Curr Treat Options Psych (2022) 9:406–418
DOI 10.1007/s40501-022-00279-x

PTSD (S Frankfurt, Section Editor)

Neuromodulation as an Augmenting Strategy for Behavioral Therapies for Anxiety and PTSD: a Narrative Review

Crystal Lantrip, PhD[1,2,*]
Yvette Z. Szabo, PhD[1,3]
F. Andrew Kozel, MD[4]
Paul Holtzheimer, MD[5,6]

Address
[*,1]Department of Veterans Affairs, VISN 17 Center of Excellence for Research On Returning War Veterans, Waco, TX 76711, USA
Email: crystal.lantrip@va.gov
[2]Department of Psychology and Neuroscience, Baylor University, Waco, TX, USA
[3]Department of Health, Human Performance and Recreation, Baylor University, Waco, TX, USA
[4]Department of Behavioral Sciences and Social Medicine, Florida State University, Tallahassee, FL, USA
[5]Department of Veterans Affairs, National Center for PTSD, White River Junction, VT, USA
[6]Department of Psychiatry, Geisel School of Medicine at Dartmouth, Hanover, NH, USA

Published online: 14 September 2022

This article is part of the Topical Collection on *PTSD*

Keywords Transcranial magnetic stimulation · Anxiety · TMS · PTSD · Trauma · Exposure therapy

Abstract

Purpose of Review Post-traumatic stress disorder (PTSD) is a prevalent problem. Despite current treatments, symptoms may persist, and neuromodulation therapies show great potential. A growing body of research suggests that transcranial magnetic stimulation (TMS) is effective as a standalone treatment for PTSD, with recent research demonstrating promising use when combined synergistically with behavioral treatments. In this review, we survey this literature including data suggesting mechanisms involved in anxiety and PTSD that may be targeted by neurostimulation.

Recent Findings Evidence suggests the mechanism of action for TMS that contributes to behavioral change may be enhanced neural plasticity via increased functionality of prefrontal and subcortical/limbic structures and associated networks. Some research has demonstrated a behavioral change in PTSD and anxiety due to enhanced extinction learning or improved ability to think flexibly and reduce ruminative tendencies. Growing evidence suggests TMS may be best used as a therapeutic adjunct, at least acutely, for extinction-based exposure therapies in patients by accelerating therapy response.
Summary While TMS has shown promise as a standalone intervention, augmentation with psychotherapy is one avenue of interest. Non-responders to current EBPs might particularly benefit from this sort of targeted approach, and it may shorten treatment length, which would help the successful completion of a course of therapy.

Introduction

Anxiety disorders constitute the largest group of mental disorders, with a prevalence rate of 18% in the USA [1]. Though no longer classified as an anxiety disorder, post-traumatic stress disorder (PTSD) is similarly characterized by arousal and avoidance. PTSD represents a prevalent problem for both civilians, particularly those with interpersonal trauma histories [2] and veterans [3]. Despite the availability of efficacious treatments, symptoms may persist in a large number of individuals [4, 5]. This is sometimes due to a lack of engaging in or completing often lengthy treatment protocols or because of symptoms persisting even after successful treatment completion. For first-line evidenced-based psychotherapies (EBPs) for PTSD, such as cognitive processing therapy (CPT) or prolonged exposure (PE), studies have found that approximately one-third of those seeking treatment drop out before completion, with higher rates in Veterans Healthcare Administration (VHA) and Department of Defense (DoD) settings [6]. Many patients may respond to EBPs; however, symptoms often do not fall below clinical thresholds even after completing a full course [4]. Therefore, there is room for improvement, and one method that shows promise is neuromodulation therapy [9].

TMS is a non-invasive neurostimulation therapy that depolarizes cortical neurons using a rapidly changing magnetic field. TMS has been FDA cleared and used as a standalone treatment for medication-resistant depression [7], obsessive–compulsive disorder [8], smoking cession [10], and anxious depression [11], and a growing body of research supports its efficacy as a standalone treatment for PTSD (see Cirillo et al., 2019, for a recent meta-analysis) [12•]. Though TMS is not currently an FDA-cleared treatment for PTSD, there is a growing body of evidence indicating that TMS alone can be an effective treatment for PTSD [9]. In addition, a recent clinical registry with 770 patients receiving treatment for depression with TMS demonstrated improvement in both depressive and trauma symptoms in those with comorbid depression and PTSD [13]. Transcranial direct current stimulation (tDCS) is another non-invasive method of neurostimulation that applies a weak direct current between two surface electrodes to modulate cortical neuron excitation [14, 15]. Neuromodulation with tDCS may increase or decrease cortical excitability depending on electron polarity and current intensity [16], with evidence to support utility in anxiety disorders [17]. Recent research has demonstrated a promising use for neurostimulation in anxiety disorders and PTSD by combining it synergistically with behavioral treatments to augment effects, but with some contradictory results. In this review, we survey this literature including data assessing mechanistic factors of anxiety disorders and PTSD that can be targeted by neurostimulation, particularly TMS, or a synergistic combination of these two treatments.

Potential mechanisms for TMS in anxiety and related disorders

Neurostimulation enhances neural plasticity

Evidence suggests that the mechanism of action for TMS that contributes to behavioral change may be enhanced neural plasticity. Neurostimulation and imaging of the visual [18] and motor cortices [19, 20] has demonstrated both early and lasting effects. Clinical treatment of psychiatric disorders with neurostimulation is presumed to induce similar change when the prefrontal cortex (PFC) is stimulated. Findings from neuromodulation research involving imaging implicate plasticity via increased functionality and connectivity of prefrontal and subcortical/limbic structures [21]. Changes in behavior are hypothesized to occur in clinical disorders, such as anxiety and PTSD, due to TMS-induced neural plasticity immediately after stimulation and over the longer term.

