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

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.