Treatment of TBI Depression

Despite its high prevalence and socio-economic burden, little research has been conducted on the treatment of TBI depression. The bulk of studies evaluating the efficacy of antidepressants for the treatment of post-TBI depression have involved selective serotonin reuptake inhibitors (SSRI's). Results from these studies are inconsistent, and generally reveal that a significant number of patients fail to respond to medication. There are currently no FDA approved drugs for the treatment of post-TBI depression or its co-morbidities, and use of antidepressants for the treatment of TBI-related neuropsychiatric illnesses is considered off-label. Below, we have summarized results from the pharmacological and non-pharmacological studies in the treatment of post-TBI depression

Cassidy[44] reported moderate-marked improvement in 5 of 9 severe TBI patients with major depression following treatment with fluoxetine. Fann et al[45] conducted an 8-week nonrandomized, single-blind, and placebo run-in trial of sertraline in 15 mild TBI patients diagnosed with major depression 3-24 months after injury. Eighty seven percent of patients responded to treatment, and remission was seen in 67%. There was also a statistically significant improvement in psychological distress, anger, aggression, functioning and postconcussive symptoms with treatment. Rapoport et al[46] reported much lower response and remission rates in an open label study of citalopram of 20-60 mg in a study of mild-moderate TBI depressed subjects. Remission rates at 6 and 10 weeks were 24 and 27% respectively. Perino et al.[47] conducted an open label trial of citalopram (20 mg/day) combined with carbamazepine (600 mg/day) in 20 TBI subjects with mood and behavioral disturbances. Compared to pre-treatment, the group was found to have significant improvements in both mood and behavior when treated with this combination.

Reports of the efficacy of tricyclic antidepressants for the treatment of TBI depression have also been inconsistent. Saran[48] reported no improvement from treatment with amitriptyline in any of 10 minor head injured patients who suffered from "depression with melancholia" in contrast to 12 control patients with primary depression and melancholia who all showed significant improvement. Dinan and Mobayed[49] also observed no significant improvement associated with amitriptyline treatment in 13 depressed minor head-injury patients when compared to 13 "functionally" depressed patients. The only randomized controlled trial[50] of tricyclic antidepressants in a study of 10 severe TBI subjects noted improvement of depressive symptoms in 6 of the 7 completers treated with desipramine. However, remission and responses rates were not calculated, and some of the participants were being treated with other psychotropics in addition to desipramine. There are some case reports of successful treatment of post-TBI depression with psychostimulants such as dextroamphetamine, methylphenidate and pemoline[51]. However patients on these medications should be monitored closely to prevent abuse or toxic effects such as headaches, irritability, seizures, cardiovascular symptoms and/or psychotic symptoms[52].

There are only two controlled trials of post-TBI depression. The first,a study by Lee et al[53] , was a double blind parallel group 3-arm trial that compared methylphenidate (20 mg/day) to sertraline (100 mg/day) and placebo. Thirty TBI subjects with depression were recruited to this 4 week study. Methylphenidate and sertraline were found to be superior to placebo. No difference was found between the 2 active drugs on depressive symptoms, but those on methylphenidate (but not sertraline) had improved cognition relative to placebo. A major limitation of the study was the lack of analyses of response and remission rates. The second study by Ashman et al.[54] compared sertraline to placebo in 52 subjects with post-TBI depression who were, on average, 17 years post injury. In this 10 week trial, subjects in both groups showed improvement. Although the group receiving sertraline had a higher response rate compared to the group treated with placebo (59% versus 32%), differences between the two groups were not significant.

Other types of treatment such as physical activity and cognitive behavior therapy (CBT) have also been studied for the treatment of post-TBI depression. Driver et al[55] studied 16 subjects and assigned them to either 8 weeks/24 sessions of swimming, or a similar number of vocational rehabilitation sessions. Those in the swim group were noted to have improvement in depression and other symptoms, such as anger, anxiety and fatigue, when compared to the group in vocational rehabilitation. Two other studies evaluating the

efficacy of aerobic exercise for the treatment of post-TBI depression noticed no statistically significant improvement in mood scores in the experimental group versus the control group[56.57]. A few CBT studies found overall improvement in mood and cognition in the intervention group compared to the control group[58-60]. However, most of these studies noted a low compliance rate. Also, none of these studies specifically studied major depression. Small uncontrolled studies have also evaluated the utility of alternative treatments for TBI depression. Maric et al[61] noted improvement in depression scores in 4 out of 6 post-TBI depressed persons with growth hormone deficiency after treatment with growth hormone for 6 months. In the only known retrospective electroconvulsive treatment study of TBI depression, Kant et al[62] noted improvement in depression in 9 out of 11 subjects. Notably, there was no decline in cognition.

As limited and inconsistent as the available data on post-TBI depression are, there are even fewer studies on the treatment of other TBI-related neuropsychiatric symptoms. Standard treatment approaches using drugs with narrow therapeutic profiles may be unsuccessful because of the complex TBI pathology, which includes focal/diffuse damage, physical/biochemical damage and involvement of multiple cortical-subcortical pathways.

We propose to address some of the limitations of previous studies of post-TBI depression by use of a novel non-invasive technique, repetitive transcranial magnetic stimulation (rTMS), that has the potential to induce widespread neuromodulation[63,64]. Studies in non-TBI depression have postulated that the therapeutic effect of rTMS is secondary to its neuromodulator effect and strengthening of synaptic connections in the fronto-subcortical-limbic circuitry[65].

Repetitive transcranial magnetic stimulation (rTMS)

TMS is a non-invasive modality for focally stimulating the peripheral and central nervous system. A changing electromagnetic field passes unimpeded through skin, muscle and bone depolarizing underlying neurons. Repetitive pulses or trains of pulses (rTMS) applied to the head can provoke long-lasting up- or down- regulation of activity at synapses, including in brain regions that regulate emotion and movement[66]. These long lasting changes in synaptic transmission are critical to the therapeutic effects of rTMS for the treatment of depression. Although the electromagnetic field only reaches 1 – 2 cm into the cortex, activation of neurons in that region trigger activation of neurons at more distal sites, as demonstrated by functional imaging studies [67] .

TMS was first utilized in the 1980's by neurologists to painlessly and non-invasively map brain function. In the early 1990's, it was noted that stimulation over the left dorsolateral prefrontal cortex (DLPFC) could affect mood[68]. Over the next ten years, more than 30 sham-controlled studies of rTMS demonstrated its efficacy for treating major depressive disorder (MDD). rTMS is not associated with any systemic side-effects experienced with pharmacological treatment. Moreover, although it is not as effective as ECT, rTMS has the advantages of not requiring anesthesia and not being associated with cognitive side-effects. It was approved as a treatment for MDD by the FDA in 2008. There are now more than 300 clinics offering rTMS for the treatment of idiopathic depression around the country.