The dorsolateral prefrontal cortex (DLPFC) is the cortical target for the current FDA-cleared treatment of depression, and the dorsomedial PFC is the approved target for OCD. These sites are also typically stimulated in anxiety, PTSD, and related disorders [22]. TMS-induced depolarization of cortical neurons has been hypothesized to impact not only on the direct site of stimulation but also on the functionally related brain regions via network connectivity [23].

TMS impacts neural networks and connectivity

One such neural network is the default mode network (DMN), which includes anterior (mPFC) and posterior midline structures (posterior cingulate) as well as lateral temporal cortices and hippocampus. The DMN is generally more active at "rest" in healthy individuals, i.e., when a person is not engaged in a specific cognitive task [24–27]. Additionally, in healthy individuals, DMN activity has been shown to be negatively correlated with regions activated during attention-demanding tasks within the cognitive control network (CCN), with regions including DLPFC and posterior parietal cortices active during tasks involving sustained attention and working memory [28]. DMN-CCN anticorrelation is associated with superior cognitive functioning, particularly cognitive flexibility and working memory [28, 29].

Underscoring its importance in psychiatric illness, abnormal connectivity of DMN-CCN has been associated with depression [30] and anxiety [31, 32]. Stress-related brain changes in the CCN contribute to deficits in cognitive control, including regulation of emotions and cognitive flexibility that perpetuate PTSD symptoms (hypervigilance, avoidance, and reexperiencing) [33, 34]. In fact, Liston and colleagues found that psychosocial stress can selectively impact CCN/frontal parietal network connectivity. Given the findings that the CCN can be affected in those with anxiety and PTSD, correcting network problems via neuropsychiatric treatment may be an important goal to reduce distress [35].

Overall, there is evidence that neurostimulation can have a significant impact on the neural substrate by inducing plasticity, and enhanced plasticity of the prefrontal cortex in psychiatric patients may contribute to changes in neural network connectivity of DMN-CCN in patients that improve clinical symptoms and functioning both immediately and over the long term.

Neurostimulation may enhance extinction learning

Successful treatment of anxiety and PTSD in exposure-based and cognitive therapies has been associated with improvements in the extinction of conditioned fear response or extinction learning [36, 37]. However, PTSD treatments have room for improvement, given that many patients continue to experience symptoms after completing EBPs [37]. Neurostimulation may enhance extinction learning and therefore be a novel treatment approach for anxiety and PTSD, or perhaps augment existing EBPs [37, 39•]. Extinction requires new learning with the retention of previously formed threat memories [40] and the formation of new memories that inhibit threat response associated with the original trauma memory [41, 42].

Laboratory studies in healthy controls, or those with phobias, have demonstrated enhancement of extinction learning with TMS. For example, Guhn and colleagues [43] conducted an experiment with high-frequency rTMS to the ventromedial prefrontal cortex (vmPFC), a region associated with recall extinction in animals [44] and humans [45, 46], versus sham in healthy participants. This two-day experiment consisted of a fear acquisition paradigm, with HF-rTMS to the vmPFC immediately prior to the extinction learning phase of the task. The following day, participants completed an extinction recall task. Compared to sham, the active group demonstrated diminished ability to differentiate between a conditioned stimulus and unpaired stimuli during day 1 extinction learning, evidenced by fear-potentiated startle, skin conductance response, and subjective arousal ratings. Active rTMS also had a persisting effect on extinction recall on day two with reduced fear-potentiated startle during extinction learning. Building on this work in clinical participants, Herrmann and colleagues [47] used HF-rTMS to the vmPFC to enhance extinction learning in a group of patients with acrophobia, or fear of heights. Participants received active or sham HF-rTMS to the vmPFC, then completed two virtual reality exposure therapy sessions of a height scene, which involved virtually going upstairs until their subjective units of distress (SUDS) reached 100, then staying until they reach an SUDS of 20. Diagnostic interviews were conducted on day two and again three months later. On day two, anxiety was reduced in the active group as well as avoidance ratings from pre- to post-therapy; however, there was no difference between active and sham at the three-month follow-up. Overall, results suggest rTMS may serve as a therapeutic adjunct, at least acutely, for extinction-based exposure therapies in patients by accelerating therapy response. It is plausible that increasing the course of TMS and exposure would extend these benefits so that they have longer-lasting impacts.

TMS may decrease rumination and enhance cognitive control

Emotion regulation refers to the ways in which individuals modulate or change their emotional experiences [48]. The FPN and DMN act in an inverse but coordinated effort to successfully regulate emotion in different situations [23, 49]. Psychiatric illness is often characterized by hypoactivity of the FPN and overactivity of the DMN. In TMS, when the DLFPC, a node of the FPN, is stimulated, local hyperpolarization upregulates the FPN and increases the downregulation of the DMN, at least in individuals with successful treatment response [50]. Previous reviews suggest that improved network function/connectivity is a likely mechanism allowing TMS to improve cognitive control.

Rumination is an emotion regulation strategy broadly characterized by repetitive reflection on negative thoughts, emotions, and past events, as well as the causes and consequences of those events and emotions [51]. Rumination has been associated with a range of mental health outcomes, such as depression, anxiety, and PTSD [34, 52–54]. Additionally, cognitive dysfunction, such as difficulty concentrating, impaired executive functioning, and subjective cognitive complaints, have been associated with rumination [54, 55]. Results of neuroimaging studies have linked self-referential processing and rumination to hyperactivation of the DMN, and the mPFC node of this network [56]. Given that abnormal activation of the DMN has been linked to numerous neuropsychiatric conditions [57] and systemic inflammation [58], it is plausible that rumination is one behavioral consequence of network dysfunction that may be improved with TMS.

