Repetitive Transcranial Magnetic Stimulation for Treatment-Resistant Depression in Active-Duty Service Members Improves Depressive Symptoms

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Objectives: Current research on the efficacy of repetitive transcranial magnetic stimulation (rTMS) over left dorsolateral prefrontal cortex as a noninvasive therapy for treatment-resistant depression is largely settled science. However, little is known about its efficacy with active-duty service members (ADSMs) with major depressive disorder. In a retrospective chart review, we examined depressive symptom ratings in ADSMs seeking treatment at the US Army Outpatient Behavioral Health Service Clinic at Eisenhower Army Medical Center, Fort Gordon, Ga.

Methods: We reviewed 121 consecutive outpatient charts, which yielded 61 ADSMs who completed a minimum of 20 rTMS sessions for refractory depression, and for whom both pretreatment and posttreatment depressive symptom ratings were available. Pre- and post-Patient Health Questionnaire 9 (PHQ-9) scores were subjected to a paired t test, and Reliable Change Indices were calculated to determine both reliable and clinical significance.

Results: Average (SD) pretreatment and posttreatment PHQ-9 scores were 15.8 (6.2) and 12.6 (7.6), respectively. Statistically significant reduction in post–PHQ-9 was demonstrated (P < 0.001), with 69% of patients lowering their ratings and 31% demonstrating reliable change (improvement >5.64). Additionally, 20% demonstrated a reliable change that placed them in the nondysfunctional range (post–PHQ-9 <9.6), demonstrating clinical significance.

Conclusions: These data confirm a course of standard rTMS to ADSMs with major depression is promising in reducing depressive symptoms. Given that success and completion rates from this clinic are similar to those reported in civilian populations (80%), rTMS may be an adequate additional treatment or augmentation strategy for refractory depression in ADSMs.

Key Words: TMS, active-duty service members, noninvasive brain stimulation, transcranial magnetic stimulation, treatment-resistant depression

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According to the National Institute of Mental Health’s 2016 National Survey on Drug Use and Health,1 major depressive disorder (MDD) affects 6.7% (16.2 million) of the US adult population. Prevalence is greater in the military,2 with approximately 12.5% of active-duty service members (ADSMs) meeting formal criteria for MDD. Many ADSMs have other medical and psychiatric comorbidities such as substance use disorders,3,4 mild traumatic brain injury,5–7 anxiety disorders,8 and/or posttraumatic stress disorder (PTSD).8–11 In a meta-analysis examining MDD and PTSD, Rytwinski et al12 found significantly higher incidence of MDD/PTSD comorbidity among military personnel when compared with civilians. Complicating matters is the perceived stigma of seeking mental health treatment within the military.12 For these reasons, continuing to explore new treatment options for ADSMs with MDD in the military setting is of paramount importance to military mental health care.

Currently, the most common form of pharmacotherapy treatments for MDD includes a regimen of 1 or more antidepressant medications that act on specific neurotransmitters involved in mood regulation.13,14 Although this has proven to be beneficial for behavioral health patients suffering from MDD, approximately one-third of such patients are prescribed antidepressants without clear benefit to their depressive symptoms and are otherwise considered to have variously termed treatment-resistant, treatment-refractory, or pharmacoresistant depression.15,16 The term treatment-resistant depression (TRD) is commonly used and is broadly defined as “the occurrence of an insufficient clinical response following adequate antidepressant therapy (in terms of dosage, duration, and compliance) among patients diagnosed with major depression.”17 There have also been attempts to stage TRD severity, but they have not been empirically validated.17,18 It has been reported that ADSMs seek alternative, nonpharmacological remedies for their behavioral health challenges at higher rates than civilian populations.19 This is most often related to fear of “official” mental health treatment being detrimental to career progression. Additionally, ADSMs may seek alternative therapies to avoid common or perceived adverse effects associated with antidepressants or risk any perceived compromise in their physical or cognitive abilities.12

Historically, treatment-resistant MDD has been treated with alternative interventions such as electroconvulsive therapy (ECT) in addition to psychotherapy20,21 and, more recently, repetitive transcranial magnetic stimulation (rTMS).22–30 While ECT has shown to be effective in reducing depressive symptoms in severe depression,21,30 aspects of it, including the use of anesthesia requiring additional medical personnel and the posttreatment recovery time due to both the seizure induction and the medication, render ECT a less optimal therapy for active military personnel.31 Transcranial magnetic stimulation received US Food and Drug Administration (FDA) approval for TRD in 2008 and is a noninvasive option for treating depression that is a viable alternative to medications and ECT with few adverse effects, minimal personnel required to administer treatment, and little to no recovery time.23,32

