Neurostimulation for treatment-resistant posttraumatic stress disorder: an update on neurocircuitry and therapeutic targets

M. Benjamin Larkin, MD, PharmD,¹ John P. McGinnis, MD, PhD,¹ Rita I. Snyder, MD,¹ Eric A. Storch, PhD,² Wayne K. Goodman, MD,² Ashwin Viswanathan, MD,¹ and Sameer A. Sheth, MD, PhD¹

¹Department of Neurosurgery and ²Menninger Department of Psychiatry and Behavioral Sciences, Baylor College of Medicine, Houston, Texas

Posttraumatic stress disorder (PTSD) is a widespread and often devastating psychiatric condition. Core symptoms include intrusive and distressing thoughts, heightened reactivity, mood changes, cognitive impairments, and consequent avoidance of trauma-related stimuli. Symptoms of PTSD are often refractory to standard treatments, and neuromodulatory techniques have therefore drawn significant interest among the most treatment-resistant patients. Transcranial magnetic stimulation has demonstrated minimal efficacy, and deep brain stimulation trials are currently ongoing. PTSD is a disorder of neural circuitry; the current understanding includes involvement of the amygdala (basolateral and central nuclei), the prefrontal cortex (ventral medial and dorsolateral regions), and the hippocampus. Neuroimaging and optogenetic studies have improved the understanding of large-scale neural networks and the effects of microcircuitry manipulation, respectively. This review discusses the current PTSD literature and ongoing neurostimulation trials, and it highlights the current understanding of neuronal circuit dysfunction in PTSD. The authors emphasize the anatomical correlations of PTSD's hallmark symptoms, offer another potential deep brain stimulation target for PTSD, and note the need for continued research to identify useful biomarkers for the development of closed-loop therapies. Although there is hope that neuromodulation will become a viable treatment modality for PTSD, this concept remains theoretical, and further research should involve institutional review board–approved controlled prospective clinical studies.

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POSTTRAUMATIC stress disorder (PTSD) symptomatology is seen in many historical documents. Nevertheless, this disorder has only recently been formally defined.¹ PTSD is currently defined as the development of core symptoms after exposure to trauma—either directly experienced, witnessed, or relayed. Hallmarks include intrusive symptoms, persistent avoidance, negative alterations in cognition/mood, and marked alteration in arousal and reactivity > 1 month, which causes clinically significant social impairment.² There is considerable heterogeneity within the disorder among individuals. In combat-re-

lated PTSD, the intrusive and increased arousal symptoms are often more severe.³

The prevalence of PTSD is markedly higher among combat veterans—up to 23% of the 1.64 million veterans returning from Operation Iraqi Freedom/Operation Enduring Freedom will suffer from PTSD.⁴ Furthermore, the financial burden is significant: treatment for all service members in 2005 reached \$1.24 billion.⁵ Current treatments for PTSD include the use of individual or group forms of cognitive behavioral therapy as well as pharmacotherapy. The efficacy of current US FDA–approved

ABBREVIATIONS ACC = anterior cingulate cortex; BLA = basolateral amygdala; CE = central nuclei; DBS = deep brain stimulation; GABAergic = γ -aminobutyric acidergic; mPFC = medial PFC; OFC = orbitofrontal cortex; PAG = periaqueductal gray; PCL = PTSD checklist; PFC = prefrontal cortex; PTSD = posttraumatic stress disorder; RDoC = Research Domain Criteria; TMS = transcranial magnetic stimulation; TR-PTSD = treatment-resistant PTSD; vmPFC = ventral medial PFC.

