Treating Post-traumatic Stress Disorder with Neuromodulation Therapies: Transcranial Magnetic Stimulation, Transcranial Direct Current Stimulation, and Deep Brain Stimulation

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Abstract

Post-traumatic stress disorder (PTSD) is a prevalent and debilitating illness. While standard treatment with pharmacotherapy and psychotherapy may be effective, approximately 20 to 30% of patients remain symptomatic. These individuals experience depression, anxiety, and elevated rates of suicide. For treatment-resistant patients, there is a growing interest in the use of neuromodulation therapies, including transcranial magnetic stimulation (TMS), transcranial direct current stimulation (tDCS), and deep brain stimulation (DBS). We conducted a systematic review on the use of neuromodulation strategies for PTSD and pooled 13 randomized clinical trials (RCTs), 11 case series, and 6 case reports for analysis. Overall, most studies reported favorable outcomes in alleviating both PTSD and depressive symptoms. Although several RCTs described significant differences when active and sham stimulations were compared, others found marginal or nonsignificant differences between groups. Also positive were studies comparing PTSD symptoms before and after treatment. The side effect profile with all 3 modalities was found to be low, with mostly mild adverse events being reported. Despite these encouraging data, several aspects remain unknown. Given that PTSD is a highly heterogeneous condition that can be accompanied by distinct psychiatric diagnoses, defining a unique treatment for this patient population can be quite challenging. There has also been considerable variation across trials regarding stimulation parameters, symptomatic response, and the role of adjunctive psychotherapy. Future studies are needed to address these issues.

Key Words Post-traumatic stress disorder (PTSD) · neuromodulation · transcranial magnetic stimulation (TMS) · transcranial direct current stimulation (tDCS) · deep brain stimulation (DBS)

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Introduction

Post-traumatic stress disorder (PTSD) is a chronic psychiatric illness that develops as a pathologic response after exposure to a major traumatic event [1]. According to the National Institutes of Health (NIH), the prevalence of PTSD in the community is 6.8%, reaching approximately 20% among military veterans [2]. Conventional PTSD treatment consists of pharmacotherapy and psychotherapy. Presently, the only FDA-approved medications for PTSD are 2 selective serotonin reuptake inhibitors (SSRIs): paroxetine and sertraline [3]. Multiple psychotherapy approaches have been studied, although exposure therapy predominates [4]. Over the years, there has been a growing interest in neuromodulation strategies for the treatment of PTSD [5, 6]. In particular, numerous studies have been published employing transcranial magnetic stimulation (TMS), transcranial direct current stimulation

(tDCS), and deep brain stimulation (DBS) [7–10]. These techniques allow for countless permutations of stimulation parameters and the possibility of applying concurrent therapies, such as exposure therapy [8]. In contrast to TMS and tDCS, DBS is an invasive neuromodulation technique. To date, only 1 study has reported the clinical effects of DBS in PTSD [7]. Understanding previous published studies on neuromodulation for PTSD could provide important insights for future trials.

Methods

This systematic review followed PRISMA guidelines (Fig. 1). A literature search was conducted for original articles with no limit for publication date up to December 2019 using PubMed/MEDLINE. The articles were required to match the following search terms: “Post-traumatic Stress Disorder,” “PTSD,” “Transcranial Magnetic Stimulation,” “TMS,” “Transcranial Direct-Current Stimulation,” “tDCS,” “Deep Brain Stimulation,” and “DBS.” The abstracts pulled in this search were reviewed by two independent investigators (FVG, BD). After excluding duplicates, relevant articles were selected for full-text review and had to meet the following inclusion and exclusion criteria: (I) inclusion (clinical studies of patients with PTSD treated with DBS, TMS, or tDCS; articles published in English) and (II) exclusion (studies including only preclinical data; articles reporting on patient populations other than PTSD; review articles; commentaries; technical notes or protocols). When articles reported duplicate data, only the study reporting the most recent follow-up results was included.

Results and Discussion

As a prevalent and often treatment-resistant condition, PTSD is a major concern and has been the focus of numerous studies aiming to develop neuromodulation therapies (e.g., vagus nerve stimulation [11–13], stellate ganglion block [14, 15], electroconvulsive therapy [16, 17], TMS [9, 10], and tDCS [8, 18]). Most of these treatments have focused on increasing prefrontal inhibitory control over the amygdala, either directly or indirectly, to reduce the excessive emotional response to an aversive memory related to the trauma [6, 19]. Along a similar line, psychotherapies, such as exposure therapy, are based on protocols of fear extinction that gradually reduce the excessive emotional response by repeatedly presenting a trigger of the traumatic event in the absence of the threatening situation [6, 11]. The use of neuromodulation therapies in association with psychotherapy may lead to greater extinction recall and, consequently, an improvement of symptoms [6, 19, 20].

PTSD is also frequently characterized by comorbid major depressive disorder [21]. It should be noted that many treatment modalities and targets have also been employed in the treatment of depression. Clinical benefit in PTSD patients could have derived in part from an improvement of depressive symptoms, although most studies were designed to treat PTSD directly rather than comorbidities.

With this rationale, several studies evaluated the feasibility and the clinical benefits of using TMS or tDCS alone or combined with psychotherapy. In this review, we evaluated 13 RCTs [9, 10, 18, 21–30], 11 case series [8, 31–40], and 6 case reports [7, 21, 41–44] on neuromodulation for PTSD, focusing on TMS, tDCS, and DBS. Details of the articles pooled for analysis in our review are summarized in Tables 1 (TMS), 2 (tDCS), and 3 (DBS).

