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215 North Main Street
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(802) 296-5132
FAX (802) 296-5135
Email: ncptsd@va.gov

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Focal Brain Stimulation for Posttraumatic Stress Disorder

Paul Holtzheimer, MD
Deputy for Research,
National Center for PTSD

Introduction

Focal brain stimulation, or focal neuromodulation, offers a unique alternative to psychotherapeutic and pharmacologic treatments for psychiatric disorders. Focal brain stimulation interventions are based in a paradigm that views psychiatric disorders as resulting from dysfunction within a structurally and functionally connected network of brain regions. This paradigm is complementary to those that presume psychiatric dysfunction results from abnormalities of neurochemicals, supporting the development of psychotropic medications, or from dysfunctional thoughts and behaviors, providing the basis for cognitively-behaviorally oriented psychotherapies. Within the neural network paradigm of psychiatric dysfunction, it is posited that altering activity at one specific brain region via focal stimulation will result in downstream functional changes throughout the network involved in the pathophysiology of a particular psychiatric condition. Additionally, it is possible that focal neuromodulation of the neural network can serve to synergize with pharmacologic and psychotherapeutic treatments: e.g., focal neuromodulation of a specific neural circuit may "prime" it to be more responsive to another intervention.

The most common focal brain stimulation approaches used for the treatment and study of psychiatric disorders include transcranial magnetic stimulation, transcranial direct current stimulation and deep brain stimulation. Transcranial magnetic stimulation (TMS) is a noninvasive technique that uses a rapidly changing magnetic field, delivered at the scalp surface, to induce an electric current in the underlying cerebral cortex. TMS can depolarize cortical neurons and can have inhibitory or excitatory effects depending on stimulation location and parameters. Typically, stimulation is limited to a 2–3 centimeter area of cortex, allowing for stimulation of discrete neural regions; however, due to the rapid decay of the magnetic field strength with distance from the coil, functionally relevant stimulation of deeper cortical and subcortical structures is not feasible with most available devices. Transcranial direct current stimulation (tDCS) is a noninvasive technique that applies a low intensity electrical current to the brain via an anode and cathode. This approach does not directly depolarize neurons but may alter the likelihood that groups of neurons will activate with subsequent provocation. Deep brain stimulation (DBS) is an invasive technique involving neurosurgical placement of stimulation electrodes within the brain, with delivery of focal electrical stimulation to a specific deep brain region. With DBS, stimulation is controlled by an implanted pulse generator that can be tuned via an external programming wand.

Using a neural network framework to develop treatments for psychiatric disorders, the main questions to be answered include: 1) which brain regions are involved in the pathophysiology of the disorder; 2) which brain regions are critical to treatment response; and 3) how might the key nodes within the network be modified for therapeutic benefit. In psychiatry, focal brain stimulation is most developed as an intervention for treatment-resistant depression (Cook, Espinoza, & Leuchter, 2014). More than three decades of brain imaging studies have helped to construct neural network models underlying depression and the antidepressant treatment response. TMS applied to the left dorsolateral prefrontal cortex is a Food and Drug Administration- (FDA-) approved treatment for medication-resistant depression, based on data suggesting that the prefrontal cortex is a critical node in the neural network involved in depression. Based on a similar database, several DBS targets for severe, treatment-resistant depression have been proposed and tested.

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Author's Address: **Paul E. Holtzheimer, MD** is affiliated with the National Center for PTSD, Executive Division, VA Medical Center (116D) 215 North Main Street, White River Junction, Vermont 05009 and with the Geisel School of Medicine at Dartmouth, Dartmouth Hitchcock Medical Center, One Medical Center Drive, Lebanon, NH 03756. Email Address: Paul.E.Holtzheimer@hitchcock.org.

Continued from cover

The neural networks involved in PTSD include those related to the experience and processing of fear, sympathetic arousal, and the cognitive/cortical control of these systems (Jovanovic & Ressler, 2010). Based on putative neural network models of PTSD, several cortical and subcortical brain regions emerge as potential targets for focal neuromodulation. Among these, the prefrontal cortex and the amygdala are currently the most promising targets for neuromodulation.

Transcranial Magnetic Stimulation as a Monotherapy or Add-on Treatment for PTSD

TMS was first studied as a monotherapy or add-on treatment for psychiatric disorders in the mid-1990s, with depression as the condition most frequently targeted. The most common TMS stimulation site for the treatment for depression has been the left dorsolateral prefrontal cortex (DLPFC) with stimulation delivered at "high frequency", e.g., ≥5 Hz, which is presumed to be excitatory to the underlying cortex. However, a number of studies in depression have applied TMS to the right DLPFC using "low frequency" stimulation, e.g., ≤1 Hz, which is presumed to be inhibitory. Finally, some studies have used bilateral stimulation, i.e., a combination of left, high frequency with right, low frequency TMS. Each of these approaches (left TMS, right TMS and bilateral TMS) has shown antidepressant efficacy in sham-controlled studies (Brunoni et al., 2017). For the treatment of depression, TMS is typically delivered in a series of daily treatment sessions, each lasting about 40 minutes to an hour. Fifteen to 30 sessions provided Monday through Friday over three to six weeks comprise a treatment course. Most of the early studies of TMS for depression used TMS as an add-on to current, stable antidepressant treatment; however, the large confirmatory trials of TMS for depression used TMS as a monotherapy for depression in medication-free patients.