In healthy participants, facilitatory effects of rTMS on emotion regulation were found using HF-rTMS prior to a directed attention task with emotional stimuli (exogenous cueing task) [59] as well as an emotional empathy task [60] in fMRI paradigms. In samples of women who received a single session of HF-rTMS over the right or left DLPFC [59, 61], right DLPFC stimulation resulted in impaired disengagement from angry faces and was associated with decreased activation in the CCN (i.e., right DLPFC, dACC, left superior parietal gyrus) and increased activity within the right amygdala. By contrast, left DLPFC stimulation resulted in diminished attentional engagement with angry faces as well as enhanced ability to empathize with depicted positive emotional stimuli. Corresponding brain activation included increased activity within the CCN (i.e., bilateral DLPFC, right dACC, bilateral posterior parietal cortices) and left orbital frontal cortex [59, 61]. Anodal transcranial direct current stimulation (tDCS) over the left DLPFC has also been found to influence the occurrence of momentary rumination in healthy volunteers after an unguided resting period, such as a decrease in self-referential thoughts [48]. Similarly, Lantrip and colleagues [62] found that HF-rTMS to the left DLPFC compared to the right facilitated affective flexibility, a performance-based test of reappraisal, in a group of healthy women.

More recently, DeWitte and colleagues [63] tested the effect of intermittent theta burst stimulation (iTBS) to the left DLPFC on post-stress adaptation as a function of depressive brooding, one facet of rumination. In a sham-controlled within-subjects crossover design, healthy participants received iTBS to the left DLFPC or sham prior to a stressor paradigm. There was no effect of iTBS on ruminative thinking or cortisol during stress recovery; however, those that had higher levels of brooding remained stable after active iTBS, whereas those in the sham condition showed an increase in ruminative thinking. In addition, only after active iTBS to the left DLPFC was there a significant reduction in cortisol secretion for high brooders.

TMS is proposed to impact psychobiological stress response

The hypothalamic–pituitary–adrenal (HPA) axis is a neuroendocrine system that initiates in response to stressful situations and, through a negative feedback loop, regulates glucocorticoid hormone levels. The HPA axis has a direct influence on immune processes and digestion and has been implicated in the pathogenesis of a range of mental and physical health conditions [64]. One theory of the mechanism of action for TMS is the impact on psychological stress response [50], which may occur via the HPA axis. Results from animal models suggest that the rTMS mechanism may be associated with the endocrine response of the hypothalamic–pituitary–adrenal (HPA) system via the secretion of cortisol [65, 66].

Neural connections between the prefrontal cortex and amygdala/hippocampus, though indirect, may be related to the effects of rTMS on the HPA axis, including cortisol. Though the medial compared to the lateral prefrontal cortex has stronger connections to the amygdala [67], and with the hippocampus and hypothalamus [68, 69], prior studies have found amygdala activation [70] and cortisol effects with DLPFC stimulation [60, 71, 72], though findings have been in both positive and negative directions. Interestingly, Baeken and colleagues [60] reported that after a stress induction task, healthy participants demonstrated a reduction in cortisol levels after only one session of HF DLPFC rTMS, indicating that perhaps an acute stress induction is needed to find the effects of TMS on cortisol, at least in healthy samples. Research pointing to dysregulation of the HPA axis in PTSD [73, 74] and against the benefit of widespread hydrocortisone augmentation in PTSD treatment [75] suggest that a more nuanced understanding of the role of neurostimulation on HPA axis functioning is needed.

TMS and neuroinflammation

An emerging area of study is the role of inflammation as a potential mechanism for psychiatric disorders and treatment effects. The impact of rTMS focused on the DLPFC results in an improvement in depression symptoms due to multiple factors including improved DMN/CCN connectivity, emotion regulation, and possibly inflammatory response given the link between network connectivity and IL-6 [58]. A growing literature has underscored the role of inflammation, particularly pro-inflammatory cytokines and acute phase proteins, in anxiety and PTSD [77, 78]. Critically, inflammation has been shown to decrease among those who respond to pharmotherapy for depression [76]. Limited neurostimulation research in this area using animal models suggests that the effect of rTMS on depression is via effects on neuroinflammation [79]. Further studies testing the potential link between network connectivity and inflammation and the impact of TMS are needed.

Summary and future directions

These findings relating to rumination, stress response, and DMN/CCN activation with neurostimulation are interesting and may provide insight into how rTMS and other neuromodulation methods impact on psychiatric symptoms and emotion regulation. Given that reduced activity of the DLPFC has been associated with reduced cognitive control as well as impaired amygdala response [80, 81], it may be that abnormal interaction of the DMN/CCN and inability to have top-down control is a mechanism underlying rumination [82] that is corrected, at least in part, with rTMS [35]. Another possibility may be that increased activity of subcortical regions including the amygdala, due to diminished top-down control, boosts the brainstem stress system and activates the HPA axis contributing to higher cortisol levels [61, 69, 83].

When taken together, it seems that the DLPFC contributes significantly to the association between stress and rumination, a transdiagnostic symptom of emotion dysregulation and psychiatric illness, and can be impacted by neuromodulation. While promising as a standalone intervention, augmenting the effects of psychotherapies for psychiatric illness with neurostimulation may be a fruitful next step for anxiety and PTSD. FDA-approved TMS for depression is 18 sessions, and many EBPs for anxiety and PTSD are 12–18 sessions [e.g., 84, 85]. Combining TMS with psychotherapy can make it more effective and possibly in a shorter timeframe. This would enhance access and potentially decrease dropout, which is a common issue in treatments for PTSD. Preliminary research on this approach has been particularly promising.