For 2 decades, rTMS of the left dorsolateral prefrontal cortex has successfully been used therapeutically to reduce depressive symptoms in individuals diagnosed with MDD,25,32 as well as those with MDD whose symptoms remain pharmacoresistant.22,23,27,34,35 Given that rTMS has been shown to be a well-tolerated and effective treatment for TRD in civilian populations,27,36 it could become an attractive alternative within the
military health care system. However, there are scant peer-reviewed publications presenting TMS use with ADSMs (rTMS or other TMS protocols). A 2018 article by Yesavage et al.\(^1\) reported on a randomized controlled trial (RCT) comparing active rTMS treatment to sham treatment in 164 military veterans and found no significant difference between the active and sham treatment arms. These results vary significantly from the positive findings in multiple civilian population-based RCTs. The study had high placebo response and was postulated by the authors to be due to the daily interaction with clinicians and rigorous monitoring; however, the results may point to a less effective response in the unique military population. A 2012 study from Carpenter et al.\(^3\) used a naturalistic study design to look at rTMS in patients receiving usual clinical care in multiple practice locations (similar to our own clinical site) and did find significant and durable positive effects when using TMS adjunctively to standard care. Here, we attempt to fill this incongruence in the literature with results from an inpatient/outpatient treatment service employing rTMS for MDD in a specific population, ADSMs.

Currently, the Outpatient Behavioral Health Service (OBHS) at Fort Gordon’s Dwight D. Eisenhower Army Medical Center, Fort Gordon, Ga, uses rTMS therapy for ADSMs with treatment-resistant MDD. Active-duty service members seeking therapy for depression come into the clinic for treatment evaluation, and if rTMS is the appropriate treatment option for them, they are initiated into the clinical protocol. The clinic is a standard behavioral health treatment program with a typical military clinical population. This article reports on the use of rTMS in ADSMs and provides promising evidence of the effectiveness of rTMS in a real-world military population.

**MATERIALS AND METHODS**

**Patient Population**

This was a retrospective study of 121 consecutive ADSMs from the OBHS at Dwight D. Eisenhower Army Medical Center. The data were drawn from an ongoing database collected for quality management review. The data were generated and collected between 2014 and 2017. Since 2014, the OBHS has used rTMS therapy to treat ADSMs with treatment-resistant MDD. Active-duty service members were referred by clinical providers to the TMS intervention suite if they were determined to have refractory depression spectrum diagnosis and had inadequate response to other therapeutic options. Active-duty service members were excluded from the rTMS treatment protocol if they did not meet FDA guidelines for TMS, which includes having nonremovable conductive or ferromagnetic metal hardware near the head (e.g., cochlear implant or bullet fragment) or a history of seizures.\(^3\)

During this time frame, more than 120 soldiers were treated, and 97 received 20 to 40 individual daily rTMS sessions for 4 to 6 weeks (ie, “completers”) using a standard FDA-approved TMS protocol for MDD.

Active-duty service members who underwent a standard course of rTMS for the treatment of MDD between January 2014 and April 2017 were referenced for possible inclusion in the present analysis. During this time frame, the OBHS provided care for 134 consecutive cases, 13 of which were patients returning for follow-up booster sessions, leaving 121 unique patients. For those who received booster rTMS sessions, only data from their first round of treatment were included in the analyses. Ninety-seven of the 121 service members completed at least 20 sessions of rTMS (the remaining 24 patients either had not yet received 20 sessions, or they discontinued treatment during the time frame), and of the 97 completers, 61 had both pretreatment and posttreatment Patient Health Questionnaire 9 (PHQ-9) scores. The PHQ-9 was used to measure clinical improvement with respect to depressive symptoms. As shown in Table 1, independent \(t\) tests and Pearson \(\chi^2\) analyses demonstrated no statistical differences across age, gender, ethnicity, educational attainment, branch of service, or medical history between patients who were included in the study (\(n = 61\)) and those excluded from study (\(n = 60\). Table 1 provides additional military characteristics including the number of deployments and time in military service, all not significantly different between included and excluded patients. The only measure for which there was a significance between groups was the number of daily TMS sessions, \(t_{115} = -4.43, P < 0.001\), which was due to the inclusionary criteria of a minimum of 20 sessions. Classifications for categorical data including ethnicity and branch of service were determined from standard Army intake demographic questionnaires, and participants voluntarily self-reported this information. Table 2 presents similar findings on baseline levels of PHQ-9, that is, no significant difference between included and excluded patients. The 60 patients not included in the analysis were excluded solely on the basis of missing PHQ-9 data or noncompletion of treatment at the time of chart review.