Based on the overlap of the phenomenology and neurobiology of depression and PTSD, TMS has also been studied as a monotherapy or add-on treatment for PTSD, though the published literature is much more limited than that for depression. Three early case series/open-label studies provided mixed support for TMS as a treatment for PTSD, though it is noted that each of these three studies differed significantly from one another in terms of stimulation site and parameters (Grisaru, Amir, Cohen, & Kaplan, 1998; McCann et al., 1998; Rosenberg et al., 2002). Following this, a series of sham-controlled studies were conducted that also differed in terms of stimulation site (left vs. right DLPFC), stimulation frequency (low vs. high) and total amount of TMS provided (ranging from a total of 1000 to 36000 pulses delivered) (Cohen et al., 2004; Boggio et al., 2010; Watts, Landon, Groft, & Young-Xu, 2012). These studies were the subject of three meta-analyses that each concluded the available data supported the efficacy of TMS as a treatment for PTSD (Berlim & Van den Eynde, 2014; Karsen, Watts, & Holtzheimer, 2014; Trevizol et al., 2016). (A fourth meta-analysis included six additional studies published in foreign language medical journals and essentially agreed with the findings from the first three meta-analyses [Yan, Xie, Zheng, Zou, & Wang, 2017].) The significant variability in study design of the individual studies precludes a determination of which TMS approach is most effective, though there is a suggestion that right DLPFC TMS, delivered at a higher "dose" (i.e., greater number of pulses) may have the greatest efficacy.

Since publication of these meta-analyses, a small case series has been published showing efficacy of 5 Hz TMS applied to the left DLPFC for patients with comorbid PTSD and depression (Philip, Ridout, Albright, Sanchez, & Carpenter, 2016). Another, small open-label study found benefit for dorsomedial cortical TMS in patients with PTSD and comorbid eating disorder (Woodside et al., 2017). A very small (*N* = 18), randomized, sham-controlled trial showed a modest benefit for 1 Hz right DLPFC TMS for patients with PTSD (Nam, Pae, & Chae, 2013).

Taken together, these data suggest that TMS may have efficacy for PTSD as a monotherapy or add-on treatment. However, the high variability between the studies must be emphasized as this limits conclusions regarding the optimal use of TMS to treat PTSD. The studies summarized above differ in terms of treatment location (left DLPFC vs. right DLPFC), stimulation frequency (low vs. high) and the number of TMS pulses delivered within a treatment session and across a treatment series. It is not completely clear which combination of treatment location and parameters are to most likely show efficacy for PTSD, though, as noted above, there is a suggestion that right DLPFC TMS applied at a higher dose (higher number of TMS pulses) shows the most promise.

Combining Focal Brain Stimulation with Other Therapies for PTSD

In addition to being a potential monotherapy or add-on treatment for PTSD, it is possible that focused stimulation of specific brain networks involved in PTSD might enhance the therapeutic response to other treatments. A sham-controlled, crossover study of nine patients with PTSD found that bilateral medial prefrontal cortical 1 Hz TMS combined with imaginal exposure therapy led to a decrease in hyperarousal symptoms associated with changes in peripheral levels of norepinephrine, thyroxine and prolactin (Osuch et al., 2009). Another small, sham-controlled study (*N* = 30) found that "deep TMS" — TMS provided with a special coil that provides broad surface stimulation but may more focally stimulate deeper cortical structures — was associated with a decrease in intrusive symptoms of PTSD when combined with a brief exposure intervention (Isserles et al., 2013). Recently, a relatively large, sham-controlled study (*N* = 103) showed that right DLPFC 1 Hz TMS combined with cognitive processing therapy led to greater reduction in PTSD severity (Kozel et al., 2018). Finally, a small case series (*N* = 4) has shown that tDCS combined with working memory training may improve cognitive and emotional function in patients with PTSD and poor working memory (Saunders et al., 2015). Although highly preliminary, these studies suggest that response to existing psychotherapeutic strategies for PTSD might be enhanced with concurrent focal brain stimulation.

As with studies supporting efficacy of TMS as a monotherapy or add-on treatment for PTSD, these data suggest TMS may be able to specifically enhance the response to psychotherapeutic interventions when used in combination. However, the database is quite small and also heterogeneous: each study used a different focal brain stimulation paradigm and combined stimulation with a different non-TMS intervention. This is a promising area for treatment development, but more research is clearly needed.

Deep Brain Stimulation for PTSD

DBS is an established intervention for patients with medication refractory movement disorders, such as Parkinson Disease and essential tremor. DBS is also approved by the FDA, under a Humanitarian Device Exemption, for the treatment of treatment-resistant obsessive-compulsive disorder. A mixed database

suggests DBS of several regions may have efficacy for treatment-resistant depression (Dandekar, Fenoy, Carvalho, Soares, & Quevedo, 2018). As DBS requires an invasive neurosurgical procedure to implant the system, treatment and study is generally reserved for patients with severe, highly treatment-refractory illness.

Although there might be many potential deep brain targets for the treatment of PTSD, the amygdala is an obvious choice given its central role in fear processing. A pilot study of DBS of the basolateral amygdala is currently underway, and notable benefit was seen in the first patient enrolled in this study (Koek et al., 2014; Langevin et al., 2016). A preclinical study in an animal model of PTSD confirms that focal stimulation of the basolateral amygdala may reduce fear and anxiety like behavior in rats (Reznikov et al., 2018).

The study of DBS for PTSD is in its earliest stages, and there is much work to be done. In addition to the amygdala, there may be other brain regions that could serve as DBS targets for the treatment of PTSD. More preclinical and human neuroimaging research will continue to better delineate the neural networks involved in PTSD, especially highly treatment-resistant PTSD, and thereby identify putative DBS targets.

Conclusion

In summary, the available data on TMS as a monotherapy treatment for PTSD are limited but do suggest the potential for efficacy. However, it is unclear which TMS cortical targets and stimulation parameters are most effective, and further study is clearly warranted. There is very preliminary evidence that TMS and tDCS may be used to augment the response to cognitive-behavioral interventions for PTSD. Finally, there is potential promise that DBS may be a safe and efficacious treatment for patients with severe and treatment-resistant PTSD.