TMS is a promising augmented intervention for anxiety and PTSD

There are several studies that have demonstrated the benefits of augmented behavioral treatment with TMS for anxiety and trauma-related disorders. One RCT compared LF active rTMS to the right dorsolateral prefrontal cortex (DLPFC) or sham plus CPT [39•]. TMS was administered just prior to weekly CPT for the standard 12–15 sessions, and CAPS (primary outcome) and PCL (secondary outcome) were measured after the 5th and 9th treatments at a 1 month, 3 months, and 6 months follow-up. Both active and sham groups improved in PTSD on the PCL and CAPS, though the active rTMS condition demonstrated significantly better symptom reduction from baseline on CAPS and PCL across CPT sessions and follow-up assessments, though improvements were stronger for patient-rated symptoms (PCL) compared to clinician-rated symptoms (CAPS).

Another pilot study examined a deep TMS (dTMS) system combined with brief exposure to PTSD with stimulation conducted after behavioral treatment, with the hypothesis that dTMS to the medial prefrontal cortex (mPFC) presented after the exposure would contribute to the extinction of fear memories and thereby reduce PTSD symptoms to a greater degree than brief exposure and sham dTMS [86]. Results were positive, suggesting that this augmentation procedure was effective. However, results from a more recent, large international multi-site randomized clinical trial (RCT) with a similar dTMS treatment presented just after an exposure paradigm were negative, such that brief exposure followed by sham dTMS was associated with better outcomes compared to brief exposure followed by active dTMS [87•]. Importantly, both active and sham TMS groups in this trial improved; however, the sham group experienced statistically superior improvement. This raises the possibility that stimulation may inhibit an otherwise effective therapy/exposure treatment when conducted in this order. The trial was discontinued early for futility [86].

Conclusions

In summary, there is a growing body of research suggesting the efficacy of TMS for anxiety disorders and PTSD as a standalone or adjunctive treatment. When used as an adjunctive treatment, it may be that the cognitive and emotion regulation-enhancing properties of TMS will facilitate exposure therapies for anxiety and PTSD in particular or facilitate improvement in affective symptoms transdiagnostically when added to EBPs for mood and other disorders. Interestingly, improvements in depression, anxiety, and PTSD symptoms are typically highly correlated in TMS studies. For individual patients, however, there can be variability in which aspects of their mental illness respond to TMS. For instance, in the aforementioned RCT combining TMS with CPT for PTSD [39•], the group receiving active TMS showed significant improvement in PTSD symptoms but not depressive symptoms when compared to sham improvement. Given recent findings from RCTs using TMS as adjunctive treatment, it may be that order of treatment is important and that presenting TMS prior to exposure to treatment or therapy for PTSD provides optimal benefit. The precise mechanisms are not known, but the present review highlights plausible avenues of cognitive control and the HPA axis, with neuroinflammation as an emerging area that warrants future study. While TMS has shown promise as a standalone intervention, augmentation with psychotherapy is one avenue of interest. Non-responders to current EBPs might particularly benefit from this sort of targeted approach, and it may shorten treatment length, which would help the successful completion of a course of therapy.

Acknowledgements

This material is the result of work with resources and the use of facilities at the Department of Veterans Affairs, VISN 17 Center of Excellence for Research on Returning War Veterans. Dr. Lantrip acknowledges the support of the VA Clinical Science Research and Developmental Career Development Award 1 IK2 CX002101-01A2. Dr. Szabo's work was partially supported by VA Rehabilitation Research & Development Career Development Award 1 IK1-RX003122. The views expressed herein are those of the authors and do not necessarily reflect the official policy or position of the Department of Veterans Affairs or the United States Government.

Declarations

Conflict of Interest
Dr. Kozel reports support from the Clinical TMS Society, Neuronetics, and NIRx. Dr. Holtzheimer reports support from UpToDate and from Oxford University Press.

Human and Animal Rights and Informed Consent
This article does not contain any studies with human or animal subjects performed by any of the authors.

References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:
• Of importance

1. Kessler RC, Angermeyer M, Anthony JC, et al. Lifetime prevalence and age-of-onset distributions of mental disorders in the World Health Organization's World Mental Health Survey Initiative. World Psychiatry. 2007;6(3):168–76.
2. Resick PA, Galovski TE, Uhlmansiek MO, Scher CD, Clum GA, Young-Xu Y. A randomized clinical trial to dismantle components of cognitive processing therapy for posttraumatic stress disorder in female victims of interpersonal violence. J Consult Clin Psychol. 2008;76(2):243–58. https://doi.org/10.1037/0022-006X.76.2.243.
3. Fulton JJ, Calhoun PS, Wagner HR, et al. The prevalence of posttraumatic stress disorder in Operation Enduring Freedom/Operation Iraqi Freedom (OEF/OIF) veterans: a meta-analysis. J Anxiety Disord. 2015;31:98–107. https://doi.org/10.1016/j.janxdis.2015.02.003.
4. Jacoby VM, Straud CL, Bagley JM, Tyler H, Baker SN, Denejkina A, Sippel LM, et al. Evidence-based posttraumatic stress disorder treatment in a community sample: military-affiliated versus civilian patient outcomes. J Trauma Stress. 2022. https://doi.org/10.1002/jts.22812.
5. Litz BT, Berke DS, Kline NK, Grimm K, Rusowicz-Orazem L, Resick PA, Foa EB, et al. Patterns and predictors of change in trauma-focused treatments for war-related posttraumatic stress disorder. J Consult Clin Psychol. 2019;87(11):1019–29. https://doi.org/10.1037/ccp0000426.
6. Tanielian, T. & Jaycox, L.H. (Eds.) (2008). Invisible wounds of war: psychological and cognitive injuries, their consequences, and services to assist recovery. Santa Monica, CA: RAND MG-720. 2008.
7. Gaynes BN, Lloyd SW, Lux L, et al. Repetitive transcranial magnetic stimulation for treatment-resistant depression: a systematic review and meta-analysis. J Clin Psychiatry. 2014;75(5):477–489; quiz 489. https://doi.org/10.4088/JCP.13r08815.
8. Voelker R. Brain stimulation approved for obsessive-compulsive disorder. JAMA. 2018;320(11):1098–1098. https://doi.org/10.1001/jama.2018.13301.
9. Karsen EF, Watts BV, Holtzheimer PE. Review of the effectiveness of transcranial magnetic stimulation for post-traumatic stress disorder. Brain Stimul. 2014;7(2):151–7. https://doi.org/10.1016/j.brs.2013.10.006.

