Brain stimulation in posttraumatic stress disorder

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Posttraumatic stress disorder (PTSD) is a complex, heterogeneous disorder that develops following trauma and often includes perceptual, cognitive, affective, physiological, and psychological features. PTSD is characterized by hyperarousal, intrusive thoughts, exaggerated startle response, flashbacks, nightmares, sleep disturbances, emotional numbness, and persistent avoidance of trauma-associated stimuli. The efficacy of available treatments for PTSD may result in part from relief of associated depressive and anxiety-related symptoms in addition to treatment of core symptoms that derive from reexperiencing, numbing, and hyperarousal. Diverse, heterogeneous mechanisms of action and the ability to act broadly or very locally may enable brain stimulation devices to address PTSD core symptoms in more targeted ways. To achieve this goal, specific theoretical bases derived from novel, well-designed research protocols will be necessary. Brain stimulation devices include both long-used and new electrical and magnetic devices. Electroconvulsive therapy (ECT) and Cranial electrotherapy stimulation (CES) have both been in use for decades; transcranial magnetic stimulation (TMS), magnetic seizure therapy (MST), deep brain stimulation (DBS), transcranial Direct Current Stimulation (tDCS), and vagus nerve stimulation (VNS) have been developed recently, over approximately the past twenty years. The efficacy of brain stimulation has been demonstrated as a treatment for psychiatric and neurological disorders such as anxiety (CES), depression (ECT, CES, rTMS, VNS, DBS), obsessive-compulsive disorder (OCD) (DBS), essential tremor, dystonia (DBS), epilepsy (DBS, VNS), Parkinson Disease (DBS), pain (CES), and insomnia (CES). To date, limited data on brain stimulation for PTSD offer only modest guidance. ECT has shown some efficacy in reducing comorbid depression in PTSD patients but has not been demonstrated to improve most core PTSD symptoms. CES and VNS have shown some efficacy in reducing anxiety, findings that may suggest possible utility in relieving PTSD-associated anxiety. Treatment of animal models of PTSD with DBS suggests potential human benefit. Additional research and novel treatment options for PTSD are urgently needed. The potential usefulness of brain stimulation in treating PTSD deserves further exploration.

Keywords: Brain stimulation; PTSD; ECT; TMS; depression; anxiety

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are available, particularly outside of the United States. However, population-based studies in Germany suggest a lower lifetime prevalence of approximately 2.0% (Spitzer et al., 2009). These data are consistent with findings from a large multinational European study that found a lifetime prevalence of 1.9% (Alonzo et al., 2004). However, data from the Netherlands are much more consistent with US rates, indicating lifetime prevalence of 7.4% (De Vries & Offl, 2009). Also, the National Comorbidity Survey Replication found lower prevalence rates in the United States (6.8%) and proposed alternatives to the standard diagnostic and statistical manual, 4th Ed. (DSM-IV) model that suggested prevalence rates below 6% (Elhai et al., 2009).

The main therapeutic approaches available for a patient with history of recent trauma include support, encouragement, and psychoeducation. However, chronic PTSD patients need more comprehensive treatments. The efficacy of available treatments for PTSD may result in part from relief of associated depressive and anxiety-related symptoms, in addition to treatment of core symptoms that derive from reexperiencing, numbing, and hyperarousal, and 41% of subjects fail to respond to pharmacotherapy (Stein, Ipser, & Seedat, 2006). Diverse, heterogeneous mechanisms of action and the ability to act broadly or very locally may eventually enable brain stimulation devices to address PTSD core symptoms in more targeted ways than are currently used in standard clinical care.

**Overview of brain stimulation**

Brain stimulation treatments have been part of the psychiatric armamentarium for the past 70 years since electroconvulsive therapy (ECT) was introduced in 1938. For many years, ECT has been recognized as a highly effective treatment option for severe depression as well as acute mania and catatonia. Today, ECT continues to be investigated and refined (Deng, Lisanby, & Peterchev, 2009; Lisanby et al., 2003a, 2003b; Payne & Prudic, 2009a,b; Spellman, Peterchev, & Lisanby, 2009; Sackeim, et al., 2008), whereas new brain stimulation modalities have emerged, and other older methods have been updated. Nearly five decades passed before non-invasive and non-convulsive treatments were developed in the form of magnetic stimulation of the brain (Barker, Jalinous, & Freeston, 1985). Recent FDA (US Food and Drug Administration) approval of repetitive transcranial magnetic stimulation (rTMS; in 10/08) for the treatment of major depression has increased interest in new psychiatric somatic treatments.