FEATURED ARTICLES

Berlim, M. T., & Van den Eynde, F. (2014). **Repetitive transcranial magnetic stimulation over the dorsolateral prefrontal cortex for treating posttraumatic stress disorder: An exploratory meta-analysis of randomized, double-blind and sham-controlled trials.** *Canadian Journal of Psychiatry, 59*, 487-496. doi:10.1177/070674371405900905 *Objective:* Repetitive transcranial magnetic stimulation (rTMS) applied to the dorsolateral prefrontal cortex (DLPFC) has yielded promising results as a treatment for posttraumatic stress disorder (PTSD). However, to date, no quantitative review of its clinical utility has been published. *Method:* We searched for randomized and sham-controlled trials from 1995 to March 2013 using MEDLINE, Embase, PsycINFO, CENTRAL, and SCOPUS. We then performed an exploratory random effects meta-analysis. *Results:* Studies on rTMS applied to the right DLPFC included 64 adults with PTSD. The pooled Hedges *g* effect size for pre and post changes in clinician-rated and self-reported PTSD symptoms were, respectively, 1.65 ($P < 0.001$) and 1.91 ($P < 0.001$), indicating significant and large-sized differences in outcome favouring active rTMS. Also, there were significant pre and post decreases with active rTMS in overall anxiety (Hedges $g = 1.24$; $P = 0.02$) and depressive (Hedges $g = 0.85$; $P < 0.001$) symptoms. Dropout rates at study end did not differ between active and sham rTMS groups. Regarding rTMS applied to the left DLPFC, there is only one study published to date (using a high frequency protocol), and its results showed that active rTMS seems to be superior overall to sham rTMS. *Conclusions:* Our exploratory meta-analysis shows that active rTMS applied to the DLPFC seems to be effective and acceptable for treating PTSD. However, the small number of subjects included in the analyses limits the generalizability of these findings. Future studies should include larger samples and deliver optimized stimulation parameters.

FEATURED ARTICLES *continued*

Boggio, P. S., Rocha, M., Oliveira, M. O., Fecteau, S., Cohen, R. B., Campanhã, C., . . . & Fregni, F. (2010). **Noninvasive brain stimulation with high-frequency and low-intensity repetitive transcranial magnetic stimulation treatment for posttraumatic stress disorder.** *Journal of Clinical Psychiatry, 71*, 992-999. doi:10.4088/JCP.08m04638blu *Objective:* We aimed to investigate the efficacy of 20 Hz repetitive transcranial magnetic stimulation (rTMS) of either right or left dorsolateral prefrontal cortex (DLPFC) as compared to sham rTMS for the relief of posttraumatic stress disorder (PTSD)–associated symptoms. *Method:* In this double-blind, placebo-controlled phase II trial conducted between October 2005 and July 2008, 30 patients with *DSM-IV*–diagnosed PTSD were randomly assigned to receive 1 of the following treatments: active 20 Hz rTMS of the right DLPFC, active 20 Hz rTMS of the left DLPFC, or sham rTMS. Treatments were administered in 10 daily sessions over 2 weeks. A blinded rater assessed severity of core PTSD symptoms, depression, and anxiety before, during, and after completion of the treatment protocol. In addition, a battery of neuropsychological tests was measured before and after treatment. *Results:* Results show that both active conditions—20 Hz rTMS of left and right DLPFC—induced a significant decrease in PTSD symptoms as indexed by the PTSD Checklist and Treatment Outcome PTSD Scale; however, right rTMS induced a larger effect as compared to left rTMS. In addition, there was a significant improvement of mood after left rTMS and a significant reduction of anxiety following right rTMS. Improvements in PTSD symptoms were long lasting; effects were still significant at the 3-month follow-up. Finally, neuropsychological evaluation showed that active 20 Hz rTMS is not associated with cognitive worsening and is safe for use in patients with PTSD. *Conclusions:* These results support the notion that modulation of prefrontal cortex can alleviate the core symptoms of PTSD and suggest that high-frequency rTMS of right DLPFC might be the optimal treatment strategy.

Cohen, H., Kaplan, Z., Kotler, M., Kouperman, I., Moisa, R., & Grisaru, N. (2004). **Repetitive transcranial magnetic stimulation of the right dorsolateral prefrontal cortex in posttraumatic stress disorder: A double-blind, placebo-controlled study.** *American Journal of Psychiatry, 161*, 515-524. doi:10.1176/appi.ajp.161.3.515 *Objective:* The efficacy of repetitive transcranial magnetic stimulation (rTMS) of the right prefrontal cortex was studied in patients with posttraumatic stress disorder (PTSD) under double-blind, placebo-controlled conditions. *Method:* Twenty-four patients with PTSD were randomly assigned to receive rTMS at low frequency (1 Hz) or high frequency (10 Hz) or sham rTMS in a double-blind design. Treatment was administered in 10 daily sessions over 2 weeks. Severity of PTSD, depression, and anxiety were blindly assessed before, during, and after completion of the treatment protocol. *Results:* The 10 daily treatments of 10-Hz rTMS at 80% motor threshold over the right dorsolateral prefrontal cortex

had therapeutic effects on PTSD patients. PTSD core symptoms (reexperiencing, avoidance) markedly improved with this treatment. Moreover, high-frequency rTMS over the right dorsolateral prefrontal cortex alleviated anxiety symptoms in PTSD patients. *Conclusions:* This double-blind, controlled trial suggests that in PTSD patients, 10 daily sessions of right dorsolateral prefrontal rTMS at a frequency of 10 Hz have greater therapeutic effects than slow-frequency or sham stimulation.