Transcranial Magnetic Stimulation

TMS is a safe, noninvasive neuromodulatory technique that uses electromagnetic fields to change local electrical activity and alter neuronal firing patterns resulting in widespread connectivity modifications [30]. Although the mechanisms of action of TMS are not fully understood, it is believed that the use of different stimulation frequencies (high frequency, > 10 Hz; low frequency, ≤ 1 Hz) results in an increase or decrease in cortical excitability [38]. Variations of the TMS protocol are theta burst stimulation (TBS) and synchronized TMS. TBS is intended to elicit long-term potentiation by using theta band rhythm stimulation, normally performed with high-frequency (50 Hz) TMS bursts with inter-burst intervals of 200 ms [45]. Synchronized TMS uses the individualized oscillatory neuronal activity in the alpha frequency band information to generate stimulation settings that are believed to restore the normal oscillatory neuronal and increase neural plasticity [40]. When used repeatedly, repetitive TMS (rTMS) becomes a powerful tool for treating psychiatric disorders with no need for anesthesia [38]. As a result, this technique has been proposed as a suitable therapeutic alternative for some neuropsychiatric disorders [46].

Several clinical trials have been published on the therapeutic effect of TMS for PTSD with promising results. In general, these studies report a significant reduction in PTSD symptoms when comparing active *versus* sham stimulation, or before *versus* after treatment conditions [10, 23, 28]. Studies investigating the therapeutic response of distinct TMS settings (e.g., low *vs* high frequency) have shown similar results, with a larger effect in patients receiving low-frequency stimulation [26, 27]. Also, it has been suggested that a larger therapeutic effect is observed in patients treated with right dorsolateral prefrontal cortex (dlPFC) stimulation compared with left dlPFC stimulation [24], though no difference was found when right *versus* bilateral dlPFC stimulation was compared [30].

Fig. 1 PRISMA flow chart describing record selection.

Although the majority of the studies were performed using TMS alone, some clinical trials investigated the effects of stimulation along with psychotherapy (e.g., cognitive processing therapy; exposure therapies). In general, these studies reported significant improvements in patients receiving combined treatments [9, 21, 22, 25].

One important aspect of noninvasive neuromodulation therapies (e.g., TMS and tDCS) is the low side effect profile

[47]. Most studies on TMS reported transient mild side effects that were easily treated with standard pharmacotherapy (e.g., headache, insomnia, and mood disturbances) [10, 21, 27, 30]. Nevertheless, 4 cases of severe adverse events were documented. These included suicidality, homicidal ideation, tonic-clonic generalized seizures, and a probably unrelated case of subconjunctival hemorrhage in a patient with a clinical history of ocular disease [22, 28, 31, 41].

Table 1 Summary of studies using TMS for post-traumatic stress disorder

Study	N, sex (M/F); age range (mean ± SD)		Treatment	Type of trauma	Associated conditions	Brain target	Outcome
	Sham	Active					
Randomized controlled trials (TMS treatment only)							
Kozel (2019)	No	Group 1: 17, 13/4; 18–50 years (38.0 ± 6.7) Group 2: 18, 12/6; 18–50 years (39.0 ± 6.0)	Stable medication and psychotherapy	ND	MDD	Unilateral right dlPFC	Group 1: improvement in PTSD (CAPS; <i>p</i> = .03; PCL-5; <i>p</i> = .001) and MDD (MADRS; <i>p</i> = .001) Group 2: improvement in PTSD (CAPS; <i>p</i> = .006; PCL-5; <i>p</i> = .001) and MDD (MADRS; <i>p</i> = .01)
Philip (2019)	25, 20/5 (48 ± 13)	25, 22/3 (53 ± 12)	Stable medication and/or psychotherapy	Multifactorial	MDD; BD; substance use disorder	Unilateral right dlPFC	Active group: nonsignificant improvement in PTSD (CAPS; <i>p</i> = .61; PCL-5; <i>p</i> = .31) and MDD (IDSSR; <i>p</i> = .07)
Ahmadizadeh (2018)	20, 20/0; 42–69 years (47.5 ± 5.6)	Group 1: 19, 19/0; 42–69 years (52.1 ± 7.6) Group 2: 19, 19/0; 42–69 years (51.8 ± 7.9)	Stable medication and psychotherapy	Combat related	No	Group 1: bilateral dlPFC Group 2: unilateral right dlPFC	Group 1: improvement in PTSD (PCL-M 62.5%) Group 2: improvement in PTSD (PCL-M 41.2%)
Nam (2013)	9, 3/6; 25–46 years (32.8 ± 6.9)	7, 3/4; 25–46 years (36.3 ± 8.8)	Stable medication and psychotherapy	Vehicle accidents; domestic violence; physical assaults	No	Unilateral right dlPFC	Active group: improvement in PTSD (CAPS 46%)
Watts (2012)	10, 9/1; 20–70 years (57.8 ± 11.8)	10, 9/1; 20–70 years (54 ± 12.3)	Stable medication and psychotherapy	Combat related; sexual abuse; assault; accident	MDD	Unilateral right dlPFC	Active group: improvement in PTSD (CAPS; <i>p</i> = .009; PCL: <i>p</i> = .0002)
Boggio (2010)	10, 2/8; 18–64 years (45.9 ± 11.4)	Group 1: 10, 4/6; 18–64 years (40.7 ± 13.6) Group 2: 10, 3/7; 18–64 years (47.1 ± 12.1)	Stable medication and psychotherapy	Sexual abuse; physical or emotional trauma	No	Group 1: unilateral left dlPFC Group 2: unilateral right dlPFC	Group 1: improvement in PTSD (PCL; <i>p</i> = .012) Group 2: improvement in PTSD (PCL; <i>p</i> = .0042) Improvement in PTSD
Cohen (2004)	6, 4/2; 25–68 years (42.8 ± 14.8)	Group 1: 8, 7/1; 22–64 years (40.8 ± 9.9) Group 2: 10, 6/4; 22–64 years (41.8 ± 11.4)	Stable medication and psychotherapy	Combat related; sexual abuse; motor vehicle accident; death of relative; work accident	No	Unilateral right dlPFC	Group 1: no significant differences Group 2: improvement in PTSD and anxiety (CPL 29.3%)
Randomized controlled trials (TMS treatment associated with psychotherapy)							
Fryml (2018)	3, 2/1; 21–50 years (30 ± 2.6)	Group 1: 3, 3/0; 21–50 years (27 ± 2.1) Group 2: 2, 2/0; 21–50 years (27 ± 2.1)	Exposure therapy + stable medication	War related	MDD, substance use disorder	Group 1: unilateral left PFC Group 2: unilateral right PFC	Active groups: improvement in PTSD (CAPS 55%) and in MDD (HRSD24; <i>p</i> = .035) Sham group: improvement in PTSD (CAPS 40%)
Kozel (2018)	49, ND; 18–60 years (32.9 ± 6)	54, ND; 18–60 years (34.6 ± 7.5)	Cognitive processing therapy + stable medication	Combat related	No	Unilateral right dlPFC	Active group: improvement in PTSD (CAPS 62.6%; PCL 44.6%)
Isserles (2013)	9, 8/1; ND (40.4 ± 10.5)	Group 1: 9, 7/2; ND (49 ± 12.5) Group 2: 8, 5/3; ND (40.5 ± 9.8)	Exposure therapy (ET) + stable medication	Military related; multifactorial	ND	Group 1: bilateral mPFC + ET Group 2: bilateral mPFC + sham ET	Group 1: improvement in the intrusive component of the CAPS scale (<i>p</i> = .039)
Osuch (2009)	No	Crossover design 9, 1/8; 24–56 years (41.4 ± 2.3)	Exposure therapy + stable medication	ND	MDD; anxiety disorder; substance abuse	Unilateral right dlPFC	Active phase: improvement in hyper-arousal symptoms of CAPS (<i>d</i> = −0.76)
Case series Carpenter (2018)	No	35, 21/14; 27–69 years (51.6 ± 10.3)	Stable medication and psychotherapy	Multifactorial	MDD	Unilateral left dlPFC	Improvement in PTSD (PCL-5 35.5%) and MDD (IDS-SR 37.6%)