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medications has been modest.^{6,7} Currently, accepted psychotherapy strategies include prolonged exposure and cognitive processing therapies.⁶

Combat-related PTSD is more severe and has lower rates of remission than noncombat-related PTSD.^{8,9} There is no consensus on the definition of treatment-resistant PTSD (TR-PTSD), but up to one-third of patients with PTSD fail to attain relief with current evidence-based therapies. Despite this, it is not uncommon for those diagnosed with combat-related PTSD to have spontaneous remission. Commonly used outcome assessment tools for PTSD symptoms include the PTSD Checklist (PCL), Clinician-Administered PTSD Scale, and the Hamilton Rating Scales for Anxiety and Depression. Each of these evaluations uses a series of questions to assess the presence and severity of a patient's PTSD or depression symptoms.¹⁰ Eftekhari et al. found that 54.5% of combat veterans had a clinically significant improvement in PCL scores, and 49% of patients no longer screened positive for PTSD with prolonged exposure therapy.¹⁴ As many as 39% of military members will achieve remission by 5 years and up to 55% by 35 years following trauma.^{11,12} A large meta-analysis of 42 studies found that 44% of victims no longer met criteria for PTSD diagnosis at a mean of 40 months from initial diagnosis using standardized measures.¹³ However, when evaluating results of patient-reported treatment outcomes, it is essential to note the minimal clinically important difference for each assessment tool, because small statistically significant changes may be clinically irrelevant.¹⁴ Notably, PTSD symptoms are not continuous and are related to internal and/or external triggers. Therefore, a patient may meet remission criteria during one assessment but not another, which suggests the possibility of overestimating remission rates.¹³

Despite improvements, nearly 60% of individuals still will not achieve remission. Chronic PTSD is linked to decreased life satisfaction, higher rates of depression, and increased suicide risk.¹⁵ One study found a 17% mortality rate over a 6-year follow-up period despite treatment.¹⁶ Thus, novel and effective treatment modalities are needed.

Our understanding of the underlying neurocircuitry must be improved to develop further treatment options for PTSD. There is increasing interest in understanding psychiatric illnesses based on functional domains as opposed to the more categorical typology based on symptom clusters.¹⁷ The National Institute of Mental Health instituted the Research Domain Criteria (RDoC) project in an effort to advance a multidimensional approach to psychiatric disorders that includes neurobiology and genetics.¹⁸ This will facilitate objective symptom measurements across functional domains linked to known neural circuits, which may lead to the discovery of new targets and treatment protocols for invasive and noninvasive brain stimulation techniques.¹⁹ We are unaware of any literature comparing resting-state functional imaging before and after combat deployment, or longitudinal studies of subjects in these populations who ultimately develop PTSD. Future prospective studies identifying these individuals and comparing their functional data to an asymptomatic cohort would also aid in the development of targeted therapies.

Given the need for a comprehensive synthesis of the

existing literature, this review discusses previous neuro-modulatory and ongoing deep brain stimulation (DBS) trials; highlights the current understanding of the neuronal circuit dysfunction in PTSD and anatomical correlations to symptoms; offers an additional DBS target for PTSD; and emphasizes the need for continued research to identify novel and specific biomarkers for future use in closed-loop systems for TR-PTSD.

Methods

We used PubMed, EMBASE, and ClinicalTrials.gov to query articles for all dates with the major search terms including deep brain stimulation (DBS), transcranial magnetic stimulation (TMS), and posttraumatic stress disorder (PTSD). The following criteria were used for article selection: 1) articles in English, 2) human trials, 3) controlled trials, 4) blinded trials, and 5) randomized trials. In total, 605 articles and 2 clinical trials were identified. After title, abstract, and full-text review, the demographics and results from 7 clinical studies and 2 ongoing clinical trials are presented. This search also revealed a dearth of aggregated information in the literature encompassing pathophysiology, neurocircuitry, and neuromodulation strategies, confirming the existence of an information gap that this review is meant to fill.