However, these modalities have not yet been intensively studied in PTSD. Brain stimulation, no longer limited to ECT, includes a wide spectrum of therapeutic modalities: transcranial magnetic stimulation (TMS), magnetic seizure therapy (MST), deep brain stimulation (DBS), direct (Epidural) cortical stimulation (DCS), vagus nerve stimulation (VNS), transcranial direct current stimulation (tDCS), and cranial electrotherapy stimulation (CES).

**Overview of brain stimulation modalities**

Brain-stimulating modalities along with their FDA approval status and indications are outlined in Table 1. Although all directly modulate neuronal activity, invasiveness and focality vary greatly (i.e., DBS is both most invasive and most focal, whereas tDCS, CES, and ECT are relatively less focal and less invasive.

**Cranial electrotherapy stimulation (CES)**

Cranial electrical stimulation (CES) involves application of a small (less than 2 mA) alternating current to affect brain function. It has been widely used clinically in Europe since 1950 and in the United States since the 1960s (Kirsch & Smith, 2000). CES became FDA sanctioned for the treatment of depression, anxiety, and insomnia in 1978. CES is an externally administered, low-power treatment that does not require sedation. It is relatively inexpensive and can be self or professionally administered, unlike all other brain stimulation modalities that must be professionally administered.

**Deep brain stimulation (DBS)**

Deep brain stimulation (DBS) requires a surgically implanted electrode that repeatedly administers electrical stimulation (Rowny & Lisanby, 2008).

As a result, DBS can be administered during ordinary activity, wherever the patient goes. Because the DBS electrode has multiple contacts that can be activated, it is highly focal and can be used to target specific brain regions. As indicated in Table 1, it has been primarily used for neurological indications. However, positive results have been noted for DBS with various targets in patients with refractory obsessive-compulsive disorder (OCD) (Denys et al., 2010; Goodman et al., 2010). Mayberg et al. reported positive results of subgenual cingulate stimulation for patients with severe treatment-resistant depression (TRD) (Mayberg et al., 2005). The resulting symptomatic improvement has been attributed to a restoration of balance between activity of limbic and frontal cortical areas (Hamani et al., 2009; Mayberg et al., 2005). DBS often improves motor symptoms in Parkinson’s disease but may exacerbate cognitive and impulsivity problems (Haebig, 2010; Haebig, et al., 2009; Voon et al., 2008; Witt et al., 2008). Scientific and ethical issues concerning the use of DBS are being actively debated (Rabins et al., 2009).
Direct (epidural) cortical stimulation (DCS), or direct cortical electrical stimulation (DCES)

This treatment is less well known, and is frequently performed concurrently with electrocorticography, when electrodes are placed directly on the exposed surface of the brain to record electrical activity from the cerebral cortex. An external stimulator may provide small electrical currents (2–4 mA for somatosensory stimulation, and approximately 15 mA for cognitive stimulation). The patient must be alert and interactive for mapping procedures focused on primary motor, sensory, and language function (Schuh & Drury, 1996). Although craniotomy is required for implantation, this device could also be used as patients go about their daily lives. Efforts to develop DCS as a therapeutic brain stimulator have not yet resulted in a widely available device. A major concern is the possibility of seizure induction.

Electroconvulsive therapy

Electricity is applied transcranially via electrodes placed on the scalp to induce a seizure under anesthesia (Rowny & Lisanby, 2008). These treatment supply larger amounts of current over a shorter period of time, and treatment can be either bilateral or unilateral. Seizure induction is necessary for the therapeutic impact of ECT, which leads to hormonal (e.g., prolactin, oxytocin, brain-derived neurotrophic growth factor), neurotransmitter, oscillatory, and hypothalamic-pituitary-adrenal axis modulation as well as alterations in synaptic plasticity through still incompletely understood mechanisms. New ECT methodology and applications continue to be developed, for example, focal electrically administered seizure therapy, a novel, experimental, more focal form of ECT (Spellman et al., 2009). ECT is in widespread use worldwide in clinical treatment for a range of indications.