Table 1 (continued)

Petrosino (2018)	No	21, 13/8; 18–75 years (51 ± 9.7 years)	Stable medication	ND	MDD	Unilateral left dlPFC	Improvement in PTSD (PCL-5 66.7% of cases) and MDD (IDSSR 76.2% of cases)
Philip (2018)	No	33, 20/13; 27–69 (51.3 ± 11.1)	Stable medication and psychotherapy	Multifactorial	MDD	Unilateral left dlPFC	Improvement in PTSD (PCL 36.4%) and MDD (IDSSR 33.3%)
Woodside (2017)	No	14, 0/14; ND (39.8 ± 10.9)	Stable medication and psychotherapy	Multifactorial	MDD, eating disorder	Bilateral dmPFC	Improvement in PTSD (PCL-C 52%) and ED (DERS 36%)
Philip (2016)	No	10, 8/2; ND (58.1 ± 13.9)	ND	Combat related; sexual abuse; multifactorial	MDD	Unilateral left dlPFC	Improvement in PTSD (PCL 80%) and MDD (QIDS 60%). 1 patient: no changes in PTSD and worsening in MDD
Oznuur (2014)	No	20, 20/0; 20–40 (28.7 ± 3.3)	Stable medication and psychotherapy	Combat related	MDD	Unilateral right dlPFC	Improvement in hyper-arousal ($p = .02$)
Rosenberg (2002)	No	12, 12/0; 47–75 (64.8 ± 9.1)	Stable medication	ND	MDD, substance abuse	Unilateral right dlPFC	Improvement in PTSD (MISS 6% $p = .02$) and MDD (Ham-D 50%)
Grisaru (1998)	No	10, 7/3; 21–53 (47 ± ND)	Stable medication and psychotherapy	War related; severe accidents; assault	ND	Bilateral motor cortex	Improvement in PTSD (IES avoidance subscale $p = .000$)
McCann (1998)	No	2, 0/2; 29 years; 42 years	ND	Physical trauma; emotional trauma	MDD	Unilateral right PFC	Improvement in PTSD (PTSD symptom scale $p = .004$)
Case reports							
Fryml (2018)	No	1, 0/1; 27 years	Stable medication and psychotherapy	ND	MDD	Unilateral left dlPFC	Improvement in PTSD (clinical evaluation)
Karris (2014)	No	1, 1/0; 41 years	ND	ND	No	Unilateral right dlPFC	Improvement in PTSD (PCL-M 62%)
Nakama (2014)	No	1, 1/0; 24 years	Stable medication	War related	MDD	Unilateral left dlPFC	Improvement in PTSD (PCL-M 51.8%) and MDD (BDI 65%)
Tillman (2011)	No	1, 1/0; 58 years	ND	Combat related	MDD	Unilateral right PFC	Improvement in hyper-arousal measured by EEG in P3a and P3b
Study	Follow-up	Adverse events	Stimulation settings				
			Frequency (Hz)	MT (%)	No. of sessions	Pulses/session	Train duration/interval (s)
Randomized controlled trials (TMS treatment only)							
Kozel (2019)	3 months	All groups: Mild: headache and discomfort	Group 1: 1 Group 2: 10	110	36 5 ss/w for 6 weeks + 3 weeks (tampering)	2400	Group 1: continuous for 40 min Group 2: 4/36 for 40 min
Philip (2019)	2 weeks	All groups: Mild: headache and discomfort Sham group: Severe: homicidal ideation and suicidality ($n = 2$) Active groups: Mild: headache and discomfort	50 (theta burst)	80	Up to 20 5 ss/w for 4 weeks Crossover design	1800	ND; 9.5 min ND; Magstim Rapid 2 + 1 System
Ahmadizadeh (2018)	4 weeks		20	100	Up to 10 3 ss/w for 2 weeks 2 ss/w for 2 weeks	Group 1: 1200 Group 2: 2400	Group 1: 2/28 for 30 min Group 2: 2/28 for 15 min
Nam (2013)	8 weeks	All groups: Mild: headache and dizziness	1	100	15 5 ss/w for 3 weeks	1200	ND; 20 min 70-mm figure 8 coil; Neuro-MS System
Watts (2012)	2 months	ND	1	90	10 5 ss/w for 2 weeks	ND	20/40; 20 min Figure 8 coil; TAMAS System
Boggio (2010)	3 months	All groups: Mild: headache, neck pain, sleepiness, and dizziness	20	80	10 5 ss/w for 2 weeks	1600	2/28 50-m figure 8 coil; Neuronetics 2100 System
Cohen (2004)	14 days	All groups: Mild: headache, neck pain, dizziness, and transient mood disturbance	Group 1: 1 Group 2: 10	80	10 5 ss/w for 2 weeks	ND	Group 1: 5/55; 20 min Group 2: 2/58; 20 min 70-mm figure 8 coil; Magstim System 90-mm circular coil; Magstim System
Randomized controlled trials (TMS treatment associated with psychotherapy)							
Fryml (2018)	5 weeks	No adverse events	10	120	8 1 ss/w for 8 weeks	6000	5/10; 30 min Figure 8 coil; Neuronetics 2100 System