The Pathophysiology of PTSD

Current Model

PTSD is a complex psychiatric disorder with multiple clinical characteristics; consequently, developing relevant preclinical models has been challenging.²⁰ Animal models are imperfect at best, and current PTSD models are adapted only to investigate the short-term outcomes regarding fear and anxiety in response to trauma.²¹ These models translate poorly to the human clinical experience, in which only a small percentage of those who develop an acute response following trauma will develop PTSD.²² These models typically evaluate fear conditioning and extinction by pairing a neutral conditioned stimulus with an aversive unconditioned stimulus—e.g., an electrical shock—which results in a new fear response to the previously neutral conditioned stimulus.²³ The extinction of this response comes from gradual exposure to the conditioned stimulus in the absence of the unconditioned stimulus and the creation of new memories that suppress the initial fear response. Thus, the extinction of the response is the ability to learn that a particular external stimulus no longer needs to be feared.¹⁰ This process is believed to involve the creation of a new competing memory rather than the erasure of an old one. However, the ability to retain this new memory is thought to be diminished.²⁴

PTSD Symptoms and Circuitry

The symptoms of PTSD are thought to result from reduced top-down control on neuronal circuits, including the amygdala, prefrontal cortex (PFC), and hippocampus, leading to dysfunctional memory processing that continually triggers an overgeneralized fear response.²⁵ It is the failure of fear extinction in environments that are non-threatening but reminiscent of the trauma, as well as a

FIG. 1. Diagram of the putative neurocircuitry and pathophysiology of PTSD. In fear extinction, the experience of the external conditioned stimulus is ultimately dissociated from the unconditioned stimulus. The hippocampus and vmPFC play essential roles in memory discrimination and fear extinction. Their interaction with the BLA complex leads to the activation of either predominantly "fear on" cells, leading to CE activation and fear persistence, or predominately "fear off" cells, leading to CE inhibition and fear extinction. The vmPFC prevents CE cell activation indirectly via dense glutamatergic connections to intercalated cell neurons. In cases of fear persistence, the CE prompts activation in the hypothalamus and PAG, leading to autonomic and behavioral responses.

generalization to other triggers, that underlies the current understanding of PTSD pathophysiology.¹⁰

Neuroimaging has advanced our understanding of the neurocircuitry and areas of involvement in PTSD; however, current modalities lack the spatial and temporal resolution necessary to delineate therapeutic targets better.²⁶ The expanded use of optogenetics in animal models has further advanced the understanding of microcircuits in PTSD; however, the potential clinical application remains unclear and largely theoretical.

Amygdala. The amygdala is composed of distinct nuclei involved in fear conditioning, including the central nuclei (CE), medial nuclei, intercalated cell clusters, and the basolateral amygdala (BLA) complex.²⁷ The BLA complex is composed of mostly (approximately 80%) glutamatergic spiny neurons, which are tonically inhibited by the remaining γ -aminobutyric acid (GABAergic) interneurons. Fear extinction is thought to be associated with an overall increase in GABAergic tone.²⁸ Selective optogenetic activation has helped identify 2 distinct groups of neurons within the amygdala: "fear on" cells, which cause activation of neurons within the CE, and "fear off" cells, which produce CE inhibition.¹⁰ The BLA receives numerous projections from cortical and subcortical regions, including the PFC and hippocampus, and it is responsible for the integration and dissemination of stimuli to the CE. The CE, which contains only GABAergic neurons, then modulates responses from the hypothalamus and brainstem regions, such as the periaqueductal gray (PAG), leading to the physiological (autonomic responses), behavioral (freezing), and the overgeneralization of fear conditioning (Fig. 1).²⁰ Current twin studies suggest that hyperactivity of the amygdala and dorsal anterior cingulate cortex (ACC) predisposes individuals to the development of PTSD.^{29,30}

There are additional hypotheses that regard the amygdala as being intimately involved in behavioral engagement, which implies its involvement with the avoidance symptoms of PTSD. Avoidance behaviors have also been associated with decreased activity in the rostral ACC

and right inferior frontal cortex, as well as hyperactivity in the right superior temporal cortex.²⁶ Avoidance symptoms do not allow for the creation of new memories that compete with the fear-evoking triggers and are central to the impaired fear extinction in PTSD, which is the basis of cognitive and behavioral therapy approaches in PTSD treatment.