Table 1. Brain stimulation modalities

| External stimulation | Electrical | Non-convulsive | Magnetic | Non-convulsive |
|----------------------|------------|----------------|----------|----------------|
| ECT                  | CES        | MST            | rTMS     |
| FDA: Class III device (Depression), 1979, no PMA | FDA: Sanctioned 1991 (sleep and anxiety) use may or may not be supervised by a professional tDCS No FDA approved Indication | No FDA approved indication | FDA: General approval (Depression (TRx1); Migraine prophylaxis) 2008; trials ongoing |
| Internal stimulation/implanted | Internal stimulation/implanted | Internal stimulation/implanted | Internal stimulation/implanted |
| N/A                  | DBS        | N/A            | N/A      |
|                      | FDA: General Approval 1997 (Essential Tremor); General Approval 2002 (Parkinson’s); HDE 2003 (Dystonia); HDE 2009 (OCD); Trial completed, PMA decision pending (Epilepsy); Trials ongoing (TRD) DCS No FDA approval; experimental only VNS | FDA: General Approval 1997 (Epilepsy); General Approval 2005 (TRD) DCS No FDA approval; experimental only VNS | FDA: General Approval 1997 (Epilepsy); General Approval 2005 (TRD) |

Key source: www.fda.gov
HDE, humanitarian device exemption; PMA, pre market approval; TRD, treatment resistant depression; CES, cranial electrical stimulation; DBS, deep brain stimulation; VNS, vagus nerve stimulation; ECT, electroconvulsive therapy; DCS, direct (epidural) cortical stimulation; tDCS, transcranial direct current stimulation; OCD, obsessive-compulsive disorder; MST, magnetic seizure therapy; rTMS, repetitive Transcranial Magnetic Stimulation.
it continues to be studied to improve clinical efficacy to reduce side effects, and to probe basic science questions. The FDA (1979) defines it as a Class III device.

**Magnetic seizure therapy**

High-intensity TMS is applied under anesthesia, to provide more focal seizures than ECT (Rowny & Lisanby, 2008). The antidepressant efficacy of MST is not yet established (Lisanby et al., 2003a). However, MST causes physiologically different seizures than ECT (Cycowicz, Luber, Spellman, & Lisanby, 2009; Lisanby et al., 2003a). The potential utility of more focal stimulation is suggested by neuroanatomical studies in which animals appear to show fewer cellular changes in the hippocampus; additional evidence suggests reduced impairment of memory and cognition compared to ECT (Dwork et al., 2004, 2009; Lisanby et al., 2003b; Kosel, Frick, Lisanby, Fisch, & Schlaepfer, 2003; Moscrip, Terrace, Sackeim, & Lisanby, 2004, 2006).

MST is magnetic, convulsive, and requires sedation during treatment. Currently, MST has no FDA approved indication.

**Repetitive transcranial magnetic stimulation**

Rapidly alternating magnetic fields are applied to the scalp to induce small, focal electrical currents in superficial cortex (Rowny & Lisanby, 2008). Pretreatment preparation includes obtaining a motor threshold (determining the intensity of stimulation needed to cause twitching of a muscle in the hand), to individualize the dosage (typically between 80 and 120% of an individual’s motor threshold). Currently, in increasing use for clinical treatment of depression, it is also being investigated for a variety of psychiatric indications, including anxiety, PTSD, OCD, schizophrenia, and autism. The FDA granted General approval for use of rTMS for Depression (Trx1) and for Migraine prophylaxis (both in 2008). A number of TMS devices with variable parameters have been and continue to be developed (Peterchev, Jalinous, & Lisanby, 2008). These controllable pulse parameter TMS (cTMS) devices would allow greater control over stimulation parameters than is possible with current sine wave stimulation methodology.