10. Young JR, Galla JT, Appelbaum LG. Transcranial magnetic stimulation treatment for smoking cessation: an introduction for primary care clinicians. Am J Med. 2021;134(11):1339–43. https://doi.org/10.1016/j.amjmed.2021.06.037.
11. Trevizol AP, Downar J, Vila-Rodriguez F, Konstantinou G, Daskalakis ZJ, Blumberger DM. Effect of repetitive transcranial magnetic stimulation on anxiety symptoms in patients with major depression: an analysis from the THREE-D trial. Depress Anxiety. 2021;38(3):262–71. https://doi.org/10.1002/da.23125.
12.• Cirillo P, Gold AK, Nardi AE, et al. Transcranial magnetic stimulation in anxiety and trauma-related disorders: a systematic review and meta-analysis. Brain Behav. 2019;9(6):e01284. https://doi.org/10.1002/brb3.1284.
TMS is an effective treatment option for patients with medication-resistant depression, and a growing number of studies are evaluating the efficacy of TMS for other neuropsychiatric disorders such as anxiety and trauma-related disorders. In this meta-analysis, a review of the literature revealed that TMS has been more widely studied in PTSD than GAD. Overall, TMS demonstrated a large treatment effect for both PTSD and GAD.
13. Madore MR, Kozel FA, Williams LM, Green LC, George MS, Holzheimer PE, Yesavage JA, Philip NS. Prefrontal transcranial magnetic stimulation for depression in US military veterans – a naturalistic cohort study in the Veterans Health Administration. J Affect Disord. 2022;297:671–8. https://doi.org/10.1016/j.jad.2021.10.025.
14. Iannone A, Cruz AP de M, Brasil-Neto JP, Boechat-Barros R. Transcranial magnetic stimulation and transcranial direct current stimulation appear to be safe neuromodulatory techniques useful in the treatment of anxiety disorders and other neuropsychiatric disorders. Arq Neuropsiquiatr. 2016;74(10):829–835. https://doi.org/10.1590/0004-282X20160115.
15. Miniussi C, Cappa SF, Cohen LG, et al. Efficacy of repetitive transcranial magnetic stimulation/transcranial direct current stimulation in cognitive neurorehabilitation. Brain Stimul. 2008;1(4):326–36. https://doi.org/10.1016/j.brs.2008.07.002.
16. Nitsche MA, Cohen LG, Wassermann EM, et al. Transcranial direct current stimulation: state of the art 2008. Brain Stimul. 2008;1(3):206–23. https://doi.org/10.1016/j.brs.2008.06.004.
17. Sagliano L, Atripaldi D, De Vita D, D'Olimpio F, Trojano L. Non-invasive brain stimulation in generalized anxiety disorder: a systematic review. Prog Neuropsychopharmacol Biol Psychiatry. 2019;93:31–8. https://doi.org/10.1016/j.pnpbp.2019.03.002.
18. Levi D, Vignati S, Guida E, et al. Tailored repetitive transcranial magnetic stimulation for depression and addictions. Prog Brain Res. 2022;270(1):105–21. https://doi.org/10.1016/bs.pbr.2022.01.024.
19. Müller-Dahlhaus F, Ziemann U. Metaplasticity in human cortex. Neuroscientist. 2015;21(2):185–202. https://doi.org/10.1177/1073858414526645.
20. Weise D, Mann J, Rumpf JJ, Hallermann S, Classen J. Differential regulation of human paired associative stimulation-induced and theta-burst stimulation-induced plasticity by L-type and T-type Ca2+ channels. Cereb Cortex. 2017;27(8):4010–21. https://doi.org/10.1093/cercor/bhw212.
21. Ruggiero RN, Rossignoli MT, Marques DB, et al. Neuromodulation of hippocampal-prefrontal cortical synaptic plasticity and functional connectivity: implications for neuropsychiatric disorders. Front Cell Neurosci. 2021;15. https://doi.org/10.3389/fncel.2021.732360.
22. Milev RV, Giacobbe P, Kennedy SH, et al. Canadian network for mood and anxiety treatments (CANMAT) 2016 clinical guidelines for the management of adults with major depressive disorder: section 4. Neurostimulation Treatments. Can J Psychiatry. 2016;61(9):561–75. https://doi.org/10.1177/0706743716660033.
23. Lantrip C, Gunning FM, Flashman L, Roth RM, Holtzheimer PE. Effects of transcranial magnetic stimulation on the cognitive control of emotion: potential antidepressant mechanisms. J ECT. 2017;33(2):73–80. https://doi.org/10.1097/YCT.0000000000000386.
24. Greicius MD, Krasnow B, Reiss AL, Menon V. Functional connectivity in the resting brain: a network analysis of the default mode hypothesis. Proc Natl Acad Sci - PNAS. 2003;100(1):253–8. https://doi.org/10.1073/pnas.0135058100.
25. Fox MD, Snyder AZ, Vincent JL, Corbetta M, Van Essen DC, Raichle ME. The human brain is intrinsically organized into dynamic, anticorrelated functional networks. Proc Natl Acad Sci. 2005;102(27):9673–8. https://doi.org/10.1073/pnas.0504136102.
26. Fransson P. Spontaneous low-frequency BOLD signal fluctuations: an fMRI investigation of the resting-state default mode of brain function hypothesis. Hum Brain Mapp. 2005;26(1):15–29. https://doi.org/10.1002/hbm.20113.
27. Kelly AMC, Uddin LQ, Biswal BB, Castellanos FX, Milham MP. Competition between functional brain networks mediates behavioral variability. Neuroimage. 2008;39(1):527–37. https://doi.org/10.1016/j.neuroimage.2007.08.008.
28. Whitfield-Gabrieli S, Thermenos HW, Milanovic S, et al. Hyperactivity and hyperconnectivity of the default network in schizophrenia and in first-degree relatives of persons with schizophrenia. Proc Natl Acad Sci U S A. 2009;106(4):1279–84. https://doi.org/10.1073/pnas.0809141106.
29. Hampson M, Driesen N, Roth JK, Gore JC, Constable RT. Functional connectivity between task-positive and task-negative brain areas and its relation to working memory performance. Magn Reson