Grisaru, N., Amir, M., Cohen, H., & Kaplan, Z. (1998). **Effect of transcranial magnetic stimulation in posttraumatic stress disorder: A preliminary study.** *Biological Psychiatry, 44*, 52-55. doi:10.1016/S0006-3223(98)00016-X *Background:* Transcranial magnetic stimulation (TMS) has become, over the last few years, a promising avenue for new research in affective disorders. In this study we have evaluated the clinical effect of slow TMS on posttraumatic stress disorder (PTSD) symptoms. *Methods:* Ten PTSD patients were given one session of slow TMS with 30 pulses of 1 m/sec each, 15 to each side of the motor cortex. *Results:* Symptoms of PTSD were assessed by using three psychological assessment scales, at four different time points. In this first, pilot, open study, TMS was found to be effective in lowering the core symptoms of PTSD: avoidance (as measured by the Impact of Event Scale), anxiety, and somatization (as measured by the Symptom Check List–90). A general clinical improvement was found (as measured by the Clinical Global Impression scale); however, the effect was rather short and transient. *Conclusions:* The present study showed TMS to be a safe and tolerable intervention with possibly indications of therapeutic efficacy for PTSD patients.

Isserles, M., Shalev, A. Y., Roth, Y., Peri, T., Kutz, I., Zlotnick, E., & Zangen, A. (2013). **Effectiveness of deep transcranial magnetic stimulation combined with a brief exposure procedure in post-traumatic stress disorder — A pilot study.** *Brain Stimulation, 6*, 377-383. doi:10.1016/j.brs.2012.07.008 *Background:* Post-traumatic stress disorder (PTSD) is a debilitating anxiety disorder induced by traumatic experiences. To date, psychotherapy and drug treatment achieve only partial success, indicating need for further development of treatment strategies. Recent research has found that impaired acquired fear extinction capability serves as an important factor at the pathogenesis of the disorder. Medial prefrontal cortex (mPFC) hypo-activity has been implicated in this extinction impairment, providing insight as to why some trauma exposed individuals will develop PTSD. *Objective:* To test whether fear extinction can be facilitated and therapeutic effect achieved by repeated mPFC deep transcranial magnetic stimulation (DTMS) of PTSD patients resistant to standard treatment. *Methods:* In a double-blind study, 30 PTSD patients were enrolled and randomly assigned into 3 treatment groups: A) DTMS after brief exposure to the traumatic event with the script-driven imagery procedure; B) DTMS after brief exposure to a non-traumatic event; C) sham stimulation after brief exposure to the traumatic event. *Results:* Significant improvement was demonstrated in the intrusive component of the CAPS scale in patients administered DTMS after exposure to the traumatic event script, while patients in the control groups showed no significant improvement. Similar trend was demonstrated in the Total-CAPS score as in the other rating scales. A significant reduction in the HR response to the traumatic script was evident in group A, further supporting the above results. *Conclusions:* Combining brief script-driven exposure with DTMS can induce therapeutic effects in PTSD patients. A wide multi-center study is suggested to substantiate these findings.

Jovanovic, T., & Ressler, K. J. (2010). **How the neurocircuitry and genetics of fear inhibition may inform our understanding of PTSD.** *American Journal of Psychiatry, 167*, 648-662. doi:10.1176/appi.ajp.2009.09071074 Exposure to traumatic events that produce extreme fear and horror is all too common in both military and civilian populations, but not all individuals develop posttraumatic stress disorder (PTSD) as a result of the exposure. What mediates risk and resilience in the development of PTSD and other stress-related psychopathology is of paramount importance to our further understanding of trauma-related psychopathology as well as the development of new treatment approaches. Biological factors, such as genotype and neurobiology, interact with environmental factors, such as childhood background and trauma load, to affect vulnerability and resilience in the aftermath of trauma exposure. One of the core symptoms of PTSD is the inability to control fear, which has led some investigators and clinicians to conceptualize PTSD as a disorder of fear or, more importantly, its inhibition. This review focuses on translational methods that have been used to examine fear conditioning and inhibition of fear in PTSD and summarizes genetic and neurobiological factors related to fear inhibition. The authors also discuss different pharmacological approaches that enhance fear inhibition and may improve treatment outcomes for patients with PTSD.

Karsen, E. F., Watts, B. V., & Holtzheimer, P. E. (2014). **Review of the effectiveness of transcranial magnetic stimulation for post-traumatic stress disorder.** *Brain Stimulation, 7*, 151-157. doi:10.1016/j.brs.2013.10.006 *Background:* Post-traumatic stress disorder (PTSD) is a psychiatric condition with significant morbidity and limited treatment options. Transcranial magnetic stimulation (TMS) has been shown to be an effective treatment for mental illnesses including major depressive disorder. *Objective:* Review effectiveness of TMS for PTSD. *Methods:* Literature review with descriptions of primary studies as well as meta-analysis of studies with a control group. *Results:* Eight primary studies were identified and three studies met criteria for meta-analysis. All studies suggest effectiveness of TMS for PTSD. Additionally, right-sided may be more effective than left-sided treatment, there is no clear advantage in high versus low frequency, and the treatment is generally well tolerated. Meta-analysis shows significant effect size on PTSD symptoms that may be correlated with total number of stimulations. *Conclusions:* TMS for PTSD appears to be an effective and well-tolerated treatment that warrants additional study to further define treatment parameters, course, and side effects.