**Transcranial direct current stimulation**

Weak direct electrical currents are applied to the scalp via sponge electrodes to polarize underlying brain tissue (Priori, Berardelli, Rona, Accornero, & Manfredi, 1998; Rowny & Lisanby, 2008; Wagner et al., 2007). Like rTMS, tDCS leads to changes in excitability of the cortex that extends beyond the period of stimulation. A recent study suggests that tDCS may also induce changes in brain synchronization and functional organization (Polania, Nitsche, & Paulus, 2010). This stimulation has been applied to a number of targets, including frontal cortical areas in the experimental treatment of depression and to the anterior temporal lobes in a paradigm that indicated a positive impact on visual memory (Chi, Fregni, & Snyder, 2010). There is no current FDA-approved indication for tDCS. As with other brain stimulation modalities, tDCS is under investigation to optimize its focality, safety, and efficacy (Bikson et al., 2008; Datta et al., 2009).

**Vagus nerve stimulation**

Electrical pulses are applied extracranially to the vagus nerve to activate vagal afferents (Rowny & Lisanby, 2008). VNS differs from the other modalities discussed in not providing direct stimulation to the cortex. VNS currently requires an implanted device, although similar stimulators not involving surgical implantation are in development. As with other implantable technologies, stimulation may continue wherever patients travel. VNS acts broadly via activating the parasympathetic nervous system. VNS received FDA General Approval in 1997 for Epilepsy and in 2005 for TRD.

The objective of this review is to ask whether specific brain stimulation modalities might be theoretically appropriate, safe, and possibly efficacious for treatment of individuals with PTSD. To answer this question, we surveyed the available literature, few studies using only a subset of available brain stimulation modalities. We discuss these minimal empirical data, review other pertinent results, and examine how brain areas relevant to PTSD could possibly be modulated by brain-stimulating devices. While acknowledging needed skepticism in the face of far too little evidence to date, we hope to present the currently available information and provide an argument for additional research into brain stimulation as a treatment for PTSD.

**Neurocircuitry of PTSD – potential biological targets**

Although clearly in its early stages of development, and not universally confirmed, evidence from several studies indicates that abnormal function and size of specific brain regions may contribute to or result from PTSD symptoms. The current understanding of PTSD neurocircuitry suggests the importance of the medial prefrontal cortex, hippocampus, and amygdala (Rauch, Shin, Whalen, & Pitman, 1998). Additionally, a meta-analysis of 19 studies and 175 subjects with PTSD suggested the importance of prefrontal, insular, and anterior cingulate cortex as well as thalamus and amygdala (Etkin & Wager, 2007). Based on this model, cortical stimulation might modulate brain activity associated with PTSD symptoms; amygdala stimulation could also potentially be useful. Although targeting of subcortical limbic regions may be technically challen-
Amygdala and reciprocal functional areas

Many studies have reported exaggerated amygdala activation in PTSD. Enhanced responsivity has been observed in PTSD versus control groups during fear conditioning (Bremner et al., 2005), in response to trauma-related injury (Shin et al., 1997), trauma-related pictures or words (Driessen et al., 2004), and fearful facial expressions (Bryant et al., 2008; Rauch et al., 2000). Some studies reported that amygdala hyperactivity is positively correlated with PTSD symptom severity (Protopopescu et al., 2005; Rauch et al., 2000); cognitive behavioral therapy (CBT) leads to decreases in amygdala activation (Felmingham et al., 2007). However, the upregulated amygdala response has not been confirmed in several PTSD studies (Bremner et al., 1999a; Lanius et al., 2001) and decreased responsivity has also been reported (Phan, Britton, Taylor, Fig, & Liberonz, 2006). These variable results may be explained by a model including separate PTSD subtypes, with either emotional overmodulation (dissociative, with elevated cortical activity) or undermodulation (hyperaroused, with decreased cortical activity) (Lanius et al., 2010). Supporting this theory, the ventromedial prefrontal cortex (vmPFC) and rostral anterior cingulate cortex have also been found to be hypo-responsive, failing to inhibit the amygdala in response to traumatic script-driven imagery (Bremner et al., 1999a; Britton, Phan, Taylor, Fig, & Liberonz, 2005), trauma-related stimuli (Bremner et al., 1999b; Hou et al., 2007; Yang, Wu, Hsu, & Ker, 2004), and negative, non-traumatic stimuli (Kim et al., 2007; Lanius et al., 2003; Phan et al., 2006; Shin et al., 2005; Williams et al., 2006) as well as during extinction (Bremner et al., 2005). Furthermore, vmPFC activation has been inversely correlated with PTSD symptom severity (Britton et al., 2005; Dickie et al., 2008; Hopper, Frewen, Van der Kolk, & Lanius, 2007; Kim et al., 2007; Shin et al., 2004a, 2005; Williams et al., 2006) and positively correlated with prescan cortisol levels (Liberonz et al., 2007). Finally, increased vmPFC activation following treatment has been associated with symptomatic improvement in some studies (Felmingham et al., 2007; Lansing, Amen, Hanks, & Rudy, 2005; Peres et al., 2007; Seedat et al., 2004).