Imaging. 2010;28(8):1051–7. https://doi.org/10.1016/j.mri.2010.03.021.
30. Sheline YI, Barch DM, Price JL, et al. The default mode network and self-referential processes in depression. Proc Natl Acad Sci U S A. 2009;106(6):1942–7. https://doi.org/10.1073/pnas.0812686106.
31. Zhao XH, Wang PJ, Li CB, et al. Altered default mode network activity in patient with anxiety disorders: an fMRI study. Eur J Radiol. 2007;63(3):373–8. https://doi.org/10.1016/j.ejrad.2007.02.006.
32. Northoff G. Anxiety disorders and the brain's resting state networks: from altered spatiotemporal synchronization to psychopathological symptoms. Adv Exp Med Biol. 2020;1191:71–90. https://doi.org/10.1007/978-981-32-9705-0_5.
33. Miles SR, Menefee DS, Wanner J, Teten Tharp A, Kent TA. The relationship between emotion dysregulation and impulsive aggression in veterans with posttraumatic stress disorder symptoms. J Interpers Violence. 2016;31(10):1795–816. https://doi.org/10.1177/0886260515570746.
34. Szabo YZ, Warnecke AJ, Newton TL, Valentine JC. Rumination and posttraumatic stress symptoms in trauma-exposed adults: a systematic review and meta-analysis. Anxiety Stress Coping. 2017;30(4):396–414. https://doi.org/10.1080/10615806.2017.1313835.
35. Liston C, Chen AC, Zebley BD, et al. Default mode network mechanisms of transcranial magnetic stimulation in depression. Biol Psychiatry. 2014;76(7):517–26. https://doi.org/10.1016/j.biopsych.2014.01.023.
36. Helpman L., Marin M-F, et al. Neural changes in extinction recall following prolonged exposure treatment for PTSD: a longitudinal fMRI study. Neuroimage Clin. 2016;12:715–723. https://doi.org/10.1016/j.nicl.2016.10.007.
37. Smith NB, Doran JM, Sippel LM, Harpaz-Rotem I. Fear extinction and memory reconsolidation as critical components in behavioral treatment for posttraumatic stress disorder and potential augmentation of these processes. Neurosci Lett. 2017;649:170–5. https://doi.org/10.1016/j.neulet.2017.01.006.
38. Hoge CW, Grossman SH, Auchterlonie JL, Riviere LA, Milliken CS, Wilk JE. PTSD Treatment for soldiers after combat deployment: low utilization of mental health care and reasons for dropout. PS. 2014;65(8):997–1004. https://doi.org/10.1176/appi.ps.201300307.
39.• Kozel FA, Motes MA, Didehbani N, et al. Repetitive TMS to augment cognitive processing therapy in combat veterans of recent conflicts with PTSD: a randomized clinical trial. J Affect Disord. 2018;229:506–514. https://doi.org/10.1016/j.jad.2017.12.046.
The findings of the RCT in veterans with PTSD demonstrated that TMS is effective for augmenting the effects of cognitive processing therapy (CPT), a widely used exposure-based psychotherapy, immediately after a course of CPT plus TMS and at follow-up several months later. These findings are important given that PTSD symptoms persist for some patients after completing a course of CPT, and TMS may offer a way to augment symptom improvement.
40. Bouton ME. Context, ambiguity, and unlearning: sources of relapse after behavioral extinction. Biol Psychiatry. 2002;52(10):976–86. https://doi.org/10.1016/s0006-3223(02)01546-9.
41. Foa EB. Psychosocial therapy for posttraumatic stress disorder. J Clin Psychiatry. 2006;67(Suppl 2):40–5.
42. Faucher CR, Doherty RA, Philip NS, Harle ASM, Cole JJE, Van't Wout-Frank M. Is there a neuroscience-based, mechanistic rationale for transcranial direct current stimulation as an adjunct treatment for posttraumatic stress disorder? Behav Neurosci. 2021;135(6):702–713. https://doi.org/10.1037/bne0000487.
43. Guhn A, Dresler T, Andreatta M, et al. Medial prefrontal cortex stimulation modulates the processing of conditioned fear. Front Behav Neurosci. 2014;8:44. https://doi.org/10.3389/fnbeh.2014.00044.
44. Quirk GJ, Mueller D. Neural mechanisms of extinction learning and retrieval. Neuropsychopharmacology. 2008;33(1):56–72. https://doi.org/10.1038/sj.npp.1301555.
45. Phelps EA, Delgado MR, Nearing KI, LeDoux JE. Extinction learning in humans: role of the amygdala and vmPFC. Neuron. 2004;43(6):897–905. https://doi.org/10.1016/j.neuron.2004.08.042.
46. Kalisch R, Korenfeld E, Stephan KE, Weiskopf N, Seymour B, Dolan RJ. Context-dependent human extinction memory is mediated by a ventromedial prefrontal and hippocampal network. J Neurosci. 2006;26(37):9503–11.
47. Herrmann MJ, Katzorke A, Busch Y, et al. Medial prefrontal cortex stimulation accelerates therapy response of exposure therapy in acrophobia. Brain Stimul. 2017;10(2):291–7. https://doi.org/10.1016/j.brs.2016.11.007.
48. Gross JJ. Antecedent- and response-focused emotion regulation: divergent consequences for experience, expression, and physiology. J Pers Soc Psychol. 1998;74(1):224–37. https://doi.org/10.1037/0022-3514.74.1.224.
49. Vanderhasselt MA, De Raedt R, Brunoni AR, et al. tDCS over the left prefrontal cortex enhances cognitive control for positive affective stimuli. PLoS ONE. 2013;8(5):e62219–e62219. https://doi.org/10.1371/journal.pone.0062219.
50. Liston C, McEwen BS, Casey BJ. Psychosocial stress reversibly disrupts prefrontal processing and attentional control. Proc Natl Acad Sci U S A. 2009;106(3):912–7. https://doi.org/10.1073/pnas.0807041106.
51. Smith JM, Alloy LB. A roadmap to rumination: a review of the definition, assessment, and