Koek, R. J., Langevin, J.-P., Krahl, S. E., Kosoyan, H. J., Schwartz, H. N., Chen, J. W. Y., . . . & Sultzer, D. (2014). **Deep brain stimulation of the basolateral amygdala for treatment-refractory combat post-traumatic stress disorder (PTSD): Study protocol for a pilot randomized controlled trial with blinded, staggered onset of stimulation.** *Trials, 15*. doi:10.1186/1745-6215-15-356 *Background:* Combat post-traumatic stress disorder (PTSD) involves significant suffering, impairments in social and occupational functioning, substance use and medical comorbidity, and increased mortality from suicide and other causes. Many veterans continue to suffer despite current treatments.

Deep brain stimulation (DBS) has shown promise in refractory movement disorders, depression and obsessive-compulsive disorder, with deep brain targets chosen by integration of clinical and neuroimaging literature. The basolateral amygdala (BLn) is an optimal target for high-frequency DBS in PTSD based on neurocircuitry findings from a variety of perspectives. DBS of the BLn was validated in a rat model of PTSD by our group, and limited data from humans support the potential safety and effectiveness of BLn DBS. *Methods/Design:* We describe the protocol design for a first-ever Phase I pilot study of bilateral BLn high-frequency DBS for six severely ill, functionally impaired combat veterans with PTSD refractory to conventional treatments. After implantation, patients are monitored for a month with stimulators off. An electroencephalographic (EEG) telemetry session will test safety of stimulation before randomization to staggered-onset, double-blind sham versus active stimulation for two months. Thereafter, patients will undergo an open-label stimulation for a total of 24 months. Primary efficacy outcome is a 30% decrease in the Clinician Administered PTSD Scale (CAPS) total score. Safety outcomes include extensive assessments of psychiatric and neurologic symptoms, psychosocial function, amygdala-specific and general neuropsychological functions, and EEG changes. The protocol requires the veteran to have a cohabiting significant other who is willing to assist in monitoring safety and effect on social functioning. At baseline and after approximately one year of stimulation, trauma script-provoked ^{18}FDG PET metabolic changes in limbic circuitry will also be evaluated. *Discussion:* While the rationale for studying DBS for PTSD is ethically and scientifically justified, the importance of the amygdaloid complex and its connections for a myriad of emotional, perceptual, behavioral, and vegetative functions requires a complex trial design in terms of outcome measures. Knowledge generated from this pilot trial can be used to design future studies to determine the potential of DBS to benefit both veterans and nonveterans suffering from treatment-refractory PTSD.

Kozel, F. A., Motes, M. A., Didehbani, N., DeLaRosa, B., Bass, C., Schraufnagel, C. D., . . . & Hart, J. (2018). **Repetitive TMS to augment cognitive processing therapy in combat veterans of recent conflicts with PTSD: A randomized clinical trial.** *Journal of Affective Disorders, 229*, 506-514. doi:10.1016/j.jad.2017.12.046
Background: The objective was to test whether repetitive Transcranial Magnetic Stimulation (rTMS) just prior to Cognitive Processing Therapy (CPT) would significantly improve the clinical outcome compared to sham rTMS prior to CPT in veterans with PTSD. *Methods:* Veterans 18–60 years of age with current combat-related PTSD symptoms were randomized, using a 1:1 ratio in a parallel design, to active (rTMS+CPT) versus sham (sham+CPT) rTMS just prior to weekly CPT for 12–15 sessions. Blinded raters evaluated veterans at baseline, after the 5th and 9th treatments, and at 1, 3, and 6 months post-treatment. Clinician Administered PTSD Scale (CAPS) was the primary outcome measure with the PTSD Checklist (PCL) as a secondary outcome measure. The TMS coil (active or sham) was positioned over the right dorsolateral prefrontal cortex (110% MT, 1 Hz continuously for 30 min, 1800 pulses/treatment). *Results:* Of the 515 individuals screened for the study, 103 participants were randomized to either active (n = 54) or sham rTMS (n = 49). Sixty-two participants (60%) completed treatment and 59 (57%) completed the 6-month assessment. The rTMS+CPT group showed greater symptom reductions from baseline on both CAPS and PCL across CPT sessions and follow-up assessments, $t(\text{df} \geq 325) \leq -2.01$, $p \leq 0.023$, one-tailed and $t(\text{df} \geq 303) \leq -2.14$, $p \leq 0.017$, one-tailed, respectively. *Limitations:* Participants were predominantly male and limited to one era of conflicts as well as those who could safely undergo rTMS. *Conclusions:* The addition of rTMS to CPT compared to sham with CPT produced significantly greater PTSD symptom reduction early in treatment and was sustained up to six months post-treatment.

Nam, D.-H., Pae, C.-U., & Chae, J.-H. (2013). **Low-frequency, repetitive transcranial magnetic stimulation for the treatment of patients with posttraumatic stress disorder: A double-blind, sham-controlled study.** *Clinical Psychopharmacology and Neuroscience, 11*, 96-102. doi:10.9758/cpn.2013.11.2.96
Objective: Several studies have suggested that repetitive transcranial magnetic stimulation (rTMS) of the right prefrontal cortex may be useful in the treatment of posttraumatic stress disorder (PTSD). The aim of this study was to compare the effect of rTMS on the right prefrontal cortex with that of sham stimulation among patients with PTSD. *Methods:* In total, 18 patients with PTSD were randomly assigned to the 1-Hz low-frequency rTMS group or the sham group for 3 weeks. Primary efficacy measures were the Clinician-Administered PTSD Scale (CAPS) and its subscales, assessed at baseline and at 2, 4, and 8 weeks. *Results:* All CAPS scores improved significantly over the study period. We found significant differences in the re-experiencing scores (F=7.47, p=0.004) and total scores (F=6.45,p=0.008) on the CAPS. The CAPS avoidance scores showed a trend toward significance (F=2.74, p=0.055), but no significant differences in the CAPS hyperarousal scores were observed. *Conclusion:* The present study showed low-frequency rTMS to be an effective and tolerable option for the treatment of PTSD. Trials using variable indices of rTMS to the right prefrontal cortex and explorations of the differences in the effects on specific symptom clusters may be promising avenues of research regarding the use of rTMS for PTSD.