Hippocampus

The majority of studies have found diminished hippocampal volumes in PTSD patients (Bossini et al., 2008; Bremner et al., 1995, 2003a; Gilbertson et al., 2002; Woon & Hedges, 2008). However, it remains to be determined whether decreased volume can explain abnormal hippocampal activation in PTSD. Supporting this connection, one twin study suggested diminished hippocampal volume as a familial risk factor for developing PTSD following psychological trauma (Gilbertson et al., 2002).

Some functional neuroimaging studies have reported decreased hippocampal activation during symptomatc states (Bremner et al., 1999a) and during memory tasks that involve both neutral and emotionally valent stimuli (Astur et al., 2006; Bremner et al., 2003a,b; Moores et al., 2008; Shin et al., 2004b). Other studies have reported reductions in resting hippocampal glucose metabolism in patients with PTSD (Molina, Isoardi, Prado, & Bentolila, 2007) and increased hippocampal activation following successful treatment (Peres et al., 2007). Additional evidence suggests that hippocampal volumes may increase following treatment with seroton reuptake inhibitors (Bossini et al., 2007; Vermetten, Vythilingam, Southwick, Charney, & Bremner, 2003).

In addition to these serotonergic changes, a recent positron emission tomography (PET) study found decreased [11C]flmazenil binding in the hippocampus, thalamus, and cortex, suggesting diminished hippocampal GABA function in PTSD (Geuze et al., 2008a). In contrast to the above results indicating impaired hippocampal function in PTSD, several studies have reported increased hippocampal activation in PTSD (Geuze et al., 2007, 2008b; Sachinvala, Kling, Suffin, Lake, & Cohen, 2000; Semple et al., 2000; Thomaes et al., 2009; Werner et al., 2009) and positive correlations between hippocampal activation and PTSD symptom severity (Osuch et al., 2001; Shin et al., 2004b). Yet, other studies have reported inverse correlations between hippocampal volumes and verbal memory deficits (Bremner et al., 1995), combat exposure severity (Gurvits et al., 1996), dissociative symptom severity (Bremner et al., 2003a; Stein, Koverola, Hanna, Torchia, & McClarty, 1997), depression severity (Villarreal et al., 2002), and PTSD symptom severity (Bremner et al., 2003a; Gilbertson et al., 2002; Villarreal et al., 2002).

The variable results discussed above indicate the need for further study and improved insight into the neurobiology of PTSD, but also suggest that the hippocampus would not be a target for focal brain stimulation, although more global interventions such as ECT and MST do cause mossy fiber sprouting in the dentate gyrus of the hippocampus (Dwork et al., 2009)

Insular cortex

Insular cortex hyperactivity in PTSD has been observed in studies involving script-driven imagery (Lanius et al., 2007; Lindauer et al., 2008), fear conditioning and extinction (Bremner et al., 2005), the anticipation of negative images (Simmons et al., 2008), the retrieval of emotional or neutral stimuli (Bremner et al., 2003b; Werner et al., 2009; Whalley, Rugg, Smith, Dolan, & Brewin, 2009), aversive smells and painful stimuli (Geuze et al., 2007; Vermetten, Schmahl, Southwick, & Bremner, 2003).
Evidence for brain stimulation in PTSD

Here, we summarize data from the major brain stimulation modalities that have been studied in PTSD. Particular emphasis will be placed on rTMS that may be useful for focal stimulation and study of specific brain regions proposed to be involved in PTSD symptomatology. Because there are very few controlled studies for these paradigms, we also discuss several uncontrolled studies and case reports.