Table 1 (continued)

	Kozel (2018)	6 months	Active group: Mild: headache All groups: Mild: headache, anxiety Group 1: Severe: tonic-clonic generalized seizure (<i>n</i> = 1) ND	1	110	12	1800	Continuous for 30 min	70-mm figure 8 coil; Magstim Rapid System
Islerles (2013)	2 months			20	120	12 3 ss/w for 4 weeks	1680	2/20; 15.5 min	H-coil; Magstim Rapid System
Osuch (2009)	ND			1	100	20 3 to 5 ss/w 2 weeks washout between arms	1800	Continuous for 30 min	Figure 8 coil; Caldwell High Speed System
Case series Carpenter (2018)	72 h		Mild: headache, insomnia, anxiety Severe: suicidality (<i>n</i> = 4)	5	120	40 5 ss/w for 7 weeks + 3 weeks (tampering) Up to 40 ND	3000 4000	5/14 5/1	ND; NeuroStar System
Petrosino (2018)	ND		ND	5	120	25 5 ss/w for 5 weeks	3000 4000	4/12 4/11 4/12	ND
Philip (2018)	ND		ND	5	120	20–30 ss/w ND	3000 600	5/10 2/8	ND; NeuroStar System
Woodside (2017)	No		Mild: transient headache	10 20 50	120	36 5 ss/w for 6 weeks + 3 weeks (tampering)	1500 3000 4000	2.5/10 4/12 4/11	ND
Philip (2016)	No		ND	5	120	20 5 ss/w for 4 weeks	600	40/20	70-mm figure 8 coil; Magstim Rapid System
Oznu (2014)	2 months		Mild: headache	1	80	10 5 ss/w for 2 weeks	ND	40/20	Figure 8 coil; Dantec Maglite System
Rosenberg (2002)	2 months		Mild: headache	5	90	Single session	30	8/52 1 ms	14-cm angular coil; Dantec Maglite System
Grisaru (1998)	28 days		Mild: headache, transiently intrusive thoughts	1	ND		ND	ND	ND
McCann (1998)	No		ND	1	80	17 3 ss/w for 2 weeks Increased to 5 ss/w	1980	2/12	Brainsway H-Coil; ND
Case reports Fryml (2018)	4 months		Mild: Transiently worsening, flashbacks, dissociation, and intrusive memories Severe: subconjunctival hemorrhage after 8th session	18	120	80 20 ss/w for 4 weeks (4 ss/day)	1700	2/26	ND; NeuroStar System
Karris (2014)	3 weeks		Severe: subconjunctival hemorrhage after 8th session	20	80	22 ss/w ND	1200	1/26	ND; NeuroStar System
Nakama (2014)	9 weeks		ND	10	100 120	22 5 ss/w for 3 weeks + 3 weeks (tampering)	3000	4/26	ND; NeuroStar System
Tillman (2011)	No		No adverse events	1	100	2 1 ss/w for 2 weeks	1200	ND	ND

BD = bipolar disorder; BDI = Beck Depression Inventory scores; CAPS = Clinician-Administered PTSD Symptom; DERS = Difficulties with Emotional Regulation Scale; dlPFC = dorsolateral prefrontal cortex; Ham-D = Hamilton Depression scale; HRSD24 = Hamilton Rating Scale for Depression; IDSSR = Inventory of Depressive Symptomatology, Self-Report; IES = Impact of Event Scale; MADRS = Montgomery-Asberg Depression Rating Scale; MDD = major depressive disorder; MISS = Mississippi Scale of Combat Severity; ND = not described; PCL-5 = PTSD Checklist for DSM-5; PCL-C = PTSD Checklist-Civilian version; PCL-M = PTSD Checklist-Military version; QIDS = Quick Inventory of Depressive Symptomatology, ss/w = session/week

It is important to highlight that TMS studies included patients with multiple types of trauma (e.g., combat-related, vehicle accidents, sexual violence), with a wide age range (18–75 years) and a slight predominance of males (Table 1). Furthermore, several patients had comorbidities such as major depressive disorder (most frequent), substance abuse, and eating disorder [25, 33, 34]. The brain target (e.g., dlPFC, medial prefrontal cortex, dorsomedial prefrontal cortex) and the stimulation parameters varied greatly across studies. TMS settings ranged from 1 to 20 Hz with intensities of 80 to 120% of the motor threshold (Table 1), with the exception of a study that used intermittent TBS [40, 47].