Osuch, E. A., Benson, B. E., Luckenbaugh, D. A., Geraci, M., Post, R. M., & McCann, U. (2009). **Repetitive TMS combined with exposure therapy for PTSD: A preliminary study.** *Journal of Anxiety Disorders, 23*, 54-59. doi:10.1016/j.janxdis.2008.03.015
Treatment for anxiety and post-traumatic stress disorder (PTSD) includes exposure therapy and medications, but some patients are refractory. Few studies of repetitive transcranial magnetic stimulation (rTMS) for anxiety or PTSD exist. In this preliminary report, rTMS was combined with exposure therapy for PTSD. Nine subjects with chronic, treatment-refractory PTSD were studied in a placebo-controlled, crossover design of imaginal exposure therapy with rTMS (1 Hz) versus sham. PTSD symptoms, serum and 24 h urine were obtained and analyzed. Effect sizes for PTSD symptoms were determined using Cohen's d. Active rTMS showed a larger effect size of improvement for hyperarousal symptoms compared to sham; 24-h urinary norepinephrine and serum T4 increased; serum prolactin decreased. Active rTMS with exposure may have symptomatic and physiological effects. Larger studies are needed to confirm these preliminary findings and verify whether rTMS plus exposure therapy has a role in the treatment of PTSD.

Philip, N. S., Ridout, S. J., Albright, S. E., Sanchez, G., & Carpenter, L. L. (2016). **5-Hz transcranial magnetic stimulation for comorbid posttraumatic stress disorder and major depression.** *Journal of Traumatic Stress, 29*, 93-96. doi:10.1002/jts.22065 Current treatment options for posttraumatic stress disorder (PTSD) offer modest benefits, underscoring the need for new treatments. Repetitive transcranial magnetic stimulation (rTMS) depolarizes neurons in a targeted brain region with magnetic fields typically pulsed at low (1 Hz) or high (10 Hz) frequency to relieve major depressive disorder (MDD). Prior work suggests an intermediate pulse frequency, 5 Hz, is also efficacious for treating comorbid depressive and anxiety symptoms. In this chart review study, we systematically examined the clinical and safety outcomes in 10 patients with comorbid MDD and PTSD syndromes who received 5-Hz rTMS therapy at the Providence VA Medical Center Neuromodulation Clinic. Self-report scales measured illness severity prior to treatment, after every 5 treatments, and upon completion of treatment. Results showed significant reduction in symptoms of PTSD (p = .003, effect size = 1.12, 8/10 with reliable change) and MDD (p = .005, effect size = 1.09, 6/10 with reliable change). Stimulation was well tolerated and there were no serious adverse events. These data indicate 5-Hz rTMS may be a useful option to treat these comorbid disorders. Larger, controlled trials are needed to confirm the benefits of 5-Hz protocols observed in this pilot study.

Reznikov, R., Bambico, F. R., Diwan, M., Raymond, R. J., Nashed, M. G., Nobrega, J. N., & Hamani, C. (2018). **Prefrontal cortex deep brain stimulation improves fear and anxiety-like behavior and reduces basolateral amygdala activity in a preclinical model of posttraumatic stress disorder.** *Neuropsychopharmacology, 43*, 1099–1106. doi:10.1038/npp.2017.207 Deep brain stimulation (DBS) is being investigated for a number of psychiatric indications, including posttraumatic stress disorder (PTSD). Preclinical studies continue to be a cornerstone for the development of new DBS applications. We investigate whether DBS delivered to the infralimbic cortex (IL), a region involved in mechanisms of stress resiliency, may counter behavioral abnormalities in rats that present persistent extinction deficits and long-term anxiety after exposure to fear conditioning. Rats undergoing fear conditioning/extinction were segregated into weak and strong extinction groups (WE >70% or SE <30% of freezing during extinction). Following 2 weeks of DBS, animals were exposed to novel recall sessions and tested in the open field, novelty-suppressed feeding, and elevated plus maze. *zif268* expression was measured in structures involved in mechanisms of fear and stress. *In vivo* electrophysiology was used to record activity from the basolateral amygdala (BLA). We found that DBS improved extinction deficits and anxiety-like behavior in WE animals, having no significant effects in SE rats. No major differences in absolute *zif268* levels were recorded across groups. However, correlation between *zif268* expression in the IL and BLA was disrupted in WE animals, a deficit that was countered by DBS treatment. Electrophysiology experiments have shown that DBS reduced BLA firing of both putative principal cells and interneurons in WE rats, with no significant differences being detected between SE and SE DBS animals. In summary, IL DBS mitigated fear, partially improved anxiety-like behavior, reversed neurocircuitry abnormalities, and reduced BLA cell firing in a preclinical model of PTSD.

Rosenberg, P. B., Mehndiratta, R. B., Mehndiratta, Y. P., Wamer, A., Rosse, R. B., & Balish, M. (2002). **Repetitive transcranial magnetic stimulation treatment of comorbid posttraumatic stress disorder and major depression.** *Journal of Neuropsychiatry and Clinical Neuroscience, 14*, 270-276. doi:10.1176/jnp.14.3.270 Twelve patients with comorbid posttraumatic stress disorder (PTSD) and major depression underwent repetitive transcranial magnetic stimulation (rTMS) to left frontal cortex as an open-label adjunct to current antidepressant medications. rTMS parameters were as follows: 90% of motor threshold, 1 Hz or 5 Hz, 6,000 stimuli over 10 days. Seventy-five percent of the patients had a clinically significant antidepressant response after rTMS, and 50% had sustained response at 2-month follow-up. Comparable improvements were seen in anxiety, hostility, and insomnia, but only minimal improvement in PTSD symptoms. Left frontal cortical rTMS may have promise for treating depression in PTSD, but there may be a dissociation between treating mood and treating core PTSD symptoms.