Several studies have demonstrated that low frequency right-sided (LFR) rTMS over the DLPFC at 1 Hz, which inhibits cortical activity, is efficacious for treating MDD, and that response rates are comparable to high frequency left-sided (HFL) rTMS over the DLPFC which is excitatory[69-70]. This finding is consistent with previously described opposing effects of the two brain hemispheres on mood regulation[67,71]. LFR rTMS is increasingly utilized by clinicians, and is being incorporated into treatment guidelines, especially for depressed patients with significant anxiety and PTSD, for which it may be more efficacious than HFLrTMS[72-74]. There are considerable advantages to using LFR rTMS over HFL rTMS. The most important advantage is that because LFR reduces cortical excitability, seizure risk is lower than with HFL treatment (which is already exceedingly low when parameter sets comply with rTMS safety guidelines). The anticonvusant effect of low frequency rTMS was recently demonstrated in a meta-analysis of studies utilizing rTMS for intractable epilepsy[75]. In addition, Dell'osso et al[76] have also noted that remission could be maintained at least for a year after acute response to LFR rTMS in a study of 11 depressed subjects. As the patient population for the proposed study may be at a higher risk for seizures than a non-TBI cohort, we

will utilize LFR to minimize this risk. Another major advantage of LFR over HFL rTMSis better tolerability of treatment, less localized discomfort at the stimulation site, less stimulation of the facial nerve, and fewer headaches[69, 77-79].

The TMS seizure risk is estimated at <0.1% of patients who are administered treatment, which is comparable to the seizure risk associated with an antidepressant medication. In studies of patients with established neuropathological lesions such as from stroke or multiple sclerosis, seizure risk from TMS also appears to be exceedingly low. Out of 1200 stroke patients who received TMS, there has been only one reported seizure in an alcoholic patient administered high frequency rTMS ipsilateral to the site of the lesion. See eIRB application section 21(section 21.5 -> Magstim Super Rapid -> 6) for a thorough review of safety issues, especially seizure risk, related to administration of LFR rTMS.

Although rTMS is now an accepted treatment for idiopathic depression, far less is known about the potential effect of rTMS on behaviors such as impulsivity and apathy that are mediated by the prefrontal cortex, and which are secondary targets in this study, in addition to depression. A recent rTMS study[84] of healthy subjects using continuous theta-burst stimulation over the right DLPFC, which is inhibitory, showed decreased impulsivity in a discounting delay reward task, when compared with sham. Little is known about the effect of rTMS on apathy. This has been explored in a few trials, especially in schizophrenia patients, using HFL rTMS, with mixed results[85].

We will also assess the potential for LFR rTMS to treat the cognitive sequelae of TBI. As mentioned above, rTMS is not associated with adverse cognitive effects, and improvement in cognitive measures has been noted in parallel with improvements in mood in depressed patients[69,86]. In non-depressed patients, transient improvement in cognition in a variety of cognitive domains has been reported with both HFL and LFR stimulation[87].

It is with this background that we propose a pilot proof of concept study to determine the effectiveness of LFR rTMS for the treatment of TBI depression and its common comorbidities.

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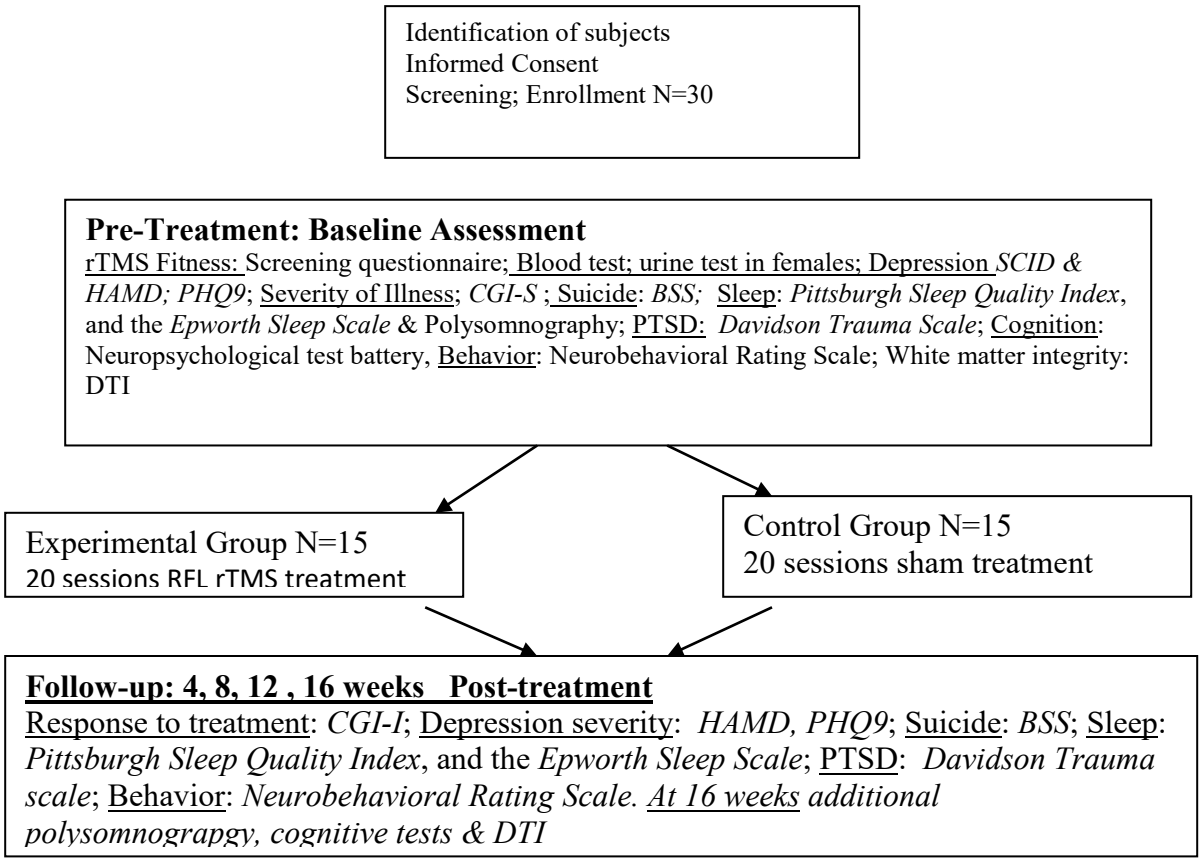
4. Study Procedures

Study Overview: The proposed proof of concept study will recruit 30 subjects with traumatic brain injury of mild-moderate severity who also meet DSM IV criteria for major depression. We will screen as many potential subjects as possible to get a total of 30 subjects.

Written informed consent will be obtained from all subjects prior to enrollment.