Transcranial Direct Current Stimulation

Similar to TMS, tDCS is a safe and noninvasive neuromodulation therapy capable of altering local electrical activity, resulting in the restoration of normal connectivity between dysfunctional neurons [8]. While TMS uses focused electromagnetic pulses (trains of stimulation), tDCS uses constant and low direct current [8, 30] to increase or decrease

cortical excitability by depolarizing (anodal) or hyperpolarizing (cathodal) neurons [48, 49]. There are fewer studies investigating the beneficial effects of tDCS for the treatment of PTSD than those evaluating TMS. Thus, the clinical evidence of the therapeutic effects of this technique relies on two clinical trials and 3 case series (Table 2).

A pilot study published in 2015 investigated the feasibility of treating PTSD symptoms with a combination of computerized working memory training and prefrontal cortex tDCS [39]. In this case series, the authors report significant improvements on cognitive and emotional performance measures that were accompanied by neurophysiological changes observed on electroencephalographic recordings [8]. Thereafter, another pilot study investigated the feasibility of using ventromedial prefrontal cortex (vmPFC) tDCS during extinction learning to improve extinction recall in PTSD patients [8]. Using normalized skin conductance reactivity as a primary outcome measure, the authors showed that vmPFC-tDCS is more effective during extinction consolidation than when applied simultaneously with extinction learning [8]. This suggests that this strategy may be an interesting way of enhancing extinction

Table 2 Summary of studies using tDCS for post-traumatic stress disorder

Study	Ahmadzadeh (2019)	van't Wout-Frank (2018)	Hampstead (2019)	van't Wout (2017)	Saunders (2015)
Study type	RCT	RCT	Case series	Case series	Case series
TDCS + psychotherapy	No	Exposure therapy	No	Fear conditioning	Working memory training
Sham group, <i>N</i> , sex, age range in years (mean ± SD)	20, 6 males (43.00 ± 2.42)	6, all males, 30–53 (40.5 ± 8.8)	No	No	No
Active group, <i>N</i> , sex, age range in years (mean ± SD)	20, 8 males (44.50 ± 2.34)	6, all males, 30–53 (40.5 ± 8.8)	6, 4 males, 20–65 (ND)	28, all males, 30–69 (56.25 ± 12.3)	4, all males, 55–65 (ND)
Treatment	Stable medication and psychotherapy	Stable medication and psychotherapy	Stable medication	Stable medication	ND
Type of trauma	ND	War zone related	Combat related; sexual trauma; traumatic death	War zone related	ND
Associated conditions	MDD	ND	MDD, GAD	Anxiety disorder	ND
Brain target	dlPFC	vmPFC	rLTC	vmPFC	PFC
Outcome	Improvement in PTSD (PCL-5: $p = .00$)	Improvement in PTSD (PCL-5: $p = .03$)	Improvement in PTSD (CAPS 7–57%; PCL-C 19–38%)	Improvement in PTSD (PCL-5: $p = .02$)	Improvement in cognition and emotion (clinical evaluation)
Follow-up	30 days	1 month	3–4 days	24 h	10 weeks
Side effects	All groups: Mild: Itching, Tingling	Active group: Mild	All groups: Mild: itching, tingling, burning	Active group: Mild: erythema	ND
Stimulation settings					
Current (mA)	2	20	2	2	10
No. of sessions	10 (5 ss/w for 2 weeks)	6 (3 ss/w for 2 weeks)	Up to 10 (5 ss/w for 2 weeks)	2 (ND)	5 (ND)
Duration (min)	20	25	20	10	20
Anode/cathode	F3/F4	AF3/PO8	F8; C4; P8; EX10/T8	AF3/PO8	AF3/M1
System	neuroConn DC Stimulator Plus	neuroConn DC Stimulator Plus	ND	neuroConn DC Stimulator Plus	Soterix Medical 1224-B

CAPS = Clinician-Administered PTSD Scale for DSM-IV; dlPFC = dorsolateral prefrontal cortex; GAD = generalized anxiety disorder; MDD = major depressive disorder; ND = not described; PCL-C = PTSD Checklist-Civilian version; PFC = prefrontal cortex; RCT = randomized controlled trial; rLTC = right lateral temporal cortex; ss/w = sessions/week; vmPFC = ventromedial prefrontal cortex

Table 3 Summary of the study using DBS for post-traumatic stress disorder

Study	Langevin (2016)
Study type	Case report
Sham group	No
Active group	1 male, 48 years
Treatment	ND
Type of trauma	War zone related
Associated conditions	No
Brain target	Bilateral basolateral amygdala
Outcome	Improvement in PTSD (CAPS 37.8%)
Follow-up	8 months
Side effects	Transient mild mood alteration
Stimulation settings	Amplitude right, 1.4 V; amplitude left, 0.7 V; pulse width, 60 μ s; frequency, 160 Hz

recall and improving PTSD symptoms [8]. Based on these findings, a double-blind randomized control trial was performed to further investigate extinction recall in patients with PTSD using vmPFC-tDCS along with sessions of a combat-related virtual reality paradigm. The study reported significant reductions in arousal and severity of PTSD in patients allocated to the active group receiving exposure therapy [29]. More recently, a RCT evaluating the efficacy of dlPFC-tDCS alone for PTSD symptoms was published reporting a significant reduction in PTSD, depressive, and anxiety symptoms in the active group immediately after treatment and after a 1-month follow-up period [18].