Saunders, N., Downham, R., Turman, B., Kropotov, J., Clark, R., Yumash, R., & Szatmary, A. (2015). **Working memory training with tDCS improves behavioral and neurophysiological symptoms in pilot group with post-traumatic stress disorder (PTSD) and with poor working memory.** *Neurocase: The Neural Basis of Cognition, 21*, 271-278. doi:10.1080/13554794.2014.890727 This pilot study investigated the feasibility of treating people suffering from both post-traumatic stress disorder (PTSD) and poor working memory by employing a combination of computerized working memory training and transcranial direct current stimulation (tDCS). After treatment, all four participants showed clinically significant improvements on a range of cognitive and emotional performance measures. Moreover, these improvements were accompanied by theoretically significant neurophysiological changes between pre- and post-treatment electroencephalographic (EEG) recordings. Specifically, the P3a component of participants' event related potentials (ERP) in response to novelty stimuli, characteristically abnormal in this clinical population, shifted significantly toward database norms. So, participants' initially slow alpha peak frequency (APF), theorized to underlie impaired cognitive processing abilities, also increased in both frequency and amplitude as a result of treatment. On the basis of these promising results, more extensive controlled studies are warranted.

Trevizol, A. P., Barros, M. D., Silva, P. O., Osuch, E., Cordeiro, Q., & Shiozawa, P. (2016). **Transcranial magnetic stimulation for posttraumatic stress disorder: An updated systematic review and meta-analysis.** *Trends in Psychiatry and Psychotherapy, 38*, 50-55. doi:10.1590/2237-6089-2015-0072 *Introduction:* Transcranial magnetic stimulation (TMS) is a promising non-pharmacological intervention for posttraumatic stress disorder (PTSD). However, randomized controlled trials (RCTs) and meta-analyses have reported mixed results. *Objective:* To review articles that assess the efficacy of TMS in PTSD treatment. *Methods:* A systematic review using MEDLINE and other databases to identify studies from the first RCT available up to September 2015. The primary outcome was based on PTSD scores (continuous variable). The main outcome was Hedges' g. We used a random-effects model using the statistical packages for meta-analysis available in Stata 13 for Mac OSX.

FEATURED ARTICLES *continued*

Heterogeneity was evaluated with I^2 (> 35% for heterogeneity) and the χ^2 test ($p < 0.10$ for heterogeneity). Publication bias was evaluated using a funnel plot. Meta-regression was performed using the random-effects model. *Results:* Five RCTs (n = 118) were included. Active TMS was significantly superior to sham TMS for PTSD symptoms (Hedges' g = 0.74; 95% confidence interval = 0.06-1.42). Heterogeneity was significant in our analysis (I^2 = 71.4% and p = 0.01 for the χ^2 test). The funnel plot shows that studies were evenly distributed, with just one study located marginally at the edge of the funnel and one study located out of the funnel. We found that exclusion of either study did not have a significant impact on the results. Meta-regression found no particular influence of any variable on the results. *Conclusion:* Active TMS was superior to sham stimulation for amelioration of PTSD symptoms. Further RCTs with larger sample sizes are fundamental to clarify the precise impact of TMS in PTSD.

Watts, B. V., Landon, B., Groft, A., & Young-Xu, Y. (2012). **A sham controlled study of repetitive transcranial magnetic stimulation for posttraumatic stress disorder.** *Brain Stimulation, 5*, 38-43. doi:10.1016/j.brs.2011.02.002 *Background:* Posttraumatic stress disorder (PTSD) is a commonly occurring and often debilitating psychiatric condition. There currently is not definitive information regarding the efficacy of repetitive transcranial magnetic stimulation (rTMS) for PTSD. *Objective:* This study seeks to examine the efficacy of rTMS for PTSD. *Methods:* Twenty subjects with PTSD were randomly assigned to receive either 10 rTMS sessions delivered at 1 Hz to the right dorsolateral prefrontal cortex (DLPRC) or 10 sham rTMS sessions to the same area. A blinded rater assessed PTSD, depressive, anxiety, and neurocognitive symptoms before treatment, after the treatment series, and during a 2-month follow-up period. *Results:* Trancranial magnetic stimulation delivered at 1 Hz to the right DLPRC resulted in statistically and clinically significant improvements in core PTSD symptoms and depressive symptoms compared with sham treatments. The effectiveness showed some degradation during the 2 months after treatments were stopped. *Conclusions:* This blinded sham controlled trial supports the efficacy of 10 sessions of right DLPRC rTMS delivered at 1 Hz for the treatment of PTSD symptoms.

Woodside, D. B., Colton, P., Lam, E., Dunlop, K., Rzeszutek, J., & Downar, J. (2017). **Dorsomedial prefrontal cortex repetitive transcranial magnetic stimulation treatment of posttraumatic stress disorder in eating disorders: An open-label case series.** *International Journal of Eating Disorders, 50*, 1231-1234. doi:10.1002/eat.22764 Posttraumatic stress disorder (PTSD) is a common comorbid condition in anorexia nervosa (AN) and bulimia nervosa (BN), and may be associated with reduced response to treatment. We report on a case series employing repetitive transcranial magnetic stimulation (rTMS) with a novel target, the dorsomedial prefrontal cortex (DMPFC). Fourteen subjects with eating disorders and comorbid PTSD received 20–30 neuronavigated DMPFC–rTMS treatments on an open-label basis. PTSD symptoms were assessed pretreatment and posttreatment with the PTSD checklist-Civilian (PCL-C) and the Difficulties in Emotional Regulation Scale (DERS). PCL-C scores were reduced by 51.99% ± 27.24% overall, from a mean of 54.29 ± 19.34 pretreatment to 24.86 ± 17.43 posttreatment ($p < .001$). Of the 14, 8 showed an improvement of >50%. DERS scores improved by 36.02% ± 24.24% overall, from 140.00 ± 22.09 at pretreatment to 89.29 ± 38.31 at posttreatment ($p < .001$). OF the 14 subjects, 5 achieved >50% improvement. These data may suggest that DMPFC–rTMS could be helpful in the treatment of PTSD in some ED patients.