All enrolled subjects will be evaluated using structured and semi-structured psychiatric interviews to determine a series of baseline outcome measures. Subjects will be randomly divided into two groups and treated in a double-blind fashion with LFR rTMS vs sham treatment; Subjects will receive a total of 20 treatments – 5/week for 4 weeks. Subjects will then be followed monthly for the next 3 months i.e. will be evaluated at 8, 12 and 16 weeks).
We have contacted the FDA regarding the proposed study and the use of rTMS in persons with TBI and have been told to proceed with applying for Hopkins IRB review rather than embarking on an IDE



Study Overview: Figure 1

Recruitment: Subjects will be recruited from several sources: (1) The Brain Injury Clinic at Johns Hopkins Bayview Medical Center (the PI is the Medical Director of the clinic), (2) The Outpatient NeuroRehabilitation Program at Johns Hopkins Hospital, (Co-investigator Dr. Kathleen Kortte is the Program Director), (3) referrals from other Johns Hopkins Medicine inpatient and outpatient clinics, (4) brain injury support groups organized by the Brain Injury Association of Maryland, and (5) IRB-approved advertisements placed in local newspapers and on the internet, and (6) other local hospitals such as the Walter Reed National Military Medical Center (WRNMMC), the Medstar National Rehabilitation Network, and Sheppard Pratt Hospital. An IRB approved 'telephone script' will be used to discuss the study with those who call in response to advertisements or flyers. Patients who are willing to participate will be brought to the research clinic to obtain written informed consents and undergo face-to-face evaluations.

Study Site: The study sites will bethe Geriatric & Neuropsychiatry Clinics at Johns Hopkins Hospital, and Johns Hopkins Bayview Medical Center. Polysomnography studies will be undertaken at the Johns Hopkins Bayview Clinical Research Unit which is a component of an Institutional Clinical Translations Research program. DTI brain scans will be completed at the Kirby Center, Kennedy Krieger Institute.

Study population. Persons with history of mild –moderate traumatic brain injury and depression will be included in the study. Potential participants will only be considered for this study once they have been

safely weaned off all psychotropic medications by their treating physicians (see inclusion and exclusion criteria below).

Study Visits: Study visits include: (1) An initial screening visit to confirm eligibility and obtain informed consent; (2) Twenty treatment visits (5 visits per week for 4 weeks); (3) Three monthly follow-up visits (week 8, 12 and 16).
The total number of visits include: 1 + 20 + 3 = 24 visits. If subjects are unable to come to Hopkins for follow-up visits, we will conduct telephone evaluations at the same timepoints.

Study Design: We propose a double-blind placebo controlled proof of concept pilot study of active versus sham LFR rTMS for the treatment of TBI depression. As noted above, all subjects will be screened prior to randomization. During the screening visit, all subjects will undergo a complete psychiatric evaluation as well as formal cognitive testing. In addition, if there is any possibility of pregnancy or unstable medical status, the PI or physician co-investigator will ask the potential subject's treating psychiatrist or primary care physician (PCP) to conduct a urine pregnancy test and/or bloodwork to rule out infections and liver, kidney or thyroid abnormalities. If the potential participant does not have a PCP or psychiatrist, a lab requisition will be provided to the participant. He/she will be considered for the study only after the lab results are reviewed by the study physician and found to be normal. .

Subjects will be randomized using a custom in-house software method, and will be stratified on time since injury: <5 years post injury versus≥5 years.

All members of the research team will be blind to individual subjects' treatment condition, with the exception of the rTMS staff member, Mr. Michael Tibbs. The success of subject blinding will be evaluated by asking subjects, during the first and last week of treatment, whether they believe that they received active or sham rTMS treatment. The rTMS technician will ask this question and note down the answer in the weekly assessment form.

Study Treatment: Subjects will receive either LFR rTMS or sham treatment.

***rTMS Treatment & Sham Treatment*:** rTMS will be delivered at the Brain Stimulation Program at The Johns Hopkins Hospital, using a Magstim Super Rapid 2 stimulator with a focal double 70-mm air cooled coil. Control patients will receive treatment using an identically appearing coil that produces the same sound and is the same weight as the active coil, but has negligible magnetic field strength. Scalp sensation in control subjects will be simulated using the sham system described in Borckardt et al[88]. Prior to each treatment, subjects will be instructed to insert earplugs. The head of the seated subjectwill be secured in a head and coil holder chair and stand assembly (Rogue Research Inc.). Motor threshold (MT) will be ascertained by delivering single pulses to the area of the motor cortex (right side) controlling the contralateral abductor pollicis brevis (APB). Electrical activity in APB will be recorded using surface electrodes. MT will be defined as the lowest intensity of stimulation that produces motor evoked potentials of at least 50 μV in 5 out of 10 trials. MT will be determined prior to the first treatment and weekly thereafter. The stimulation site for LFR over the DLPFC will be F4 of the International 10-20 System for Electrode Placement. . Treatment will be delivered by a TMS technician, or by co-investigator Dr. Reti, or by another physician credentialed to deliver TMS at The Johns Hopkins Hospital and approved by the IRB.

To determine optimal TMS treatment parameters we have reviewed the published literature reporting LFR rTMS for the treatment of major depression, and also rely on our own clinical experience using LFR rTMS to treat patients with idiopathic depression. We also take into account that although we are excluding subjects at increased risk for seizure with rTMS, such as those with a history of epilepsy, abnormal EEGs or focal abnormality on brain imaging, our TBI study population may nonetheless be at a higher risk.

Although LFR rTMS is often delivered to patients at 120% MT (consistent with FDA approval of HFL rTMS at 120% MT), most studies of LFR rTMS use 110% MT, which would carry a lower seizure risk than 120% MT. Accordingly, we will use 110% MT in our study. Two leading TMS groups studying LFR rTMS as an antidepressant have used 900 pulses daily over 4 weeks[78] and 1600 pulses daily over 2 weeks[70] in controlled studies. Both produce similar decreases in HAMD at their respective endpoints. Other sham-controlled studies have demonstrated an antidepressant effect with as few as 300 – 600 pulses daily delivered for 2 – 3 weeks[69, 74, 89]. Pulses are sometimes delivered in one continuous train[70,78] and at other times they have been delivered in several trains separated by an intertrain interval (ITI) of 30 – 60seconds[69,89,90], which could reduce seizure risk still further. We propose to deliver 1200 pulses daily at 110% MT for 4 weeks using four trains of 300 pulses daily separated by an ITI of 60 seconds. This parameter set also lies well within TMS safety guidelines most recently updated in Rossi et al[91].

The rTMS treatment sheet will be used after each treatment to record treatment parameters, treatment interruption, if any, and adverse events during treatment. The form has been uploaded in the IRB application under Section 19 – 'Supplemental Study Documents..

All participants will also receive supportive care. This will include education about TBI and depression and a discussion of the importance of maintaining structure/routine, regular physical exercise, engaging in hobbies and maintaining balanced/regular nutrition. Subjects who become suicidal or develop problems that require aggressive treatment during the course of the study will be withdrawn, and followed at the PI's Brain Injury Clinic, if appropriate care can be provided on an outpatient basis. If outpatient care is not appropriate, the PI will be responsible for admitting subjects to the psychiatric inpatient units at either Johns Hopkins Bayview Medical Center or Johns Hopkins Hospital.