Transcranial magnetic stimulation

In the earliest report of rTMS in PTSD by McCann et al. (1988), two patients with pretreatment fludeoxyglucose PET scans showing increased right cerebral metabolism relative to healthy controls received 1Hz rTMS (80% of motor threshold) delivered to the right dorsolateral prefrontal cortex. One patient had 17 daily treatments of 1200 pulses over a 1-month period and reported improvement in PTSD symptoms but not reductions in overall anxiety symptoms; the second patient received 1 Hz rTMS stimulation over the same region 30 times during a 6-week period and also reported significant symptomatic improvement. Unfortunately, relapse occurred within the 1-month period following rTMS discontinuation.

On repeat scans following rTMS treatment, normalization of right frontal and paralimbic metabolic hyperactivity was noted when compared to the baseline images. However, given the lack of treatment controls, the observed clinical improvement could be secondary to placebo effect or the natural course of illness rather than specific treatment effects.

In another open-label study of 10 PTSD patients, a single session of low-frequency (0.3 Hz) TMS at 100% of motor threshold was applied bilaterally (Grisaru, Amir, Cohen, & Kaplan, 1998). Transient improvement was noted from 1 to 7 days after the stimulation on both self and observer ratings of avoidance, anxiety, and somatization.

In PTSD patients with comorbid depression, rTMS over the left frontal cortex was applied adjunctively at 90% of motor threshold, over 10 days, although two-thirds of the patients showed an antidepressant response with significant improvement in insomnia, anxiety, and hostility, and a negligible improvement in the core PTSD symptoms was noted (Rosenberg et al., 2002). A study by Cohen et al. (2005) randomly assigned 24 PTSD patients to receive rTMS at low frequency (1 Hz) or high frequency (10 Hz) or sham rTMS in a double-blind trial. Ten daily treatment sessions were provided over the course of 2 weeks; PTSD severity, depression, and anxiety were assessed before, during, and after completion of treatment. Relative to 1-Hz or sham, 10 daily treatments of 10 Hz rTMS at 80% of motor threshold over the right dorsolateral prefrontal cortex improved anxiety and was also found to markedly improve PTSD core symptoms (i.e., reexperiencing, avoidance).

A recent double-blind, sham-controlled trial, randomly assigned 30 patients with PTSD to receive 10 treatments over 2 weeks of 20 Hz rTMS of the right dorsolateral prefrontal cortex (DLPFC), 20 Hz rTMS of the left DLPFC, or sham rTMS (Boggio et al., 2009). This study found that stimulation of both the left and right DLPFC led to a significant improvement in PTSD symptoms (i.e., hyperarousal, intrusive thoughts, vigilance, withdrawal, emotional numbness, etc.), but that right-sided rTMS was more efficacious. These effects on PTSD were persistent and remained significant when patients were assessed 3 months after treatment. In addition, depression, assessed by HAM-D at days 5 and 10, improved significantly after left-sided rTMS, but similar improvement was not seen with right-sided rTMS. However, right-sided treatment was found to significantly improve anxiety measured by HAM, at days 5 and 10 Trends toward improvement in cognitive function, assessed by Stroop Test, Raven Colored Progressive Matrices, Wisconsin Card Sorting Test, and Digit Span Test, were noted with both right- and left-sided rTMS and right-sided rTMS produced significant improvement in verbal fluency. These findings suggest that modulatation of the prefrontal cortex, particularly right DLPFC, may be useful in alleviating the core symptoms of PTSD.

Brain stimulation may also be useful in combination with psychotherapy to facilitate modification of traumatic memories via stimulation of cortical, affective, and association areas.