Yan, T., Xie, Q., Zheng, Z., Zou, K., & Wang, L. (2017). **Different frequency repetitive transcranial magnetic stimulation (rTMS) for posttraumatic stress disorder (PTSD): A systematic review and meta-analysis.** *Journal of Psychiatric Research, 89*, 125-135. doi:10.1016/j.jpsychires.2017.02.021 Posttraumatic stress disorder (PTSD) is a psychiatric disorder. Repetitive transcranial magnetic stimulation (rTMS) has been found to be effective for treating PTSD, but whether different frequencies have different effects remains controversial. We conducted this systematic review and meta-analysis to address this question. We searched the literature for studies written in English or Chinese in 9 electronic databases from the databases' inception to August 1, 2016. Additional articles were identified from the reference lists of identified studies and from personal reference collections. Eighteen articles were included, and 11 were suitable for the meta-analysis (Combined sample size was 377 (217 in active rTMS groups, 160 in sham-controlled groups)). Low-frequency (LF) rTMS resulted in a significant reduction in the PTSD total score and the depression score (1. PTSD total score: pooled SMD, 0.92; CI, 0.11–1.72; 2. Depression: pooled SMD, 0.54; CI, 0.08–1.00). High-frequency (HF) rTMS showed the following results: 1. PTSD total score: pooled SMD, 3.24; CI, 2.24–4.25; 2. re-experiencing: pooled SMD, –1.77; CI, –2.49-(-1.04); 3. Avoidance: pooled SMD, –1.57; CI, –2.50-(-0.84); 4. hyperarousal: pooled SMD, –1.32; CI, –2.17-(-0.47); 5. depression: pooled SMD, 1.92; CI, 0.80–3.03; and 6. Anxiety: pooled SMD, 2.67; CI, 1.82–3.52. Therefore, both HF and LF rTMS can alleviate PTSD symptoms. Although the evidence is extremely limited, LF rTMS can reduce overall PTSD and depression symptoms. HF rTMS can improve the main and related symptoms of PTSD. However, additional research is needed to substantiate these findings.

ADDITIONAL CITATIONS

Brunoni, A. R., Chaimani, A., Moffa, A. H., Razza, L. B., Gattaz, W. F., Daskalakis, Z. J., & Carvalho, A. F. (2017). **Repetitive transcranial magnetic stimulation for the acute treatment of major depressive episodes: A systematic review with network meta-analysis.** *JAMA Psychiatry, 74*, 143-152. doi:10.1001/jamapsychiatry.2016.3644 This article provides one of the most comprehensive meta-analyses of studies of TMS for the treatment of depression and confirms the efficacy of the most common TMS approaches (left DLPFC high frequency, right low frequency, and bilateral).

Cook, I. A., Espinoza, R., & Leuchter, A. F. (2014). **Neuromodulation for depression: Invasive and noninvasive (deep brain stimulation, transcranial magnetic stimulation, trigeminal nerve stimulation).** *Neurosurgy Clinics of North America, 25*, 103-116. doi:10.1016/j.nec.2013.10.002 This article provides a comprehensive review of the available focal brain stimulation approaches that have been investigated in the treatment of depression.

ADDITIONAL CITATIONS *continued*

Dandekar, M. P., Fenoy, A. J., Carvalho, A. F., Soares, J. C., & Quevedo, J. (2018). **Deep brain stimulation for treatment-resistant depression: An integrative review of preclinical and clinical findings and translational implications.** *Molecular Psychiatry.* Advance online publication. doi:10.1038/mp.2018.2 This article provides a comprehensive review of DBS as a treatment for treatment-resistant depression. In addition to reviewing the clinical data, this review also incorporates a review of the relevant preclinical studies.

Langevin, J.-P., Koek, R. J., Schwartz, H. N., Chen, J. W. Y., Sultzer, D. L., Mandelkern, M. A., . . . & Krahl, S. E. (2016). **Deep brain stimulation of the basolateral amygdala for treatment-refractory posttraumatic stress disorder [Letter to the editor].** *Biological Psychiatry, 79*, e82-e84. doi:10.1016/j.biopsych.2015.09.003 This letter to the editor describes a single case of a 48 year old Veteran enrolled in a study of bilateral DBS of the amygdala for the treatment of highly treatment-refractory PTSD. At baseline, the participant showed strong amydgala activation (increased metabolism on a positron emission tomography scan) during recall of traumatic material. Following 8 months of amygdala DBS, the patient showed a notable improvement in PTSD symptoms.

McCann, U. D., Kimbrell, T. A., Morgan, C. M., Anderson, T., Geraci, M., Benson, B. E., . . . & Post, R. M. (1998). **Repetitive transcranial magnetic stimulation for posttraumatic stress disorder [Letter to the editor].** *Archives of General Psychiatry 55*, 276-279. This letter to the editor describes two patients who received open-label right prefrontal 1 Hz rTMS for the treatment of PTSD. Both patients reported improvement in PTSD symptoms during the 4-6 week treatment course. However, PTSD symptoms returned about one month after the last rTMS treatment.