conceptualization of this multifaceted construct. Clin Psychol Rev. 2009;29(2):116–28. https://doi.org/10.1016/j.cpr.2008.10.003.

52. Nolen-Hoeksema S. The role of rumination in depressive disorders and mixed anxiety/depressive symptoms. J Abnorm Psychol. 2000;109(3):504–11.
53. McLaughlin KA, Nolen-Hoeksema S. Rumination as a transdiagnostic factor in depression and anxiety. Behav Res Ther. 2011;49(3):186–93. https://doi.org/10.1016/j.brat.2010.12.006.
54. Watkins ER, Roberts H. Reflecting on rumination: consequences, causes, mechanisms and treatment of rumination. Behav Res Ther. 2020;127:103573. https://doi.org/10.1016/j.brat.2020.103573.
55. Szabo YZ, Nelson SM, Lantrip C. Cognitive complaints in neuropsychologically normal adults: a brief report on the roles of childhood abuse and rumination. Traumatology. 2020;26(1):29–34. https://doi.org/10.1037/trm0000209.
56. Zhou HX, Chen X, Shen YQ, et al. Rumination and the default mode network: meta-analysis of brain imaging studies and implications for depression. Neuroimage. 2020;206:116287. https://doi.org/10.1016/j.neuroimage.2019.116287.
57. Mohan A, Roberto AJ, Mohan A, et al. The significance of the default mode network (DMN) in neurological and neuropsychiatric disorders: a review. Yale J Biol Med. 2016;89(1):49–57.
58. Marsland AL, Kuan DCH, Sheu LK, et al. Systemic inflammation and resting state connectivity of the default mode network. Brain Behav Immun. 2017;62:162–70. https://doi.org/10.1016/j.bbi.2017.01.013.
59. De Raedt R, Leyman L, Baeken C, et al. Neurocognitive effects of HF-rTMS over the dorsolateral prefrontal cortex on the attentional processing of emotional information in healthy women: an event-related fMRI study. Biol Psychol. 2010;85(3):487–95. https://doi.org/10.1016/j.biopsycho.2010.09.015.
60. Baeken C, Marinazzo D, Wu GR, et al. Accelerated HF-rTMS in treatment-resistant unipolar depression: insights from subgenual anterior cingulate functional connectivity. World J Biol Psychiatry. 2014;15(4):286–97. https://doi.org/10.3109/15622975.2013.872295.
61. Baeken C, Van Schuerbeek P, De Raedt R, et al. The effect of one left-sided dorsolateral prefrontal sham-controlled HF-rTMS session on approach and withdrawal related emotional neuronal processes. Clin Neurophysiol. 2011;122(11):2217–26. https://doi.org/10.1016/j.clinph.2011.04.009.
62. Lantrip C, Delaloye S, Baird L, et al. Effects of left versus right dorsolateral prefrontal cortex repetitive transcranial magnetic stimulation on affective flexibility in healthy women: a pilot study. Cogn Behav Neurol. 2019;32(2):69–75. https://doi.org/10.1097/WNN.0000000000000190.
63. De Witte S, Baeken C, Pulopulos MM, et al. The effect of neurostimulation applied to the left dorsolateral prefrontal cortex on post-stress adaptation as a function of depressive brooding. Prog Neuropsychopharmacol Biol Psychiatry. 2020;96:109687. https://doi.org/10.1016/j.pnpbp.2019.109687.
64. Spencer RL, Deak T. A users guide to HPA axis research. Phys Behav. 2017;178:43–65. https://doi.org/10.1016/j.physbeh.2016.11.014.
65. Post A, Keck ME. Transcranial magnetic stimulation as a therapeutic tool in psychiatry: what do we know about the neurobiological mechanisms? J Psychiatric Res. Published online 2001:23.
66. Hedges DW, Massari C, Salyer DL, et al. Duration of transcranial magnetic stimulation effects on the neuroendocrine stress response and coping behavior of adult male rats. Prog Neuropsychopharmacol Biol Psychiatry. 2003;27(4):633–8. https://doi.org/10.1016/S0278-5846(03)00052-6.
67. Ray RD, Zald DH. Anatomical insights into the interaction of emotion and cognition in the prefrontal cortex. Neurosci Biobehav Rev. 2012;36(1):479–501. https://doi.org/10.1016/j.neubiorev.2011.08.005.
68. Jankord R, Herman JP. Limbic regulation of hypothalamo-pituitary-adrenocortical function during acute and chronic stress. Ann N Y Acad Sci. 2008;1148:64–73. https://doi.org/10.1196/annals.1410.012.
69. Dedovic K, Duchesne A, Andrews J, Engert V, Pruessner JC. The brain and the stress axis: the neural correlates of cortisol regulation in response to stress. Neuroimage. 2009;47(3):864–71. https://doi.org/10.1016/j.neuroimage.2009.05.074.
70. Baeken C, De Raedt R, Van Schuerbeek P, et al. Right prefrontal HF-rTMS attenuates right amygdala processing of negatively valenced emotional stimuli in healthy females. Behav Brain Res. 2010;214(2):450–5. https://doi.org/10.1016/j.bbr.2010.06.029.
71. George MS, Wassermann EM, Williams WA, et al. Changes in mood and hormone levels after rapid-rate transcranial magnetic stimulation (rTMS) of the prefrontal cortex. J Neuropsychiatry Clin Neurosci. 1996;8(2):172–80. https://doi.org/10.1176/jnp.8.2.172.
72. Evers S, Hengst K, Pecuch PW. The impact of repetitive transcranial magnetic stimulation on pituitary hormone levels and cortisol in healthy subjects. J Affect Disord. 2001;66(1):83–8. https://doi.org/10.1016/s0165-0327(00)00289-5.
73. Szeszko PR, Lehrner A, Yehuda R. Glucocorticoids and hippocampal structure and function in PTSD. Harv Rev Psychiatry. 2018;26(3):142–57. https://doi.org/10.1097/HRP.0000000000000188.
74. Meewisse ML, Reitsma JB, de Vries GJ, Gersons BP, Olff M. Cortisol and post-traumatic stress disorder in adults: systematic review and meta-analysis. Br J Psychiatry. 2007;191:387–92. https://doi.org/10.1192/bjp.bp.106.024877.
75. Lehrner A, Hildebrandt T, Bierer LM, et al. A randomized, double-blind, placebo-controlled trial of