Very recently, deep transcranial magnetic stimulation (dTMS) has shown promise in augmenting antidepressant medications to improve depression via deep modulation over prefrontal areas, although negative cognitive-emotional reactivation was found to interfere with the therapeutic effects of dTMS (Isserles et al., 2010). Future studies may use TMS to investigate the role of other regions and networks in PTSD. The vmPFC may provide one such target as its activity is often, though not always, reduced relative to an overactive amygdala in PTSD (Lanius et al., 2010). These studies will be facilitated by continued development of TMS technology that can focally reach deeper cortical
Cranial electrotherapy stimulation (CES)
Cranial electrical stimulation (CES) technology has been used to treat anxiety, sleep difficulties, depression, addictions, and related conditions since early in the twentieth century. However, there are no published studies of CES for PTSD. A meta-analysis conducted at the Harvard School of Public Health concluded that CES was significantly more effective than sham treatment in improving anxiety but that inconsistent study methodology and lack of blinding complicated interpretation of these data (Klawansky et al., 1995).

Recently, better controlled studies have been performed, which may be relevant in considering this treatment for PTSD: A double-blind placebo-controlled study of 33 dental patients assessed whether CES could be useful for reducing anxiety during routine dental procedures, and found significant reductions of anxiety in the active CES group (Winick, 1999). These results are further supported by an open-label study of 12 patients with Generalized anxiety disorder that found that CES showed promise in reducing anxiety (Bystritsky, Kerwin, & Feusner, 2008). Recently, a feasibility study of CES in breast cancer treatment reported a trend toward reduction in depressive symptoms (Lyon, Schubert, & Taylor, 2010). Another CES-related protocol, subthreshold sine-wave transcutaneous electrical nerve stimulation, was found to reduce some (systolic blood pressure, pulse rate, and anxiety) but not all (diastolic blood pressure, peripheral vascular tension) physiological and psychological markers of stress in 90 healthy subjects exposed to a standardized mental stress, arithmetic performance (Taylor, Lee, & Katims, 1991). A comparison of CES with tDCS suggested that the CES might work by synchronizing and enhancing the efficiency of endogenous neurophysiological activity, rather than simple polarization as seen with tDCS (Zaghi, Acar, Hultgren, Boggio, & Fregni, 2010). In light of these studies, the relative safety and affordability of CES makes it an interesting target for further research in PTSD.

Electroconvulsive therapy
Despite strong evidence for ECT efficacy in relieving treatment-resistant depression, few studies have investigated the efficacy of ECT in PTSD. A 35-year-old woman with war trauma-related PTSD and depression, resistant to pharmacotherapy and psychotherapy, showed significant amelioration of her depression, emotional numbness, and recurrent intrusive thoughts, following treatment with unilateral ECT (Helsley, Sheikh, Kim, & Park, 1999). A similar case report of a 38-year-old woman with medication-resistant major depression and PTSD that emerged after an assault suggested that bilateral ECT could help to improve PTSD symptoms as well as depressive symptoms (Hanretta & Malek-Ahmadi, 2006). Subsequently, a prospective study of 20 patients with severe, chronic, extensively antidepressant-refractory PTSD, who received a fixed course of six bilateral ECT treatments twice weekly as outpatients, reported mean improvements of 40% on the Clinician Administered Posttraumatic Stress Disorder Scale with an 82% response rate (Margoob, Ali, & Andrade, 2010). Treatment gains were maintained at 4–6 month follow-up, and improvements in the core symptoms of PTSD were deemed to be independent of improvements in depression. A retrospective study examining outcomes of ECT in patients with comorbid MDD and PTSD compared pretreatment and posttreatment symptoms using the Montgomery-Asberg Depression Rating Scale and the PTSD Checklist, to determine that ECT led to significant improvement in symptoms of major depression, with some amelioration of PTSD symptoms (Watts, 2007).

These studies suggest that ECT may improve core symptoms of PTSD independent of improvement in depression, and may be a useful treatment option for patients with severe, chronic, treatment refractory PTSD.

Vagus nerve stimulation
An open-label study of adjunctive VNS treatment suggested that this treatment was well tolerated and possibly efficacious in patients with a range of anxiety disorders, including treatment-resistant OCD, panic disorder, or PTSD, who had failed to respond to several medication trials as well as CBT (George et al., 2008).