These results are encouraging, as the therapeutic effects of tDCS were generally positive and the observed side effects were mild (Table 2). Nevertheless, it is important to highlight that most of studies recruited only patients with combat-related PTSD, with a vast majority of male individuals (71%). Also, age ranged from 20 to 69 years and most patients presented comorbidities, such as major depressive disorder and generalized anxiety disorder (Table 2). Furthermore, the anatomical target and the stimulation parameters were distinct between studies, including the PFC, PFC subregions, and temporal cortex, with varying current intensities (e.g., 2 to 20 mA) and session duration (e.g., 10 to 25 min).

Deep Brain Stimulation

DBS is an invasive neuromodulation technique that consists of the placement of electrodes in deep brain targets, followed by the delivery of electrical stimulation to modulate local and neural activity [50]. DBS has been extensively used to treat movement disorders [51–53] and is currently delivered through a humanitarian exemption for the treatment of obsessive-compulsive disorder in the USA, while it has CE marking and is approved in Europe [54, 55]. There is one case report using DBS for the treatment of PTSD (Table 3). A 48-year-old man with treatment refractory combat-related PTSD

received bilateral DBS to the basolateral amygdala. The authors reported over 35% symptomatic improvement after 8 months of stimulation with no major adverse events [7].

Conclusion

Although numerous studies highlight the possible beneficial use of rTMS and tDCS for the treatment of PTSD, the exact mechanism of action remains unclear. It seems that the most effective target for rTMS is the right dlPFC and that more than 5 sessions are necessary for significant improvement. Within the range of tested settings, stimulation intensity or frequency did not seem to be important contributors to clinical outcome. tDCS, on the other hand, can be used as a psychotherapy treatment enhancer and facilitate symptom reduction.

Various studies included in this review reported favorable outcomes in alleviating both PTSD and depressive symptoms. Although several RCTs described significant differences when active and sham stimulation were compared, others found marginal or nonsignificant differences between groups. The fact that patients receiving sham treatment were often found to be improved highlights the magnitude of the placebo effect in this population. Longer follow-up periods will be necessary to better characterize not only the placebo response but also the duration of the therapeutic benefit and possible signs of refractoriness/relapse after neuromodulation treatment [56–59].

A positive and encouraging note in the studies reviewed was the low side effect profile of neuromodulation strategies in PTSD. The vast majority of articles reported absent or mild adverse events. Of the 636 patients included in the 30 studies pooled for review, only four developed serious adverse event [22, 28, 31, 41]. All of these occurred in TMS studies, likely due to the disproportionate number of TMS-treated patients ($n = 424$) compared to tDCS ($n = 90$) and DBS ($n = 1$).

Given that PTSD is a highly heterogeneous condition that can be accompanied by distinct psychiatric diagnoses, defining a unique treatment for this patient population can be quite challenging. There has also been considerable variation across trials regarding stimulation parameters, symptomatic response, and the role of adjunctive psychotherapy. Future studies will need to adopt standardized targeting and stimulation parameters and focus on well-defined PTSD subgroups.