The symptoms of altered arousal and reactivity are generally attributed to hypoactivity of the medial PFC (mPFC) and hippocampus, as well as hyperactivity of the amygdala and bed nucleus of the stria terminalis.³¹ Also, individuals with PTSD commonly exhibit aggression to a perceived threat. The neural circuits regulating aggression are not yet fully understood. However, previous studies suggest the involvement of the amygdala, PAG, and locus ceruleus, which is associated with threat detection and with the autonomic response and altered activity in those with PTSD.^{32,33} Other studies demonstrate aggression and impulsive behavior being related to decreased cortical regulation from mPFC structures, ventral medial PFC (vmPFC) and dorsal ACC, which recognize threats and determine the appropriate response—as well as the orbitofrontal cortex (OFC) and BLA, which are essential in the regulation and maintenance of the response.^{34,35}

Prefrontal Cortex. The intrusive symptoms of PTSD are thought to be due to emotional undermodulation (i.e., a failure of cortical inhibition of the limbic system).³⁶ The amygdala is a critical limbic structure associated with emotional reactivity whose inhibition is controlled by the mPFC.³⁷ The mPFC plays a crucial role in regulating conditioned fear.²⁸ The purpose of the vmPFC is to integrate sensory, emotional, environmental, and memory cues, whereas the dorsolateral PFC regulates appropriate behavioral responses.³⁸ Individuals with PTSD demonstrate hypoactivity of the mPFC and a hyperactive amygdala, whereas the extent of fear extinction is associated with the size and activity of vmPFC and amygdala connectivity.^{39,40} Neuroimaging studies of combat veterans demonstrate decreased blood flow in the vmPFC during exposure to

trauma-related stimuli.³⁹ Additionally, those with PTSD show increased insular activity and decreased rostral ACC activity.⁴¹ The insula is thought to have a role in the sensation of interoception and bodily awareness, whereas the rostral ACC regulates attention, emotion, and arousal.^{42,43}

The persistent negative emotional experience found in individuals with PTSD is frequently described as a problem of emotional regulation.²⁶ When presented with negative valence imagery, patients with PTSD have difficulty downregulating emotional reactions, such as sadness and anxiety, compared to those without the disorder.⁴⁴ The constricted affect and decreased interest in previously meaningful activities are thought to be related to a dysfunctional reward processing circuitry that involves many areas, including the ventral tegmental area, amygdala, OFC, insula, ACC, dorsomedial PFC, striatum, and the motor cortex.⁴⁵ These areas are involved in seeking rewarding stimuli as well as experiencing pleasure once such rewards are attained.⁴⁶ Hypoactivity of both the striatum and PFC in response to rewarding stimuli has been shown in people who have PTSD. Decreased activity of the vmPFC, anterior insula, and inferior frontal gyrus is also seen in individuals unable to recognize or name emotional states during situations designed to induce symptoms of PTSD.^{26,47} The activity of the mPFC plays a key role in both reward and depression-like behavior; high-frequency burst stimulation of the mPFC has been shown to exert antidepressant effects.⁴⁸

Individuals with PTSD also demonstrate increased PFC activity during sustained attention and decreased activity with more difficult inhibition tasks, which may reflect a reduced ability to regulate PFC function during more demanding tasks.⁴⁹ In rodent models the correlation of hippocampus theta oscillations with both theta and single-unit activity in the PFC is important in tests of spatial working memory. Additionally, optogenetic manipulation of ventral hippocampal-PFC afferent pathways was demonstrated to be critical for spatial cues. These studies suggest that dysfunction in these large-scale neural networks affects memory processing that may be crucial in patients with PTSD.²⁶

Hippocampus. The hippocampus is crucial for declarative memory and learning processes. Neuroimaging performed to investigate activity of the hippocampus in PTSD patients has been less revealing.²⁰ Individuals with PTSD have been shown to have a reduction in hippocampal size; however, it is unclear whether the trauma induces hippocampal atrophy or whether reduced hippocampal volume predisposes someone to developing PTSD.⁵⁰ Studies suggest that pretrauma deficits in executive functioning tasks are further exacerbated following trauma and contribute to a worsened recovery and increased risk of developing PTSD.⁵¹ However, in rodent models following trauma, acute and chronic corticosteroid secretion induced significant molecular and gene expression changes, resulting in impaired neurogenesis in the dentate gyrus, decreased long-term potentiation in the CA1, and dendritic retraction in the CA3 regions of the hippocampus.²⁶ Additionally, human twin studies suggest that reduced connectivity between the mPFC and hippocampus is acquired and reduces fear extinction capacity.^{29,30}