Justification for use of Placebo:
The post-TBI depression field is currently at equipoise regarding the efficacy of antidepressant medications vs. placebo. There are no studies that have done a risk-benefit assessment on the use of anti-depressants vs placebo in the treatment of post-TBI depression. As the proposed treatment trial duration is only 16 weeks and all participants will have regular follow-up visits, those receiving sham treatment will not be at a great disadvantage compared to those receiving active LFR rTMS, as they will also receive regular supportive care. There is no evidence in psychiatric research that short-term treatment with placebo produces lasting harm (Addington and Quitkin 1999). However, if during follow-up visits, it is ascertained that a participant's depression is worsening with development of active suicidal thoughts, the participant will be withdrawn from the study for more active treatment (inpatient admission vs day hospital admission vs. aggressive outpatient treatment with medications). Careful screening of all participants will be done and no one who has responded well to a particular medication in the past will be enrolled in the study. Finally, the study will be carefully discussed with all participants emphasizing the risks and benefits of joining the study. All participants will also be encouraged to talk to their physicians about the pros and cons of joining a placebo-controlled trial.
In summary, the proposed study has the potential to reveal the effectiveness of LFR rTMS over placebo or vice-versa, underscoring the clinical utility and scientific merit of the study.

Justification for use of a two arm study versus a cross-over design study:
A cross-over design has the potential to confound study results, as the effect of rTMS treatments may last considerably longer than the duration of administration, and this prolonged effect is of unpredictable and unmeasurable duration. For this reason, crossover designs are no longer used to assess the efficacy of antidepressants/rTMS in treatment of major depression in general. As such, we do not feel it would be appropriate for assessing the efficacy of LFR rTMS for the treatment of post-TBI depression.

Informed Consent: The PI or her research coordinator (trained by the PI) will obtain written informed consent of all patients recruited into the study. The details of the study, including its potential risks and benefits, will be discussed with all participants. As much time as necessary will be spent to obtain a written informed consent from each participant, including time to discuss and answer any questions regarding the

study. Procedures for obtaining informed consent and evaluating the ability to give truly informed consent will follow those that have been approved by the Johns Hopkins and the DoD Institutional Review Boards (IRBs). Any data to be used in statistical analyses will be collected only after obtaining informed consent. To ensure that subjects understand the study's purpose and procedures, participants will be asked to answer the following five questions:

1) Do you understand that this is a research study?
2) Do you realize that participation in the study is entirely voluntary?
3) Do you understand that you will be assigned to either the experimental group or the control group?
4) Do you understand that you will have 20 treatment sessions, 5/week over 4 weeks?
5) Do you understand that you will be followed at monthly intervals for 3 months after treatment?

The same procedure including the 5 questions will be used at each of the follow-up visits (4, 8 and 12 weeks) to ensure that continual cognitive capacity to consent is maintained.

The following will be made clear to all subjects interested/enrolled in the study: A Department of Defense (DoD) organization is funding the study; representatives of the U. S. Army Medical Research and Materiel Command (USAMRMC or the DOD) are authorized to review research records; if requested, private health information willbe disclosed to representatives of the USAMRMC.

For those subjects referred to the PI by other physicians from Hopkins, a HIPAA waiver will be obtained to contact them directly. Very often, the Hopkins physicians may call the PI or her research coordinator and provide the name and telephone number of a person that he/she believes meetsstudy inclusion criteria and who has given verbal consent. The PI/research coordinator will then call this patient directly to explain the study and invite them to participate if he/she meets the study inclusion criteria.

Inclusion/Exclusion Criteria

Adult TBI patients will be considered for the study in accordance with the following inclusion and exclusion criteria.

Inclusion criteria:

a) Adults aged 18 and over
b) H/o closed head injury
c) Must meet DoD criteria for mild or moderate TBI
d) Time duration since injury greater than 3 months
e) Must meet criteria for major depression as assessed by the Structured Clinical Interview for DSM-IV (SCID) and a score greater than 10 on the HAM-D17

Exclusion criteria:

a) Subjects with skull fracture
b) Less than 3 months since injury
c) Subjects who meet DoD criteria for severe TBI
d) Subjects who are on psychotropics or mood stabilizing medications (e.g. antidepressants, antipsychotics, anxiolytics, sedative/hypnotics.
e) Subjects who are medically unstable
f) History of active substance abuse x 1 month
g) Current psychotic illness
h) Evidence of frontal lesions on brain scan (including patients who have undergone surgery for hemorrhage or clot evacuation in the frontal lobe, and patients who have had frontal lobe contusions and or subdural hematoma in the frontal regions)
i) Individuals with a significant neurological disorder that could increase risk for seizures such as brain tumor, cerebral aneurysm, any h/o seizures and/or family h/o seizures

j) Dementia
k) Mini Mental State Exam score of less than or equal to 24
l) A positive and unmitigated response to any question on the Transcranial Magnetic Stimulation Safety Screen questionnaire
m) ECT treatment within 6 months prior to the screening visit
n) History of treatment with rTMS therapy for any disorder
o) History of treatment with Vagus Nerve Stimulation (VNS)
p) History of treatment with Deep Brain Stimulation (DBS)
q) Cardiac pacemakers, implanted medication pumps, intracardiac lines,
r) Intracranial implant (e.g., aneurysm clips, shunts, stimulators, cochlear implants, or electrodes) or any other metal object within or near the head, excluding the mouth,that cannot be safely removed.
s) Implanted neurostimulators
t) Known or suspected pregnancy
u) Investigators, personnel affiliated with this study, and their immediate families.

5. Drugs/ Substances/ Devices

The device used in this study is a Magstim Super Rapid 2 stimulator with a focal double 70-mm air cooled coil, for the administration of LFR rTMS. rTMS has been used successfully in the treatment of idiopathic depressive disorders, but its safety and tolerability has not been tested in patients with post-TBI depression. Because this is a two-arm rTMS versus sham treatment study, subjects will be randomly assigned to either active rTMS or sham treatment. All subjects will receive 20 treatments (active or sham) for 5 days a week for a total of 4 weeks. All subjects will be brought back for follow-up visits at weeks 8, 12 and 16.

Concomitant medications

Subjects who are currently on psychotropics or mood stabilizing medications (e.g. antidepressants, antipsychotics, anxiolytics, sedative/hypnotics, will be excluded from the study. If subjects who otherwise meet inclusion criteria are on psychotropics that have not been effective and are willing to be off medications to participate, they will be included in study. Potential participants will only be considered for this study once they have been safely taken off all psychotropic medications by their treating physicians.

Study participants will continue to receive concomitant medications necessary to treat co-morbid medical conditions, such as hypertension diabetes and so forth.
The two exceptions to use of concomitant psychotropics during the course of the study is that patients may use trazodone up to 150 mg at bedtime as a sleep aid, and also may use up to three 0.5 or 1 mg doses of lorazepam for acute agitation per week during the course of the study.

All participants will also receive supportive care. This will include education about TBI and depression, and discussion of the importance of maintaining structure/routine, regular physical exercise, engaging in hobbies and maintaining balanced/regular nutrition

The rationale for choosing the device to be used.

There is no Food and Drug Administration (FDA) approved drug for the treatment of TBI-related NPS symptoms/syndromes. There are only two controlled medication trials in TBI-associated depression, and neither provided strong evidence that antidepressants are superior to placebo. A major limitation of previous studies has been their focus on limited symptoms and use of agents with narrow therapeutic profiles. We propose to address some of these limitations by use of a novel non-invasive technique, LFR rTMS, that has the potential to induce widespread neuromodulation.