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References

- American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders (DSM-5®). American Psychiatric Pub; 2013.
- Richardson LK, Frueh BC, Acierno R. Prevalence estimates of combat-related post-traumatic stress disorder: critical review. *Aust N Z J Psychiatry* 2010;44:4–19.
- Akiki TJ, Abdallah CG. Are There Effective Psychopharmacologic Treatments for PTSD? [Internet]. *J Clin Psychiatry*. 2018. Available from: <https://doi.org/10.4088/jcp.18ac12473>.
- Grasser LR, Javanbakht A. Treatments of Posttraumatic Stress Disorder in Civilian Populations [Internet]. *Curr Psychiatry Rep*. 2019. Available from: <https://doi.org/10.1007/s11920-019-0994-3>.
- Reznikov R, Binko M, Nobrega JN, et al. Deep Brain Stimulation in Animal Models of Fear, Anxiety, and Posttraumatic Stress Disorder. *Neuropsychopharmacology*. 2016;41:2810–2817.
- Gouveia FV, Gidyk DC, Giacobbe P, et al. Neuromodulation Strategies in Post-Traumatic Stress Disorder: From Preclinical Models to Clinical Applications. *Brain Sci* [Internet]. 2019;9. Available from: <https://doi.org/10.3390/brainsci9020045>.
- Langevin J-P, Koek RJ, Schwartz HN, et al. Deep Brain Stimulation of the Basolateral Amygdala for Treatment-Refractory Posttraumatic Stress Disorder. *Biol Psychiatry* 2016;79:e82–e84.
- Van't Wout M, Longo SM, Reddy MK, et al. Transcranial direct current stimulation may modulate extinction memory in posttraumatic stress disorder. *Brain Behav* 2017;7:e00681.
- Kozel FA, Motes MA, Didehbandi 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.
- Nam D-H, Pae C-U, Chae J-H. Low-frequency, Repetitive Transcranial Magnetic Stimulation for the Treatment of Patients with Posttraumatic Stress Disorder: a Double-blind, Sham-controlled Study. *Clin Psychopharmacol Neurosci* 2013;11:96–102.
- Noble LJ, Meruva VB, Hays SA, et al. Vagus nerve stimulation promotes generalization of conditioned fear extinction and reduces anxiety in rats. *Brain Stimul* 2019;12:9–18.
- Peña DF, Childs JE, Willett S, et al. Vagus nerve stimulation enhances extinction of conditioned fear and modulates plasticity in the pathway from the ventromedial prefrontal cortex to the amygdala. *Front Behav Neurosci* 2014;8:327.
- George MS, Ward HE Jr, Ninan PT, et al. A pilot study of vagus nerve stimulation (VNS) for treatment-resistant anxiety disorders. *Brain Stimul* 2008;1:112–121.
- Rae Olmsted KL, Bartoszek M, Mulvaney S, et al. Effect of Stellate Ganglion Block Treatment on Posttraumatic Stress Disorder Symptoms: A Randomized Clinical Trial. *JAMA Psychiatry* 2019;1–9.
- Hanling SR, Hickey A, Lesnik I, et al. Stellate Ganglion Block for the Treatment of Posttraumatic Stress Disorder: A Randomized, Double-Blind, Controlled Trial. *Reg Anesth Pain Med* 2016;41:494–500.
- Ahmadi N, Moss L, Hauser P, et al. Clinical outcome of maintenance electroconvulsive therapy in comorbid Posttraumatic Stress Disorder and major depressive disorder. *J Psychiatr Res* 2018;105:132–136.
- Kaster TS, Goldbloom DS, Daskalakis ZJ, et al. Electroconvulsive therapy for depression with comorbid borderline personality disorder or post-traumatic stress disorder: A matched retrospective cohort study. *Brain Stimul* 2018;11:204–212.
- Ahmadizadeh MJ, Rezaei M, Fitzgerald PB. Transcranial direct current stimulation (tDCS) for post-traumatic stress disorder (PTSD): A randomized, double-blinded, controlled trial. *Brain Res Bull* 2019;153:273–278.
- Koek RJ, Roach J, Athanasiou N, et al. Neuromodulatory treatments for post-traumatic stress disorder (PTSD). *Prog Neuro-Psychopharmacol Biol Psychiatry* 2019;92:148–160.
- VanElzakker MB, Staples-Bradley LK, Shin LM. The Neurocircuitry of Fear and PTSD [Internet]. *Sleep and Combat-Related Post Traumatic Stress Disorder*. 2018. p. 111–125. Available from: https://doi.org/10.1007/978-1-4939-7148-0_10.
- Frymly LD, Pelic CG, Acierno R, et al. Exposure Therapy and Simultaneous Repetitive Transcranial Magnetic Stimulation: A Controlled Pilot Trial for the Treatment of Posttraumatic Stress Disorder. *J. ECT* [Internet]. 2018; Available from: <https://doi.org/10.1097/YCT.0000000000000505>.
- 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;6:377–383.
- Watts BV, Landon B, Groft A, et al. A sham controlled study of repetitive transcranial magnetic stimulation for posttraumatic stress disorder. *Brain Stimul* 2012;5:38–43.
- Boggio PS, Rocha M, Oliveira MO, et al. Noninvasive brain stimulation with high-frequency and low-intensity repetitive transcranial magnetic stimulation treatment for posttraumatic stress disorder. *J Clin Psychiatry* 2010;71:992–999.
- Osuch EA, Benson BE, Luckenbaugh DA, et al. Repetitive TMS combined with exposure therapy for PTSD: a preliminary study. *J Anxiety Disord* 2009;23:54–59.
- Cohen H, Kaplan Z, Kotler M, et al. Repetitive transcranial magnetic stimulation of the right dorsolateral prefrontal cortex in post-traumatic stress disorder: a double-blind, placebo-controlled study. *Am J Psychiatry* 2004;161:515–524.
- Kozel FA, Andrew Kozel F, Van Trees K, et al. One hertz versus ten hertz repetitive TMS treatment of PTSD: A randomized clinical trial [Internet]. *Psychiatry Research*. 2019. p. 153–162. Available from: <https://doi.org/10.1016/j.psychres.2019.01.004>.
- Philip NS, Barredo J, Aiken E, et al. Theta-Burst Transcranial Magnetic Stimulation for Posttraumatic Stress Disorder. *Am J Psychiatry* 2019;176:939–948.
- van't Wout-Frank M, Shea MT, Larson VC, et al. Combined transcranial direct current stimulation with virtual reality exposure for posttraumatic stress disorder: Feasibility and pilot results. *Brain Stimul*. [Internet]. 2018; Available from: <https://doi.org/10.1016/j.brs.2018.09.011>.