Neuromodulation: Current Status and Future Directions

The neural circuitry for PTSD is complex, composed of several parallel and inhibitory connections involving both macro- and microcircuits that involve multiple regions of the brain, including the amygdala, PFC, cingulate cortex, insula, and hippocampus, which are implicated in a heterogeneous symptom presentation. Current advances in the understanding of these networks have challenged previous concepts for the pathogenesis of PTSD. It is now understood that PTSD-related dysfunction of various areas results in multiple symptoms of the disorder.²⁶ For example, dysfunction of the amygdala can lead to symptoms of intrusion, avoidance, arousal, and reactivity. Likewise, dysfunction of the subdivisions of the PFC results in symptoms of intrusion, as well as negative alterations in cognition and mood. Current advancements in the understanding of the neural circuitry for PTSD have prompted both noninvasive and invasive brain stimulation trials—TMS and DBS, respectively.

Transcranial Magnetic Stimulation. TMS is capable of stimulating brain tissue noninvasively without the surgical risks associated with DBS, albeit with a small risk of seizure induction. Excitation of the cortex occurs with high-frequency stimulation (> 1 Hz), whereas low-frequency stimulation (≤ 1 Hz) reduces cortical activity.⁵² TMS coils are designed to modulate either small and superficial or broad and deep areas.⁵³ The time-varying magnetic field produced by the devices induces an electrical field, the effect of which is governed by the intensity, frequency, and temporal spacing of the delivered electromagnetic energy.⁵⁴

Electroencephalographic studies have shown alpha power decreases in the right hemisphere in patients with PTSD when exposed to trauma-related imagery, which has been further confirmed with the use of SPECT studies with auditory stimulation.⁵⁵ Thus, clinical studies have been aimed at the modulation of the right dorsolateral PFC. Seeking to delineate the benefits of various TMS parameters, multiple studies have suggested some possible clinical benefits compared to placebo, albeit with considerable variability and, in most cases, small sample sizes (Table 1). These studies demonstrate rather small clinical improvement despite significant results, and most studies show notable improvement in sham groups as well. The improvements seen in the sham groups underline the importance of the need for rigorous controls and proper statistical comparisons between intervention and control groups.

Moreover, given the number of scales and time intervals tested in the typical TMS trial, some positive results should be expected by chance alone, even if there were no true effect. Current evidence limits the ability to draw significant conclusions regarding outcomes or optimal treatment parameters. More rigorous research is needed to optimize TMS treatment variables, including the appropriate apparatus, target, stimulation frequency, and parameters, to delineate its true efficacy better.

Deep Brain Stimulation. DBS uses surgically implanted electrodes to deliver electrical stimulation to specific brain targets. The risks of DBS are not insignificant, although the procedure is generally considered to be safe.