Justification and safety information if FDA approved drugs will be administered for non-FDA approved indications or if doses or routes of administration or participant populations are changed. NA

Justification and safety information if non-FDA approved drugs without an IND will be administered. NA. We anticipate that the Johns Hopkins IRB will classify our trial as significant risk, in which case we will require an IDE from the FDA.

6. Study Statistics

General Description

a. Definition and selection of dataset: Intention-to-treat (ITT) will include all subjects who are randomized to participate in the protocol. The per-protocol (PP) population will include all subjects in the ITT population who meet the additional criteria of no major protocol violations and compliance with study treatment. Baseline demographic and clinical features, including medical comorbidity, pain, fatigue, and post-concussive symptoms will be included in the ITT dataset. Effect assessment will be included inboth the ITT and PP dataset.

b. Basic exploratory analyses will first be conducted, including checking of distributional assumptions, assessment of relationships among covariates, and missing-value multiple imputations.

c. Continuous variables will be described using means, standard deviations, medians, minimums and maximums, and 95% confidence intervals for parameter estimation. Graphical display (spaghetti plots) of the outcome scores will also be generated for 5 visits (baseline, end of 20 LFR rTMS sessions, week 8,12, and 16) by group. Category and count variables will be described using frequency or proportions.

d. Analyses will be conducted using STATA 11.2 (StataCorp, Texas, 2009) or R 2.13.2 (2011). All statistical tests will be judged for significance based upon a two-sided p-value of less than 0.05.

Primary objective: To determine the effectiveness of LFR rTMS for the symptomatic treatment of: (a) post-TBI depression as assessed by the Hamilton Depression Rating Scale (HAMD), Patient Health Questionnaire 9 (PHQ9) and the Clinical Global Impression-Improvement (CGI-I) scale; and (b) suicidal ideation as assessed by Beck Scale for Suicide Ideation (BSS).

Hypothesis:

a. Participants in the rTMS group (Experimental group), when compared to the sham treatment group (Control group) will have statistically significantly lower HAMD PHQ 9 scores (improvement in depression) and higher CGI-I scores (global improvement) at the end of the active treatment period (i.e., after 20 sessions) and during the follow-up period (i.e., week 8, 12, and 16 follow-up).

b. Participants in the rTMS group (Experimental group) compared to the sham treatment group (Control group) will have significantly lower scores on the BSS (i.eless suicidality) at the end of the active treatment period (i.e., after 20 sessions) and during the follow-up period (i.e., week 8, 12, and 16 follow-up).

Data Collection: The PI will be responsible for conducting comprehensive clinical evaluations on all subjects and for maintaining the psychiatric, medical and TBI data. rTMS and sham treatments will be administered by Dr. Reti, another TMS credentialed psychiatrist or the TMS technician. Data pertaining to treatments will be maintained by the TMS Program Coordinator. Three TMS forms (adverse effects, Weekly assessment & Operator form) have been uploaded for review. Co-investigator, Dr.McCann will be responsible for the sleep data and Dr. Kortte will be responsible for the cognitive data. At the end of the study, the PI and her research coordinator will be responsible for obtaining databases from each of the co-investigators, and merging data into a master database.

Variables and Measures:

Demographic & Clinical Variables: Demographic information including age, gender, education level, vocational status, living situation, annual income and marital status will be collected as part of the baseline evaluation. Other pertinent clinical variables, such as cause of trauma (assault vs. motor vehicle accident),

and litigation status will also be recorded. The VA/DoD definition of severity of TBI will be used to assess severity of TBI.

Psychiatric Disturbances: The presence or absence of major depression and other psychiatric illness will be determined by administration of the Structured Clinical Interview for DSM IV (SCID-IV[94]). The SCID-IV is designed to identify major Axis I DSM IV diagnoses. It is administered by a clinician and includes an introductory overview followed by nine modules, seven of which represent major Axis-I diagnostic classes. Using a decision tree approach, the SCID guides the clinician in testing diagnostic hypotheses as the interview is conducted. The output of the SCID is a record of the presence or absence of each of the disorders being evaluated, for current episode and for lifetime occurrence. It has been found to be diagnostically accurate and significantly better than the unstructured traditional diagnostic assessments[95]. The major mental Illness variable will be the presence or absence of any major mental illness (e.g., presence/absence of major depression, presence/absence of PTSD).

Depression: The severity of major depression will be assessed by the Hamilton Depression rating scale (HAM-D). This is a 17-item scale that evaluates depressed mood, vegetative and cognitive symptoms of depression. Its validity has been demonstrated in a number of studies and its inter-rater reliability has been consistently high across a number of studies[96]. The depression variable will be the total score on the HAM-D with higher scores indicating the presence of more depressive symptomatology. Severity of depression will also be assessed using a second scale the Patient Health Questionnaire 9 (PHQ9). The PHQ9 is brief, and can be completed by the patient and used over the telephone.

Suicide: Beck Scale for Suicide Ideation (BSS): BSS is a clinician rating scale administered as a semi-structured interview that measures severity, pervasiveness, and characteristics of suicidal thoughts and plans in adults. The total score ranges from 0 to 38, with higher scores indicating more intense levels of suicidal ideation The internal consistency, concurrent validity, test-retest reliability and predictive validity has been established[97].

Treatment response: The Clinical Global Impression (CGI)[98,99] scales are used to rate the severity of illness and assess response to treatment. CGI-Severity scale (CGI-S) is used to assess the severity of illness and CGI – Improvement scale (CGI-I) is used to assess treatment response in psychiatric patients. Both are 7-items scale. The CGI-S ranges from 1= normal to 7 = extremely ill.. The CGI-I rates participants improvement from baseline: 1=very much improved; 7=very much worse.

Primary Efficacy Measures: Changes in HAMD, PHQ9 and BSS;

Statistical Analysis

a. All subjects will be tracked over the study period in order to capture (1) the number subjects randomized to each group; (2) the number of subjects who drop-out or are lost to follow-up, and (3) the compliance of each subject across the study period.

b. Baseline balance analyses: At baseline, the two groups (Experimental and Control) will be compared on demographic and clinical features, including medical comorbidity, pain, fatigue and post concussive symptoms.

c. Effectiveness analyses: Random effects models will be used to evaluate the efficacy of the intervention as assessed by HAMD and PHQ9 with comparison of the slopes of the rTMS (Experimental) and sham treatment groups (Control). Random effects models will also be used to compare the two groups over time, controlling for baseline variables found to be statistically significant between the two groups, and the coefficient of interest, such as the interaction between time and treatment assignment. Similar analysis will be done for the CGI-I and BSS scores.

In addition, remission rates (as defined by HAMD score ≤ 7 or PHQ9 = 0) and Improvement rates (as defined by CGI-I scores ≤ 2) between the two groups will be calculated using Fischer's Exact test.

Secondary Objective: To determine the effectiveness of LFR rTMS for the treatment of common co-morbid neuropsychiatric symptoms: (a) Post traumatic stress disorder (PTSD) (b) Sleep disturbance and (c) Cognitive deficits.