The authors discuss vagus nerve innervation of brain regions involved in anxiety regulation (i.e., locus coeruleus, orbitofrontal cortex, insula, hippocampus, and amygdala) and suggest that it might be involved in various somatic and cognitive symptoms of anxiety disorders. However, concerns about the efficacy of this highly invasive procedure in the more studied treatment of depression will likely limit further investigation of this treatment for PTSD.

Summary and conclusions
This article reviews the current state of knowledge regarding brain stimulation in the treatment of PTSD. Given minimal available data, it is not yet possible to firmly establish the safety, tolerability, and efficacy of these treatments in this population. However, the increasing momentum of brain stimulation research as well as technical advances such as dTMS, along with the optimization of treatment parameters, offers the possibility that brain stimulation may eventually become an additional useful tool for treating and understanding PTSD.
Technical advances in brain imaging, including PET, functional magnetic resonance imaging, diffusion tensor imaging, and electroencephalography will increase our understanding of PTSD and may help guide development of brain-stimulation techniques.

Although brain stimulation is currently used in the treatment of movement disorders, depression, and OCD, the use of brain stimulation in PTSD remains strictly investigational at this time.

Newer brain stimulation modalities such as MST, TMS, and dTMS offer alternatives to the more established ECT. MST may eventually offer the possibility of a convulsive treatment that is more targeted than ECT. However, neither rTMS nor MST have been shown to be as effective as ECT in treating severe depression (Rowny and Lisanby, 2008) that often accompanies PTSD. Also, TMS does not require anesthesia or analgesia, does not adversely affect memory, and parameters have been adjusted so that this treatment very rarely causes seizures (Chen et al., 1997; Green, Pascual-Leone, & Wasserman, 1997; Rossi, Hallett, Rossini, & Pascual-Leone, 2009; Wasserman, 1998). Furthermore, TMS is non-invasive, can be applied with temporal and spatial focalization, causes negligible discomfort and few side effects relative to medications. As dTMS is further developed, it may become possible to safely stimulate deeper cortical and perhaps subcortical areas important in the pathophysiology of PTSD. ECT may successfully address depression and anxiety that often associate with PTSD, but its ability to address core symptoms remains controversial (Margool, Ali, & Andrade, 2010). Although fewer studies using CES or VNS for PTSD have been performed than using rTMS, these methods also deserve further study. Although CES may be redefined as a condition driven primarily by a complex dysregulation of fear and arousal, rather than the type of anxiety typically seen in non-traumatic anxiety disorders, modalities that show promise for relieving anxiety (e.g., CES) may be useful in treating PTSD. DBS involves highly invasive procedures, and therefore would require much greater evidence before use in PTSD patients. However, animal models suggest potential targets, including the right basolateral nucleus of the amygdala (Langevin, De Salles, Kosoyan, & Krah, 2010) or the dysgranular insular cortex (Stehberg, Levy, & Zangen, 2009). Additionally, work to identify hyper- or hypoactive brain regions may provide additional targets (Hamani et al., 2009; Mayberg et al., 2005).

Although current treatments used in management of PTSD show some efficacy, many patients would benefit from additional treatment options. Current pharmacological treatments better manage the associated depressive and anxiety-related aspects of PTSD than the core symptoms that derive from aberrant fear response and hyperarousal. With further methodological refinement, brain stimulation may provide additional tools for altering the activity of specific brain regions that contribute to these symptoms. In addition to relieving these symptoms, brain stimulation may provide additional insight into disease processes through its influence on neuronal function, from synaptic plasticity to circuit-level oscillations.

The potential relevance of any of the brain-stimulating devices in the treatment of PTSD remains to be determined. Beyond delineation of efficacy, the clinical use of these techniques in volatile patients, such as those with PTSD, will present additional safety and management challenges. For example, even after demonstration of efficacy, the more invasive modalities such as DBS and VNS would likely only be applicable in patients with severe, treatment-resistant symptoms. With these caveats, it is clear that these emerging technologies deserve further research. Future research will enable assessment of efficacy, and may provide additional tools for conceptual understanding and clinical management of PTSD.

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