TABLE 1. TMS trials

Authors & Year	No. (total)	Outcome Measures	Intensity	Anatomic Target	Group	Pulse Frequency/No. of Pulses/No. of Sessions	Results
Ahmadizadeh & Rezaei, 2018 ⁶⁷	58	PCL-M	100%	DLPFC	Unilat Bilat	20 Hz/1200 pulses/10 sessions 20 Hz/1200 pulses/10 sessions	Significant improvement in both uni- & bilat TMS PCL-M score, no significant difference btwn groups
Cohen et al., 2004 ⁶⁸	24	CAPS, PCL, TOPTSDS, HAM-A, HAM-D	80%	rDLPFC	Low High	1 Hz/100 pulses/10 sessions 10 Hz/400 pulses/10 sessions	High frequency significantly improved PCL, TOPTSDS, HAM-A compared to low frequency & sham
Osuch et al., 2009 ⁷⁴	9	CAPS, SADS, HAM-D, IES	100%	rDLPFC	Active	1 Hz/30 pulses/20 sessions	No significant difference
Watts et al., 2012 ⁷⁵	20	PCL, BDI, STAI, BNCE	90%	rDLPFC	Active	1 Hz/20 pulses/10 sessions	Significant improvement in CAPS, PCL, & BDI
Isserles et al., 2013 ⁶⁹	30	CAPS, PSS-SR, HAM-D, BDI	120%	Bilat mPFC	Active	20 Hz/1680 pulses/12 sessions	Significant improvement in CAPS for exposure + stimulation only
Kozel, 2018 ⁷⁰	103	CAPS, PCL, M-PTSD, QIDS, IPF	110%	rDLPFC	Active	1 Hz/1800 pulses/12 sessions	Significant improvement in CAPS & PCL, but more so w/ cognitive processing therapy
Kozel et al., 2019 ⁷¹	35	CAPS, IPF, MADRS, PCL-5, QIDS-SR, IPF	110%	rDLPFC	Low High	1 Hz/2400 pulses/36 sessions 10 Hz/2400 pulses/36 sessions	Significant improvement in CAPS & PCL, but no difference btwn low- & high-frequency stimulation

BDI = Beck Depression Inventory; BNCE = Brief Neurobehavioral Cognitive Examination; CAPS = Clinician-Administered PTSD Scale; DLPFC = dorsolateral prefrontal cortex; HAM-A = Hamilton Anxiety Rating Scale; HAM-D = Hamilton Depression Rating Scale; IES = Impact of Event Scale; IPF = Inventory of Psychosocial Functioning; M-PTSD = Mississippi Scale for Combat-Related PTSD; MADRS = Montgomery-Åsberg Depression Rating Scale; PCL-M = PTSD Checklist–Military Version; PCL-5 = PTSD Checklist for DSM-5; PSS-SR = PTSD Symptom Scale–Self-Report Version; QIDS = Quick Inventory of Depressive Symptomatology; QIDS-SR = QIDS–Self-Report; rDLPFC = rostral DLPFC; SADS = Schedule for Affective Disorders and Schizophrenia; STAI = State-Trait Anxiety Inventory; TOPTSDS = Treatment Outcome PTSD Scale.

The risk of hemorrhage is approximately 1%–3% per lead, and for infection it is 1%–9%.^{56,57} Although more invasive than TMS, DBS offers the advantage of targeting deeper structures and greater control over how the energy is delivered. However, DBS is limited as well by its broad nature of stimulation to surrounding anatomical structures. As with TMS, the effects of DBS are parameter dependent. It is generally thought that the pulse width determines the size of the region affected by stimulation; that amplitude is related to the strength of the effect; and that frequency determines the network's response—i.e., activation or inhibition. High-frequency stimulation, the most common delivery mode for DBS, has been described as mimicking the effects of a lesion; however, even that common assumption has been challenged.^{6,58}

Two ongoing trials are investigating the use of DBS

for PTSD: one of the subgenual cingulate and the other targeting the basolateral nucleus of the amygdala (Table 2). There are no currently available published trial data. However, results for 2 patients in the BLA study have been published.⁵⁹ In the first patient there was a $\geq 40\%$ reduction in symptom severity based on the Clinician-Administered PTSD Scale at 4 years, and resolution of severe combat nightmares and dissociative symptoms after implantation of bilateral ventral BLA leads with high-frequency stimulation (right: 4.2 V, 130 Hz, 60 μ sec; left: 1.7 V, 130 Hz, 60 μ sec). The second patient regained the ability to engage in previously avoided social activities and benefitted from improved anger symptoms with unilateral stimulation (right: 1.2 V, 130 Hz, 60 μ sec). Although initial results appear promising, published results of the completed study are necessary.