Hypothesis: Participants in the rTMS group (Experimental group) compared to the sham treatment group (Control group) will have statistically significantly improvement on the: (a) Davidson Trauma Scale (DTS) (b) the Pittsburgh Sleep Quality Index(PSQI), theEpworth Sleepiness scale (EPS), and sleep polysomnogram (PSG) measures and (c) Cognitive domains including global cognitive functioning, memory, attention and executive function at the end of the active treatment period (i.e., after 20 sessions) and during the follow-up period (i.e., weeks 8, 12, and 16).

Variables:

Posttraumatic Stress Disorder: The Davidson Trauma Scale (DTS)[100] will be administered to measure severity of post-traumatic stress disorder. This is a 17-item self-report scale. The frequency and severity of symptoms are reported on a 4 point scale (0=not at all; 4= everyday); distress is also rated on a 4 point scale with higher scores indicating more severe distress. The scale is valid, with high internal consistency [101]. The PTSD variable will be the total score on the DTS.

Subjective Measurement of Sleep Disturbance: Two different subjective sleep scales will be administered at the initial and all follow-up visits. At the initial visit, subjects will also be interviewed for their pre-TBI sleep status. The Epworth Sleepiness Scale[102] is a well validated scale to assess daytime sleepiness. The Pittsburgh Sleep Quality Index (PSQI)[103] is a self-report questionnaire that examines sleep quality and disturbances in adults. It has been shown to be a valid and useful sleep disturbance screening measure for patients with TBI[104].

Objective Measures of Sleep Disturbances: Polysomnogram (PSG): Subjects' willingness to have sleep studies will be evaluated at the time of the initial evaluation, and only those willing will be enrolled in the study. For PSGs, participants will be admitted to the Johns Hopkins Bayview Clinical Research Unit, which is a component of an Institutional Clinical Translations Research program, for 2 overnight sleep studies (initial study at baselineand second study at week 16).. At both of these timepoints, subjects will undergo standard PSGs on 2 consecutive nights. The first PSG will be conducted for adaptation purposes. Only data from the second night will be used in data analyses. In summary, there will be a total of 4 PSGs, two pre and 2 post treatment. At both these times, the first night is adaptation night and data will not be used in statistical analyses. Data from the second night will be used in statistical analyses

EEG montages used in PSGs will include 6 EEG channels. These will include frontal, central, and temporal electrodes with a non-mastoid linked reference to minimize non-homogeneous current flow and possible misinterpretation of asymmetry data. In addition, right and left electro-oculograms will be linked to a single mastoid reference (EOGs), and 3 EMGs will be collected, including a bipolar submentalis EMG, and 2 bipolar tibial EMGs and an EKG. Respiratory function will be measured via a nasal pressure transducer & oral-nasal airflow thermocouple, pulse oximetry and piezoelectric abdominal and thoracic strain gauges. Periodic leg movement (PLM) measures will also be collected**.** Registered PSG technicians responsible for recording and scoring polysomnograms will be blinded to study hypotheses. Primary sleep PSG measures of interest include: sleep latency, total sleep time, time spent in each sleep stage, wake after sleep onset time, sleep efficiency, periodic limb movements/hr, and Apnea-Hypopnea Index.

Neuropsychological Tests: All subjects will complete neuropsychological testing at two time points: during the baseline visit and at the 3-month follow-up visit. The test battery will be constructed to allow evaluation of multiple domains of cognitive functioning, including global cognitive functioning, executive functioning, attention, and memory (Table 6). Briefly, the raw scores on all cognitive measures will be converted to scaled scores using the cumulative frequency distribution of each measure. Scaled scores will then be regressed on age, gender, race, years of education, and estimated premorbid IQ based on the revised National Adult Reading Test (NART)[105,106] . No additional control for education is necessary.

Table 6: Neuropsychological Tests

Montreal Cognitive Assessment	Test of global cognitive functioning
Wechsler Test of Adult Reading (WTAR)	Pre-morbid Intelligence
Trails B	Test of Executive functioning
Controlled Oral Word Association Test (COWAT)	Test of Executive functioning
Wisconsin Card Sorting test (WCST)	Test of Executive Functioning
Stroop Test	Test of Executive Functioning
Brief test of Attention (BTA)	Test of auditory attention
Trails A	Test of visual attention
Hopkins Verbal learning test (HVLT)	Verbal Memory Test
Brief Visual Memory Test (BVMT)	Visual Memory Test

Behavior Problems: The Neurobehavioral Rating Scale—Revised (NBRS-R) will be used to measure behavioral disturbances following TBI. The NBRS-R is a clinician-based multidimensional instrument and has been validated as a secondary outcome measure to assess behavior problems after brain injury[107].

Secondary Efficacy Measures: DTS; PSQI, EPS, PSG and cognitive measures.

Statistical Analysis: Analyses will be similar to Aim1. Random effects model will be used to compare of the slopes of the LFR rTMS (Experimental group) versus the sham treatment group (Control group) on the Davidson Trauma Scale scores. Random effects models will also be used to compare the two groups over time, controlling for baseline variables found to be statistically significant between the two groups, and the coefficients of interest, such as the interaction between time and treatment assignment.

This same statistical analysis approach will be used to compare the two groups on the sleep scales (PSQI & EPS) and on the primary PSG sleep variables, global cognitive functioning and memory, attention and executive functioning.

Exploratory Analyses:
The two groups will also be compared using similar statistical analyses of the NBRS-R scores. Additionally, a subset of subjects will also undergo MRI/DTI at baseline and at 3-month follow-up timepoint. DTI measures that will be used include fractional anisotropy (FA) and mean diffusivity (MD). The two groups will be compared on FA and MD values obtained at baseline and at 3-month follow-up using t-tests and linear regression analysis. Regions of interest will include frontal and temporal regions, fornix, cingulate, anterior limb of the internal capsule and genu and splenium corpus callosum.

Neuroimaging Analyses: As noted above, s subset of subjects will undergo MRI DTI scans pre- and post-LFR rTMS treatment. At the time of the initial screening, all subjects will be assessed for MRI safety using the questionnaire below. A positive answer to any one of the question will exclude them from having MRI. Also, only subjects who definitively agree to have brain MRI will have the scan.

MRI Questionnaire

Please reply yes or no to the following questions.
Do you have the following?:
Brain aneurysm clips
Any type of artificial heart valve
A heart defibrillator or pacemaker
Inner ear (cochlear) implants
Recently placed artificial joints

Any type of vascular stent
Any metal pieces in your body or eyes

DTI data will be acquired with a single-shot, echo-planar imaging (EPI) sequence with sensitivity encoding (SENSE), using a parallel-imaging factor of 2.5. The imaging matrix is 96 X 96 with a field-of-view of 212 X 212 mm (nominal resolution, 2.2 mm), zero-filled to 256 X 256 pixels. Transverse sections of 2.2 mm thickness will be acquired parallel to the anterior commissure-posterior commissure line. A total of 60-65 sections will cover the entire hemisphere and brainstem without gaps. Diffusion-weighted images at b = 700 s/mm^2 along 32 directions will be acquired in addition to five additional images with minimal diffusion weighting (b ≈ 33 mm^2/sec). The scanning time per dataset will be approximately 4 minutes. To enhance the signal-to-noise ratio, this procedure will be repeated 3 times. From this, fractional anisotropy (FA) and mean diffusivity (MD), and eigenvalues will be calculated. In this proposal, we will perform hypothesis-based regional analysis of the DTI-derived parameters using manual regions of interest (ROI). ROI will include frontal and temporal regions, the fornix, cingulate, anterior limb of the internal capsule, genu and splenium corpus callosum. We will also perform whole-brain analyses using a brain normalization technique developed in Dr. Mori's lab[108]. Combination of the two approaches (manual regional and automated whole brain analyses) will ensure the robustness and regional specificity of the ROI-based findings.