**Measures**

Our measure is drawn from a standard battery of self-report questionnaires administered electronically (via Behavioral Health Data Platform) to nearly every service member receiving care within Department of Defense–affiliated behavioral health clinics within and outside the continental United States.

**Patient Health Questionnaire 9**

The PHQ-9\(^4\)–\(^6\) was utilized to measure depression severity; its 9 items assess symptom severity over the previous 2-week period, with total scores ranging from 0 to 27, with lower scores indicating less symptom severity. This measure was chosen by the Department of Defense to function as the primary depression screening and response tool because it has been widely studied and validated and has been found to have good internal consistency (Cronbach \(\alpha\) of 0.89).\(^6\) The baseline measure for PHQ-9 (pre–PHQ-9) was recorded prior to the start of rTMS treatment, and the posttreatment PHQ-9 (post–PHQ-9) was recorded after a full round of at least 20 rTMS sessions.

**Procedures**

The NeuroStar TMS Therapy System (Neuronetics, Inc, Malvern, Pa) was utilized. A standard course of rTMS involves patients, including the present patient sample, receiving pulsed magnetic current at 120% motor threshold at 10 Hz with 4 seconds of pulses followed by 10- to 26-second rest repeating for a total of 3000 pulses per session. Typically, treatments occur 5 days a week for 4 to 6 weeks, for a recommended total of 90,000 pulses. Thirty rTMS sessions are preferred, but 20 completed sessions are the minimum for a complete, FDA-approved, standard course. All patients included in this study completed a standard course of rTMS that consisted of at least 20 sessions.

**Data Analysis**

**Effect of rTMS on Treatment Outcome (PHQ-9) and Clinical Significance Test**

To test whether depressive symptoms changed significantly over the course of treatment, a paired \(t\) test was performed on the pre–PHQ-9 and post–PHQ-9 scores. We used Jacobson and Truax’s\(^9\) Reliable Change Index to test for a reliable change and clinical significance. A reliable change in symptom severity
TABLE 1. Demographic Characteristics, Military Branch, and Self-reported Medical History of ADSMs With Means (SD) or Frequencies (%) for Included and Excluded Patients