TABLE 2. DBS trials

Clinical Trial	Stimulation Frequency	Primary Outcomes	Secondary Outcomes	Anatomical Target	Results
NCT03416894 ⁷³	NA	SAFTEE collateral effects scale	HAM-D, BDI, BAI, CAPS, DTS, SPRINT, CGI, GAF, SF-36, STAI, HAM-A, SDS, PANAS	Subgenual cingulate	NA
NCT02091843 ⁷²	130 Hz, 60 μ sec	Frequency & severity of all adverse events	CAPS	BLA	Limited*

BAI = Beck Anxiety Inventory; BDI = Beck Depression Inventory; CAPS = Clinician-Administered PTSD Scale; CGI = Clinical Global Impression; DTS = Davidson Trauma Scale; GAF = Global Assessment of Functioning; HAM-A = Hamilton Anxiety Rating Scale; HAM-D = Hamilton Depression Rating Scale; NA = not available; PANAS = Positive and Negative Affect Schedule; SAFTEE = Systematic Assessment for Treatment Emergent Events; SDS = Sheehan Disability Scale; SF-36 = 36-Item Short Form Health Survey; SPRINT = Short PTSD Rating Interview; STAI = State-Trait Anxiety Inventory.

* Published results of 2 patients (see text).⁵⁹

FIG. 2. Diagram representation of vmPFC stimulation for PTSD in a fear-persistent state. The concept underlying stimulation of vmPFC is its ability to reduce the activity of the central amygdala both via an overall increase in the GABAergic tone within the BLA complex and via increased stimulation of intercalated cells in a fear-persistent state. High-frequency vmPFC stimulation may be able to mitigate hippocampal or an external stimulus's resultant stimulation of the central amygdala, thus biasing the network's activity toward fear extinction.

An alternative hypothesis for the use of DBS for treatment of PTSD involves changing the activity of regions distant from the target via activation of neuronal projections.²² Infralimbic neurons have dense glutamatergic projections to intercalated cells and are implicated in fear extinction and the prevention of CE cell activation via BLA neurons.²⁸ Animal models have identified that high-frequency stimulation of the infralimbic neurons/vmPFC results in the decreased firing frequency of BLA principal cells, which is thought to be secondary to an increase in GABA release via interneurons, as well as increased intercalated cell stimulation and inhibition of CE.^{22,28} Reznikov et al. used mice with weak fear extinction, which may more closely resemble a clinical PTSD in humans. Stimulation resulted in mitigated fear responses, improved anxiety behavior, and prevented return of PTSD-like symptoms.^{22,60}

Optogenetic studies have shown that inhibition of neurons projecting from the prelimbic cortex inhibits the expression of conditioned fear behaviors. In contrast, the inhibition of infralimbic neurons prevents the formation rather than retention of memories during fear extinction training. There is continued debate among comparative neuroanatomists on the exact homologies between the human and rodent PFC. Still, it is suggested that the vmPFC homolog in rodents consists of the prelimbic and infralimbic cortices,²⁶ making the vmPFC an attractive potential target for the treatment of PTSD (Fig. 2). It is worth noting that findings from optogenetic studies may not directly transfer to DBS, because optogenetics allows cell type–

specific alterations (but of course requires genetic alterations), whereas DBS is not specific at the level of cellular subtypes.

Closed-Loop Stimulation. The development of more refined neuromodulation protocols using closed-loop DBS, as opposed to open-loop DBS, could improve the precision of therapeutic stimulation. An open-loop system delivers only a preprogrammed stimulus. In contrast, a closed-loop system is capable of detecting and analyzing peripherally collected data, after which it is then able to deliver the appropriate stimulus to elicit the desired clinical outcome. Several central and peripheral biomarkers reflecting physical changes related to sympathetic activation such as alteration in heart rate or blood pressure, pupillary dilation, piloerection, skin conductive changes, or even endocrine markers related to a dysfunctional hypothalamic-pituitary-adrenal axis have been considered.⁶¹ However, these biomarkers do not specifically represent the pathology associated with PTSD. The use of sensors in areas known to be related to the PTSD circuitry to measure local field potential changes in response to external stimuli may help improve specificity. In animal trials, increases in BLA potentials in the gamma range occurred after a trauma reminder.⁶² Currently there are 2 commercially available devices capable of closed-loop brain stimulation, both of which have research capabilities that allow for the extraction of data.⁶¹ Comparing peripheral and central biomarkers with local field potential recordings from both asymp–

tomatic and symptomatic PTSD episodes could identify more reliable biomarkers.