Other Scales: Other scales described below will be used to assess medical comorbidity, pain, fatigue and postconcussive symptoms all of which can confound the results and will be controlled in the different regression analyses.

Medical Co-morbidity: The General Medical Health Rating (GMHR)[109] will be used to assess overall medical co-morbidity. The scale is simple to use and provides a rating of overall general medical health taking into consideration all medical problems and medications. The scores on this scale ranges from 1 (poor; unstable medical health) to 4 (stable; excellent health). The PI has used this scale previously in her TBI studies.

Pain: The SF-36 bodily pain scale[110] will be used to assess pain. It has been found to be a valid measure of pain assessment.

Fatigue: The Fatigue Severity Scale[111] will be used to assess the severity of fatigue. It has been used both clinically and for research applications, and has been used in the assessment of fatigue in neurological and non-neurological conditions.

Post-Concussive Symptoms: As a myriad of post-concussive symptoms are present after TBI, the Rivermead Postconcussive Questionnaire[112] will be used to determine post-concussive symptoms and calculate the total score.

Power Analysis:
The power calculation for this study is based on the study by Fann et al[45] and our clinical experience. In the open labeled study of sertraline (Zoloft) for the treatment of TBI depression, Fann et al found a response rate (decrease in Hamilton depression scale score of > or = 50%) of 87% and remission rate (Hamilton depression scale score of < or = 7 at the end of treatment) of 67%. Based on these results, we hypothesize improvement in symptoms on the HAMD of 60-70% in the experimental group; and based on our clinical experience, we hypothesize a remission rate of 10% in the Control group. The table (Table 7) below depicts sample sizes for these remission rates with various degrees of power. As this is a pilot study, we have chosen a sample size (N=30) that is feasible and that will allow us to complete the study in the allocated time. Results from this study will help us to develop future studies with larger sample sizes and more conservative numbers. Sample size was calculated with (StataCorp, Texas, 2009) alpha was set at 0.05.

Table 7: Calculation of Sample Size.

Power	Remission rate in Experimental group (control group is 0.1)	N1 (Experimental group)	N2 (control group)	N (total)
0.9	0.7	15	15	30
0.8	0.7	13	13	26
0.75	0.7	12	12	24
0.7	0.7	11	11	22
0.6	0.7	10	10	20
0.9	0.6	21	21	42
0.8	0.6	17	17	34
0.75	0.6	16	16	32
0.7	0.6	15	15	30
0.6	0.6	13	13	26

Safety and tolerability: The following safety measures will be used:

1) Collection of vital signs
2) Collection of adverse events/side effects. All adverse events including minor rTMS side-effects like post-treatment headache as well as serious and unexpected adverse events like seizure will be recorded. All participants will be encouraged to call or page the PI if they notice any adverse effect or if they are concerned about any medical issues. Side effects will be monitored at each treatment and office visit.

An Adverse Events questionnaire will be used to record study side-effects. This questionnaire will capture the date, visit number, adverse event description, event start date, event end date, relationship to the device, severity, whether it is a SAE (Serious Adverse Event), action taken and outcome, The PI and/or, Medical Monitor and clinical co-investigators will make decisions regarding the severity of the side-effects, the relationship to the device and whether or not it a SAE.

Early stopping rules:
Subjects will be removed from the study early if it becomes clear that the risks of continuing treatment outweigh the benefits of continuing the study. In this research study, there is no alternative treatment other than treatment with LFR rTMS vs sham. If subjects are unable to complete the study, they will be either be absorbed in the PI's Brain Injury clinic or referred to appropriate treatment centers, if they so desire.

The following will be used to define unacceptable tolerability:
This decision will be made by a review committee chaired by the Medical Monitor.

(a) Clinically judged treatment-related death in one research participant. Clinically judged medication related death in one research participant. If a death occurs the case will be reviewed to decide if the death was medication related. The review committee will include Dr. Rao (PI), and members of the Data & Safety monitoring board: Dr. Constantine Lyketsos, Dr. Christopher Marano and Dr. Paul Rosenberg. All members of the DSM board are psychiatrists and faculty Johns Hopkins University. The 3 DSM members are not connected with the study.

Dr. Christopher Marano will also serve as the medical monitor. He is currently involved in several clinical trials and therefore, is well-suited for this role. As the medical monitor, his job will be to: (a) review and provide appropriate recommendations to address unanticipated problems that may arise during the study, and

(b) if anything adverse happens during the study period, he will provide an unbiased written report to the Johns Hopkins IRB and Department of Defense Human Research Protection Office (DoD HRPO) within 10 days of the event. He will not work under the supervision of the PI or any other research staff but will be available to the PI and research team to address any issues that arise during the study period. He will have the authority to stop the study, remove subjects from the study and take whatever steps are necessary to protect the safety and well-being of research volunteers until the IRB can assess the medical monitors report.

(a) Clinically judged treatment related hospitalization and/or emergency room visit in 20 % or more participants.

(b) Drop out of the study secondary to intolerable side-effects in 30% or more of participants
If any of the above happens, the study will be immediately terminated.

If either of the above happens, the study will be immediately terminated.

Otherwise, the Adverse-Events Protocol will be used to track the nature, visit time, and severity of side-effects

The PI and her research team will meet regularly to discuss the progress of the study.
In summary, all unanticipated problems involving risk to subjects or others related to participation in the study will be promptly reported both to Hopkins IRB and to the USAMRMC, Office of Research Protections, Human Research Protection Office (tel:301-619-2165; email - hsrrb@det.amedd.army.mil<mailto:hsrrb@det.amedd.army.mil or by facsimile 301-619-7803).
A complete written report will follow the initial notification. In addition to the methods above, the complete report will also be sent to the U.S. Army Medical Research and Materiel Command, ATTN: MCMR-ZB-PH, 504 Scott Street, Fort Detrick, Maryland 21702-5012."

7. Risks & Benefit

As with any medical treatment, rTMS carries a risk of side effects. However, rTMS is generally well-tolerated and only a small percentage of patients discontinue treatment because of side effects which are even less frequent with LFR than with HFL rTMS.

During the treatment, the patient may experience tapping, facial twitching, or painful sensations at the treatment site during stimulation. These types of sensations are reported by about one third of patients receiving rTMS. In addition, about half of patients treated with rTMS experience headaches. Both discomfort and headaches tend to get better over time and headaches generally respond very well to over-the counter pain medications. Because the TMS device produces a loud click with each pulse, patients must wear earplugs during treatment to minimize the risk of hearing loss. There have been no reported cases of permanent hearing loss with properly functioning hearing protection.