hydrocortisone augmentation of prolonged exposure for PTSD in U.S. combat veterans. Behav Res Ther. 2021;144:103924. https://doi.org/10.1016/j.brat.2021.103924.

76. Lindqvist D, Dhabhar FS, James SJ, et al. Oxidative stress, inflammation and treatment response in major depression. Psychoneuroendocrinology. 2017;76:197–205. https://doi.org/10.1016/j.psyneuen.2016.11.031.

77. Passos IC, Vasconcelos-Moreno MP, Costa LG, et al. Inflammatory markers in post-traumatic stress disorder: a systematic review, meta-analysis, and meta-regression. Lancet Psychiatry. 2015;2(11):1002–12. https://doi.org/10.1016/S2215-0366(15)00309-0.

78. Michopoulos V, Powers A, Gillespie CF, Ressler KJ, Jovanovic T. Inflammation in fear- and anxiety-based disorders: PTSD, GAD, and beyond. Neuropsychopharmacology. 2017;42(1):254–70. https://doi.org/10.1038/npp.2016.146.

79. Tian L, Sun SS, Cui LB, et al. Repetitive transcranial magnetic stimulation elicits antidepressant- and anxiolytic-like effect via nuclear factor-E2-related factor 2-mediated anti-inflammation mechanism in rats. Neuroscience. 2020;429:119–33. https://doi.org/10.1016/j.neuroscience.2019.12.025.

80. Phan KL, Wager T, Taylor SF, Liberzon I. Functional neuroanatomy of emotion: a meta-analysis of emotion activation studies in PET and fMRI. Neuroimage. 2002;16(2):331–48. https://doi.org/10.1006/nimg.2002.1087.

81. Quaedflieg CWEM, Meyer T, Smulders FTY, Smeets T. The functional role of individual-alpha based frontal asymmetry in stress responding. Biol Psychol. 2015;104:75–81. https://doi.org/10.1016/j.biopsycho.2014.11.014.

82. De Raedt R, Koster EHW. Understanding vulnerability for depression from a cognitive neuroscience perspective: a reappraisal of attentional factors and a new conceptual framework. Cogn Affect Behav Neurosci. 2010;10(1):50–70. https://doi.org/10.3758/CABN.10.1.50.

83. Arnsten AFT. Stress weakens prefrontal networks: molecular insults to higher cognition. Nat Neurosci. 2015;18(10):1376–85. https://doi.org/10.1038/nn.4087.

84. O'Donnell ML, Lau W, Chisholm K, Agathos J, Little J, Terhaag S, Brand R, et al. A pilot study of the efficacy of the unified protocol for transdiagnostic treatment of emotional disorders in treating posttraumatic psychopathology: a randomized controlled trial. J Trauma Stress. 2021;34(3):563–74. https://doi.org/10.1002/jts.22650.

85. Foa E, Hembree EA, Rothbaum BO, Rauch S. Prolonged exposure therapy for PTSD: emotional processing of traumatic experiences – therapist guide. 2nd ed. New York: Oxford University Press; 2019.

86. Isserles M, Shalev AY, Roth Y, et al. Effectiveness of deep transcranial magnetic stimulation combined with a brief exposure procedure in post-traumatic stress disorder – a pilot study. Brain Stimul. 2013;6(3):377–83. https://doi.org/10.1016/j.brs.2012.07.008.

87.• Isserles M, Tendler A, Roth Y, et al. Deep transcranial magnetic stimulation combined with brief exposure for posttraumatic stress disorder: a prospective multisite randomized trial. Biol Psychiatry. 2021;90(10):721–728. https://doi.org/10.1016/j.biopsych.2021.04.019.

The findings of the RCT demonstrated that the order of treatment when using TMS to augment the effect of behavior therapy is likely important in PTSD. This experimental paradigm first administered the behavioral exposure, then administered deep TMS. They found that both the control and active conditions improved, but the control group experienced statistically superior improvement.

Publisher's Note