The National Institute of Mental Health RDoC is a research platform that targets functional domains of psychiatric disorders in a multidimensional approach focused on behavioral and thought patterns, neurobiology, and genetics, intending to improve clinical outcomes.¹⁷ The RDoC approach will hopefully enhance researchers' ability to objectively measure symptoms across functional domains linked to known PTSD circuitry to specifically design behavioral tasks to assess the impact of neuromodulation within each domain.¹⁹ For example, rather than measuring symptom severity by using phenomenological symptom scales, which may be susceptible to subjectivity and bias, changes after treatment could be measured along dimensions of approach versus avoidance behavior or emotional stability versus lability that better quantify the underlying pathology. Recorded neuronal signals could then be combined with behavioral data and analyzed appropriately (e.g., machine or deep learning techniques) for a wide range of psychiatric conditions.¹⁹

Along these lines, the Defense Advanced Research Projects Agency initiated the Systems-Based Neurotechnology for Emerging Therapies (SUBNETS) program, a part of the US federal Brain Research through Advancing Innovative Neurotechnologies (BRAIN) Initiative, with the goal of creating implanted, next-generation, closed-loop neural stimulators and therapeutic systems for the treatment of neuropsychiatric illnesses.⁶³ Since its inception, there have been several publications that described the ability to predict changes in mood from intracranially recorded neural signals. Sani et al. developed dynamic neural encoding models to delineate timescales of decoded mood states in human subjects with epilepsy who self-reported mood intermittently over multiple days.⁶⁴ Kirkby et al. discovered that increased variability between the amygdala and hippocampus correlated with variations in self-reported worsening mood and anxiety.⁶⁵ Rao et al. demonstrated that unilateral stimulation of the lateral OFC led to acute improvements in mood among subjects with moderate to severe depression.⁶⁶

These findings are an essential step toward the development of a closed-loop system for other psychiatric illnesses. Proposed designs would be able to record and stimulate multiple regions of the brain with onboard control and telemetry capabilities.¹⁹ Symptoms of PTSD are not continuous, and effective modulation of proposed targets may not require constant stimulation. Closed-loop systems could provide additional information regarding neural circuit dysfunction and improve symptom control in a more specific, "on-demand" manner.

Conclusions

PTSD is a widespread and often devastating psychiatric condition made up of a heterogeneous group of symptoms. In the most severe treatment-resistant cases, neurostimulation has garnered increasing interest. The multiple brain regions involved vary in their degree of contribution to the overall symptomatology, prompting consideration for treatment individualization. There is a need for

improved techniques to identify therapeutic targets better. The "RDoC-style" transdiagnostic approach may provide much-needed objective data in assessing this psychiatric illness and its molecular biomarkers, improving our understanding of symptomatology and treatment response, and the likelihood of successful implementation of specific neuromodulatory strategies and closed-loop systems. We suggest research aimed at the use of pre- and postdeployment resting-state functional imaging among military members and high-frequency stimulation of the vmPFC as another potential target for those who develop TR-PTSD. Although there is hope that neuromodulation will become a viable treatment modality for PTSD, this concept remains theoretical, and further research should involve institutional review board–approved controlled prospective clinical studies.

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Author Contributions

Conception and design: Larkin, Viswanathan, Sheth. Acquisition of data: Larkin, McGinnis. Analysis and interpretation of data: Larkin, McGinnis, Snyder, Storch, Goodman. Drafting the article: Larkin, McGinnis, Snyder. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Larkin. Study supervision: Larkin, Viswanathan, Sheth.

Correspondence

M. Benjamin Larkin: Baylor College of Medicine, Houston, TX. michael.larkin@bcm.edu.