The most serious known risk of rTMS is the triggering of a seizure. Although there have been a few case reports of seizures with the use of TMS devices, the risk is extremely small and even lower with LFR than with HFL. Moreover, patients with a personal or family history of a seizure disorder or with focal brain pathology will be excluded from the study. Also, the TMS stimulation parameters utilized in this trial fall well within established safety guidelines for the use of TMS that are designed to minimize the risk of seizures with this technique.

As with all antidepressant treatments, there is a small risk for the emergence of mania with rTMS therapy. Also, rTMS therapy is not effective for all patients with depression, and there is a risk that the patient's depression will get worse. Moreover, 50% of subjects in this trial will receive sham stimulation.
There are no known adverse cognitive effects associated with rTMS therapy.

TMS should not be used by anyone who has non-removable magnetic-sensitive metal in their head or within twelve inches of the electromagnetic coil. Objects that may have this kind of metal include: aneurysm clips or coils; stents in your neck or brain; implanted stimulators; cardiac pacemakers or implantable cardioverter defibrillator (ICD); cardiac stents; electrodes for monitoring brain activity; metallic implants in the ears or eyes; shrapnel or bullet fragments; facial tattoos with metallic or magnetic sensitive ink; other metal devices or objects implanted in or near the head. Patients with any such objects will be excluded from the trial.

The risks of exposure to TMS in pregnancy are unknown. Therefore, women of childbearing capacity who are eligible for the study will be asked to take a pregnancy test and will be required to use protection during the study. Pregnant women will be excluded.

There are no known long-term adverse effects reported with the use of rTMS. However, as this is a relatively new treatment, there may be unforeseen risks in the long-term that are currently unknown.
In summary, Most common side effects of rTMS include seizures, headache, scalp discomfort at the site of stimulation, tingling, spasms or twitching of facial muscles, lightheadedness, discomfort from noise during treatment. Less common side-effects include seizures, mania, particularly in people with bipolar disorder and hearing loss due to inadequate ear protection during treatment

If subject experiences seizures or any of the side effects develop and become intolerable, the subject will be removed from the study treatment.

Participants are at risk for injury from MRI if they have pacemakers, aneurysm clips (metal clips on the wall of a large artery) or shrapnel fragments. Welders and metal workers are also at risk for injury because of possible foreign bodies in the eye. The magnetic field in the scanner may make pacemakers or watches malfunction and may make metal objects move or be dislodged. Therefore participants will be asked to remove all metallic objects on their clothing or jewelry before entering the scanner room. If subjects become uncomfortable in the scanner, they will have an alarm system at their disposal to stop the scan immediately. They may also become frustrated or bored or claustrophobic during these scans. They can be removed from the magnet at any point in the test.

Psychological risks include: worsening of depression. The research team will monitor the subject regularly, provide twenty-four hour access, and carefully educate the subject and caregiver about these risks and about when to call the research team. Subjects will be removed from the study early if it becomes clear that the risks of continuing treatment outweigh the benefits of continuing the study.

There are risks of confidentiality regarding the results of the evaluation, which might be used to discriminate against the person. All patients' files will be kept in locked cabinets. Additional confidentiality safeguards include: use of uniquely-coded study numbers, and maintenance of separate files of statistical vs. potentially identifying information. At all times, information about participants will be kept anonymous to study personnel other than the study staff. All members of the research team will have participated in human subjects training. Procedures for the protection of human research subjects will continue to be supervised and approved by the Institutional Review Board. Information will be disclosed whenever necessary only to the FDA, IRB, or the Department of Defense (DoD)..

There are no known social, legal, or other risks at this time. If such risks become known, the research team will immediately inform all subjects.

In this research study, there is no alternative treatment other than rTMS treatment. If subjects are unable to complete the study, they will be referred to appropriate treatment centers.

Steps taken to minimize the risks: As above

Plan for reporting unanticipated problems or study deviations: Any unanticipated problems or study deviations will be reported to Hopkins IRB and the DoD.

Financial risks to the participants: There are no financial risks to the patients.

All subjects will be instructed to call if they experience any new or worsening in symptoms.

Benefits
Study benefits include free comprehensive psychiatric evaluations, sleep studies and brain scans. These results if requested by the study participants will be made available to them.

There are currently no established protocols for the treatment of post-TBI depression & comorbidities. Hence the results of this study will make a significant contribution to the TBI literature. Results from this pilot study will be used to design study with larger sample size.

If the proposed rTMS treatment is found to be efficacious, it can be transferred to clinical practice for soldiers with TBI-associated depression and other psychiatric symptoms. rTMS has minimal long-term side effects and is not known to negatively interact with pharmacotherapies. rTMS has the potential to have a broader impact on multiple areas of life functioning and, thus, has the potential to lead to improved instrumental life activities, employability, community re-integration and overall quality of life. Soldiers with increased emotional stability and improved cognitive skills can more effectively manage stress which, in turn, can dramatically reduce the probability of developing disorders associated with chronic stress.

The major strength of this study is that it will be the first study to determine the effectiveness of low frequency right-sided rTMS for the treatment of common psychiatric disturbances that often co-occur with TBI. If successful, this will be a major advancement in the treatment of TBI because rTMS, has minimal long-term side effects and is not known to negatively interact with other drugs – important factors to be considered in this medically fragile population. Other unique aspects of the proposal include: (a) the use of a treatment strategy that is not purely symptom-based but has the potential to enhance cortical reorganization, increase synaptic connectivity and enable functional rehabilitation (b) the potential to study the pathophysiologic impact of rTMS on white matter connectivity as determined by DTI and (c) the possible beneficial effect of rTMS on other TBI related problems such as pain, spasticity, gait, coordination. Finally, if the results of the clinical trial are not positive, the study will still yield novel and abundant information on the nature of TBI sleep disturbance as well as anatomical correlates of TBI related neuropsychiatric disturbances, which have potential as diagnostic and prognostic markers

8. Payment and Remuneration

Subjects will be paid $54.00 for travel & snacks per visit.

1000.00 will be paid to each subject for their visits and treatment ($175.00/week for each of the 4 weeks they get rTMS/sham treatment; $75.00 for each of the 3 follow-up visits; bonus of $75.00 at the end of study).

In addition, they will be paid $400.00 for the overnight sleep studies ($200.00 for pre-treatment and $200.00 for post treatment). Subjects will have to spend 2 nights at the sleep lab, both at pre and post-treatment (total 4 nights).

The total cost per subject for 30 subjects will be $1,400 for participation and completion of study.
Twenty five subjects will receive an additional $50.00 for the brain scan done pre-treatment and $50.00 for scan done post treatment. These twenty five subjects will receive $1400.00 + $100.00 = $1500.00. All payments will be by cash, as we have done in our previous TBI studies.

As per the Department of Defense (DoD) rules, active duty research volunteers cannot receive any payment for participation unless they are off duty or on leave during the time they are participating in the study.

9. Costs

The cost of treatment (rTMs or Sham) is $70.00 per treatment.
The cost for MRI 3T scanner for an hour of scanning = $645.00.
The cost for 2-overnight Polysomnography = $450.00

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