| Demographics, mean (SD) or n (%) | Included in TMS Efficacy Analysis (n = 61) | Excluded From TMS Efficacy Analysis (n = 60) | P |
|----------------------------------|---------------------------------------------|---------------------------------------------|---|
| Age, y                           | 34.8 (8.9)                                  | 32.5 (8.6)                                  | 0.150 |
| Sex                              |                                             |                                             | 0.169 |
| Male                             | 51 (83.6)                                   | 44 (73.3)                                   |    |
| Female                           | 10 (16.4)                                   | 16 (26.7)                                   |    |
| Ethnicity                        |                                             |                                             | 0.215 |
| Caucasian                        | 43 (70.5)                                   | 40 (66.7)                                   |    |
| African American                 | 10 (16.4)                                   | 15 (25.0)                                   |    |
| Latino/Hispanic                  | 5 (8.2)                                     | 0 (0.0)                                     |    |
| Asian American                   | 1 (1.6)                                     | 1 (1.7)                                     |    |
| Native American                  | 0 (0.0)                                     | 1 (1.7)                                     |    |
| Other                            | 1 (1.6)                                     | 1 (1.7)                                     |    |
| Unknown                          | 1 (1.6)                                     | 2 (3.3)                                     |    |
| Education level                  |                                             |                                             | 0.899 |
| GED                              | 1 (1.6)                                     | 1 (1.7)                                     |    |
| High school                      | 12 (19.7)                                   | 12 (20.0)                                   |    |
| Some college                     | 7 (11.5)                                    | 6 (10.0)                                    |    |
| Associate's degree               | 10 (16.4)                                   | 8 (13.3)                                    |    |
| Bachelor's degree                | 11 (18.0)                                   | 6 (10.0)                                    |    |
| Master's degree                  | 4 (6.6)                                     | 4 (6.7)                                     |    |
| Doctorate                        | 4 (6.6)                                     | 1 (1.7)                                     |    |
| Unknown                          | 12 (19.7)                                   | 22 (36.7)                                   |    |
| Military service                 |                                             |                                             | 0.234 |
| Branch                           |                                             |                                             |    |
| Army                             | 50 (82.0)                                   | 55 (91.7)                                   |    |
| Navy                             | 6 (9.8)                                     | 2 (3.3)                                     |    |
| Marines                          | 0 (0.0)                                     | 2 (3.3)                                     |    |
| Air Force                        | 2 (3.3)                                     | 1 (1.7)                                     |    |
| Coast Guard                      | 1 (1.6)                                     | 0 (0.0)                                     |    |
| Multiple branches                | 0 (0.0)                                     | 0 (0.0)                                     |    |
| Unknown                          | 2 (3.3)                                     | 0 (0.0)                                     |    |
| No. deployments, mean (SD)       | 2.1 (2.5)                                   | 1.5 (1.3)                                   | 0.193 |
| Years in service, mean (SD)      | 12.7 (7.6)                                  | 11.8 (8.2)                                  | 0.647 |
| Medical history                  |                                             |                                             |    |
| History of                       |                                             |                                             |    |
| (yes/no/unknown)                 |                                             |                                             |    |
| Cerebrovascular accident (stroke)| 0/61/0                                      | 0/56/4                                      | *   |
| Parkinson disease                | 0/49/12                                     | 0/42/18                                     | *   |
| Dementia                         | 0/49/12                                     | 1/42/17                                     | 0.283 |
| Multiple sclerosis               | 0/49/12                                     | 0/42/18                                     | *   |
| Epilepsy                         | 0/60/1                                      | 1/54/5                                      | 0.294 |
| ADD/ADHD                         | 10/40/11                                    | 10/29/21                                    | 0.527 |
| Depression                       | 61/0/0                                      | 57/0/3                                      | 0.332 |
| PTSD                             | 15/33/13                                    | 10/30/20                                    | 0.517 |
| Alcohol/drug use                 | 21/35/5                                     | 17/26/17                                    | 0.837 |
| Residential treatment            | 13/48/0                                     | 12/48/0                                     | 0.859 |

(Continued next page)

RESULTS

Demographic Characteristics

Further characterization of the 61 patients included in this study reveals that the average age was 34.8 (SD, 8.9). Eighty-four percent were male, 71% were white, 16% were African American, 8% were Latino/Hispanic, and 59% had participated in some college. Eighty-two percent were Army, 10% were Navy, and 3% were Air Force. Seventy-nine percent were considered senior noncommissioned officers (ie, advanced to rank E-5+) or commissioned officers. Average time in service was 12.7 (SD, 7.6) years, and the average number of deployments was 2.1 (2.5). Medically, none of the patients had a self-reported preexisting history of cerebrovascular accident or stroke, Parkinson disease, dementia, multiple sclerosis, or epilepsy, whereas 17 (28%) endorsed having had at least 1 concussion. Common psychiatric comorbidities included PTSD (25%) and substance abuse (34%), with as many as 21% having undergone residential treatment for addiction/dual diagnosis. From a psychotherapeutic medical management perspective, 41%, 90%, and 8% of study participants had undergone a trial of anxiolytic, antidepressant, or mood stabilizer, respectively.
Some ADSMs were included after a failed trial of therapy secondary to either refusal or inability to undergo a trial of medication. Average number of rTMS sessions completed across a trial of treatment was 29.0 (SD, 4.8), and the average duration of rTMS treatment, start to finish, for study participants was 45.4 (SD, 14.2) days. See Table 1 for complete demographic characteristics and medical histories.

**Study Objective: Examining Clinical Effectiveness of rTMS in a Military Setting**

Overall, posttreatment PHQ-9 scores decreased compared with pretreatment scores. Average pretreatment baseline PHQ-9 score was 15.8 (SD, 6.2), whereas average posttreatment scores decreased to 12.6 (SD, 7.6). A paired t test revealed that the average 3.16-point decrease in depressive symptom ratings was significant, \( t_{60} = 3.796, P < 0.001 \), with a medium effect size (Cohen \( d = 0.46 \)). See Figure 1 for a scatterplot of pretest and posttest scores.