30. Ahmadizadeh, Rezaei. Unilateral right and bilateral dorsolateral prefrontal cortex transcranial magnetic stimulation in treatment post-traumatic stress disorder: A randomized controlled study. *Brain Res Bull* 2018;140:334–340.
31. Carpenter LL, Conelea C, Tyrka AR, et al. 5 Hz Repetitive transcranial magnetic stimulation for posttraumatic stress disorder comorbid with major depressive disorder. *J Affect Disord* 2018;235:414–420.
32. Philip NS, Barredo J, van't Wout-Frank M, et al. Network Mechanisms of Clinical Response to Transcranial Magnetic Stimulation in Posttraumatic Stress Disorder and Major Depressive Disorder. *Biol Psychiatry*. 2018;83:263–272.
33. Woodside DB, Colton P, Lam E, et al. Dorsomedial prefrontal cortex repetitive transcranial magnetic stimulation treatment of posttraumatic stress disorder in eating disorders: An open-label case series. *Int J Eat Disord* 2017;50:1231–1234.
34. Philip NS, Ridout SJ, Albright SE, et al. 5-Hz Transcranial Magnetic Stimulation for Comorbid Posttraumatic Stress Disorder and Major Depression. *J Trauma Stress* 2016;29:93–96.
35. Oznur T, Akarsu S, Celik C, et al. Is transcranial magnetic stimulation effective in treatment-resistant combat related posttraumatic stress disorder? *Neurosciences*. 2014;19:29–32.
36. Rosenberg PB, Mehndiratta RB, Mehndiratta YP, et al. Repetitive transcranial magnetic stimulation treatment of comorbid posttraumatic stress disorder and major depression. *J Neuropsychiatr Clin Neurosci* 2002;14:270–276.
37. Hampstead BM, Mascaro N, Schlaefelin S, et al. Variable symptomatic and neurophysiologic response to HD-tDCS in a case series with posttraumatic stress disorder. *Int. J. Psychophysiol.* [Internet]. 2019; Available from: <https://doi.org/10.1016/j.jpsycho.2019.10.017>.
38. Grisaru N, Amir M, Cohen H, et al. Effect of transcranial magnetic stimulation in posttraumatic stress disorder: a preliminary study. *Biol Psychiatry* 1998;44:52–55.
39. Saunders N, Downham R, Turman B, et al. 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*. 2015;21:271–278.
40. Petrosino NJ, Zandvakili A, Carpenter LL, et al. Pilot Testing of Peak Alpha Frequency Stability During Repetitive Transcranial Magnetic Stimulation. *Front Psychiatry* 2018;9:605.
41. Karris BC, Capobianco M. Subconjunctival hemorrhage after high frequency right-sided repetitive transcranial magnetic stimulation. *Brain Stimul* 2014;7:494–495.
42. Nakama H, Garcia A, O'Brien K, et al. Case report of a 24-year-old man with resolution of treatment-resistant major depressive disorder and comorbid PTSD using rTMS. *J ECT* 2014;30:e9–e10.
43. Tillman GD, Kimbrell TA, Calley CS, et al. Repetitive Transcranial Magnetic Stimulation and Threat Memory: Selective Reduction of Combat Threat Memory P300 Response After Right Frontal-Lobe Stimulation. *J Neuropsychiatr* 2011;23:40–47.
44. McCann UD. Repetitive Transcranial Magnetic Stimulation for Posttraumatic Stress Disorder [Internet]. *Archives of General Psychiatry*. 1998. p. 276–279. Available from: <https://doi.org/10.1001/archpsyc.55.3.276>.
45. Oberman L, Edwards D, Eldaief M, et al. Safety of theta burst transcranial magnetic stimulation: a systematic review of the literature. *J Clin Neurophysiol* 2011;28:67–74.
46. Gonsalvez I, Baror R, Fried P, et al. Therapeutic Noninvasive Brain Stimulation in Alzheimer's Disease. *Curr Alzheimer Res* 2017;14:362–376.
47. Rossi S, Hallett M, Rossini PM, et al. Safety, ethical considerations, and application guidelines for the use of transcranial magnetic stimulation in clinical practice and research. *Clin Neurophysiol* 2009;120:2008–2039.
48. Reato D, Salvador R, Bikson M, et al. Principles of Transcranial Direct Current Stimulation (tDCS): Introduction to the Biophysics of tDCS [Internet]. *Practical Guide to Transcranial Direct Current Stimulation*. 2019. p. 45–80. Available from: https://doi.org/10.1007/978-3-319-95948-1_2.
49. Thair H, Holloway AL, Newport R, et al. Transcranial Direct Current Stimulation (tDCS): A Beginner's Guide for Design and Implementation [Internet]. *Frontiers in Neuroscience*. 2017. Available from: <https://doi.org/10.3389/fnins.2017.00641>.
50. Dandekar MP, Fenoy AJ, Carvalho AF, et al. Deep brain stimulation for treatment-resistant depression: an integrative review of pre-clinical and clinical findings and translational implications. *Mol Psychiatry* 2018;23:1094.
51. Guzzi G, Della Torre A, Chirchiglia D, et al. Critical reappraisal of DBS targeting for movement disorders. *J Neurosurg Sci* 2016;60:181–188.
52. Krishnan S, Pisharady KK, Divya KP, et al. Deep brain stimulation for movement disorders. *Neurol India* 2018;66:S90–S101.
53. Lozano AM, Hutchison WD, Kalia SK. What Have We Learned About Movement Disorders from Functional Neurosurgery? *Annu Rev Neurosci* 2017;40:453–477.
54. Rapinesi C, Kotzalidis GD, Ferracuti S, et al. Brain Stimulation in Obsessive-Compulsive Disorder (OCD): A Systematic Review. *Curr Neuropsychopharmacol* 2019;17:787–807.
55. Graat I, Figue M, Denys D. The application of deep brain stimulation in the treatment of psychiatric disorders. *Int Rev Psychiatry* 2017;29:178–190.
56. Mallinckrodt CH, Zhang L, Prucka WR, et al. Signal detection and placebo response in schizophrenia: parallels with depression. *Psychopharmacol Bull* 2010;43:53–72.
57. Agid O, Siu CO, Potkin SG, et al. Meta-regression analysis of placebo response in antipsychotic trials, 1970–2010. *Am J Psychiatry* 2013;170:1335–1344.
58. Rutherford BR, Pott E, Tandler JM, et al. Placebo response in antipsychotic clinical trials: a meta-analysis. *JAMA Psychiatry* 2014;71:1409–1421.
59. Mancini M, Wade AG, Perugi G, et al. Impact of patient selection and study characteristics on signal detection in placebo-controlled trials with antidepressants [Internet]. *J Psychiatr Res*. 2014. p. 21–29. Available from: <https://doi.org/10.1016/j.jpsychires.2014.01.001>.

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