**Reliable Change and Clinical Significance**

Forty-two patients (69%) showed an improvement (reduction) in PHQ-9 scores. Nineteen patients (31%) demonstrated a reliable change (ie, >5.65-point reduction), with 12 of those 19 individuals (20%) falling in the nondysfunctional range after a standard rTMS treatment, with posttreatment PHQ-9 scores less than 9.56 (our clinical cutoff, see above for explanation). See Table 1 for a scatterplot of pre–PHQ-9 and post–PHQ-9 scores with the reliable change bands displayed. Scores that fall beyond the right diagonal band on the scatterplot indicate a reliable improvement. Scores that additionally fall below the normative cutoff of 9.6 represent patients who had both a reliable and clinically significant change.

**Influence of Comorbidities and Prescription Medication**

Among those patients included in the main efficacy analysis, roughly half (n = 31) had comorbidity with PTSD only (n = 10) or substance abuse only (n = 16) or both (n = 5). Results of the linear regression assessing the influence of comorbidity (ie, none, PTSD, substance abuse, or both) on treatment outcome (ie, the difference between pre- and post–PHQ-9) revealed that there was no difference as a result of comorbidity (all \( P_S < 0.47 \)). Importantly, this indicates there was no reported difference in improvement in depressive symptoms whether the patient had no comorbidity or had MDD plus PTSD, substance abuse, or both. See Figure 2 for a graph showing mean difference scores by comorbidity, with error bars representing the SEM. The number of daily rTMS sessions between patients with and without comorbidity differed significantly, \( t_{59} = 2.72, P = 0.009 \). On average, those with comorbidities received fewer individual sessions (27.4 [SD, 5]) than those with only MDD (30.6 [SD, 4]). Linear regression was used to test if prescription drug history (antidepressants, anxiolytics, mood stabilizers, or neuroleptics) predicted patient PHQ-9 difference scores. The result of the regression indicates the 4 predictors explained 21.5% of the variance (\( R^2 = 0.22, F_{2.4.35} = 2.4, P = 0.07 \)). Additionally, we found that mood stabilizers significantly predicted difference scores (\( \beta = 0.38, P = 0.015 \)), which is consistent with the findings of a small 2010 study by Harel et al, which found rTMS improved bipolar depressive symptoms.

**DISCUSSION**

In this analysis of data from a retrospective chart review of consecutive ADSM patients treated with rTMS in a military treatment facility, we were able to demonstrate that rTMS is an efficacious nonpharmacological treatment option for active military with refractory (treatment-resistant) depression. We had a slightly less robust effect size (Cohen \( d = 0.46 \) on the paired t test of pre–/post–PHQ-9)
CONCLUSIONS

In this study, we were able to demonstrate that rTMS for treatment of refractory depression is an adequate treatment or augmentation option for ADSMs with MDD. The mean response was significant but less robust than those seen with ECT and may not be sufficient for the more severely depressed ADSMs. Although ADSMs are typically more transient due to frequent moves by both provider and ADSM, and they have higher operational work demands than civilian employees that may make them less likely to complete treatment, only 24 of 121 (20%) did not complete an adequate number of rTMS sessions in the present study. Some of the more recent patients were simply in the middle of their first standard course, whereas others terminated completely. This completion rate demonstrates that rTMS can be applied to a military population with comparable success to civilian populations. A second frequently voiced concern regarding rTMS in ADSMs is that commanders would have concerns about ADSMs’ time away from duty; we have not had commander concerns regarding mission decrement due to ADSMs receiving this treatment and in fact have found commanders to be quite supportive and appreciative of improved soldier functioning. Repetitive TMS appears to be a functional alternative treatment for active service members stationed on or near base (ie, none of the patients included were deployed).

This study contributes significantly to the field of noninvasive brain stimulation by demonstrating that rTMS is an effective alternative to or augmentation of the usual standard-of-care treatment for depressive symptoms in the military. Additionally, this study provides successful replication of rTMS efficacy in both general terms and its specific use within a military population.

This retrospective review should be followed up with an RCT in ADSMs. Future studies may compare rTMS to other types of noninvasive electrical brain stimulation, such as neuronavigation-guided rTMS, intermittent theta burst TMS, or high-definition transcranial direct current stimulation, to determine which is most efficacious, least disruptive, portable, and cost-effective. Currently, rTMS is not widely available to service members as it is used only at select treatment facilities. With the ongoing concern for ADSM suicide50,51 (321 in 201852), the limited treatment options available, and the high percentage of ADSMs whose depression is treatment-resistant, the authors believe rTMS shows promise as an effective therapy for military personnel.

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