Neuromodulation Approaches for the Treatment of Post-Traumatic Stress Disorder: Stimulating the Brain Following Exposure-based Therapy

Marie-France Marin^{1,2} · Mohammed R. Milad^{1,2}

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Abstract Exposure-based therapies, medications, or device-based brain stimulation techniques are now current therapies that are offered to individuals suffering from post-traumatic stress disorder. Despite the refinement and evolution of these different interventions, some individuals still remain symptomatic. Neuroscience-based knowledge suggests that fear conditioning and extinction paradigms are a good experimental model to mimic exposure-based therapy. The field has recently put considerable efforts to test various pharmacological compounds that could be used as adjuncts to therapy by increasing the consolidation of the memory that is being formed during the therapy session. In this review, we propose to use device-based brain stimulation techniques to augment the efficacy of exposure-based therapy in individuals suffering from PTSD. Rather than using it as a therapeutic tool on its own, we describe how device-based brain stimulation techniques could be used to target regions known to be dysregulated when learning and/or recalling safety memory traces in PTSD patients.

Keywords Extinction learning · Exposure-based therapy · Post-traumatic stress disorder · Anxiety disorders · Device-based brain stimulation techniques · Memory consolidation · Ventromedial prefrontal cortex · Amygdala

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✉ Mohammed R. Milad
milad@nmr.mgh.harvard.edu

¹ Department of Psychiatry, Massachusetts General Hospital, 149 13th Street, Charlestown, MA 02129, USA

² Department of Psychiatry, Harvard Medical School, Boston, MA, USA

Introduction

Although current treatments offered to individuals suffering from post-traumatic stress disorder (PTSD) have proven to be efficient, there remains a critical subset of individuals who do not respond to treatment or end up relapsing after a certain time. The field has made tremendous efforts in the last decades or so to develop new molecules to improve pharmacotherapy or to apply some of these molecules as adjuncts to behavioral therapies in order to augment their efficacy [1–5].

A more recent and emerging field that has received significant interest in the treatment of various mental health disorders are device-based brain stimulation methods. Among these, deep-brain stimulation (DBS) has been the most documented especially for its use in treating obsessive-compulsive disorder and depression [6–10]. Vagal nerve stimulation (VNS), transcranial magnetic stimulation (TMS), and transcranial direct current stimulation (tDCS) have also gained popularity, notably for the treatment of refractory depression [11–17]. More recently, various studies have shown that these stimulation techniques could also be used for the treatment of fear-related disorders, such as PTSD [18•].

The general idea behind these different brain stimulation methods is to restore the brain's homeostasis. Based on the premise that various psychopathologies exhibit dysregulated functioning and/or connectivity between specific brain regions, the device can theoretically be used to restore the functioning and/or connectivity of these regions, by imposing an artificial rhythm that mimics a therapeutic pattern, similar to what would be observed among healthy subjects.

The advantage of some of these techniques over pharmacotherapy is that we can target specific brain regions and have more localized effects and, therefore, reduce potential side effects that medication could generate by acting in multiple organs. Despite multiple studies showing efficacy of these

different methods relative to a sham control condition or to another form of non-brain stimulation therapy, the exact parameters to best optimize the treatment in terms of timing and location still pose some questions.

As mentioned earlier, most of the studies using neuromodulation techniques have been performed in depression and obsessive-compulsive disorders. PTSD has been less studied thus far, but there are still promising findings. One study aims to test the impact of high-frequency DBS of the basolateral amygdala in combat veterans suffering from PTSD [19]. The research protocol has been published, but the final results of this controlled trial have not been published yet. The other studies have mostly been performed with TMS. For example, daily treatments (10 sessions) of high-frequency (10 Hz) repetitive TMS (rTMS) to the right dorsolateral prefrontal cortex (dlPFC) have been shown to improve anxiety, reexperiencing and avoidance symptoms in PTSD individuals [20]. Another study tested 20 Hz stimulation of the right or left dlPFC. They showed improvement for both active conditions, with more pronounced effects for the right stimulation side [21]. Other studies have reported positive effects with low-frequency stimulation (1 Hz) of the right dlPFC [22, 23]. Overall, a recent exploratory meta-analysis suggested that rTMS to the right dlPFC is an effective treatment for PTSD [18•].

In this short review, we will focus on how device-based brain stimulation methods could be used for the treatment of PTSD. We revisit the use of these as adjuncts to therapy, similar to various pharmacological compounds that have recently been investigated for their capacity to augment the safety learning that takes place during therapy for PTSD.

Extinction Learning and Recall: The Bases for Exposure-based Therapy

Exposure-based therapy has been used and validated as a very efficient therapy for treating fear-related disorders [24–26]. In this type of therapy, one of the main objectives is to expose the patient to cues that elicit fear, anxiety, and/or distress in order to gradually decrease the negative connotation associated with it so that the patient stops experiencing these distressing symptoms when confronted with the cue. To this date, the best laboratory model to mimic the therapeutic learning that takes place during this form on therapy is the fear conditioning and extinction paradigm [27]. During this type of paradigm, a neutral cue is paired with an aversive outcome, such as an electrical stimulation. Rapidly, the neutral cue becomes conditioned (CS+) such that its presentation alone elicits a conditioned response (CR), suggesting that associative learning has taken place. In other words, during this fear-conditioning phase, the subject learns that the cue precedes a negative outcome, so the presentation of the cue alone is sufficient to elicit

a fear response, usually measured in humans by using skin conductance responses (SCRs). Following the acquisition of fear, extinction learning takes place where the CS+ is presented repeatedly without the aversive stimulus. Over time, the subject learns that the cue no longer predicts the aversive stimulus. This fear reduction during extinction learning is reflected by a decrease in the conditioned response [27, 28]. More recently, some laboratory paradigms have added a delayed extinction memory test where they bring back participants at least 1 day after extinction learning. During this extinction recall memory test, the CS+ is presented again, and fear levels are measured. If the memory acquired during extinction learning has been consolidated, the fear levels expressed in response to the CS+ should be relatively low given that the cue has undergone extinction. On the contrary, if fear is elevated upon CS+ presentation despite good extinction learning, this suggests that there was deficient memory consolidation and/or retrieval process.

When tested in the laboratory, individuals suffering from PTSD acquire fear and extinction to levels that mimic those observed among healthy controls. They do however exhibit deficient extinction memory recall when tested after a delay [29, 30•, 31]. In other words, although extinction learning is taking place, the safety memory trace that is formed during training does not consolidate and transfer to the long-term memory system, making it inaccessible when tested at the delayed recall. This pattern mimics a clinical phenomenon that has been observed over the years, which is that within-session extinction performance does not predict clinical improvement.

Therefore, recent efforts have been dedicated to find ways to augment the consolidation of the memory trace that is being formed during extinction learning. By increasing the consolidation process, the safety memory trace should be stronger and more likely to be retrieved and expressed when tested later on for delayed extinction memory recall. If this phenomenon could be produced in laboratories, one could think to eventually translate it in the clinical world so that the enhancing strategy could be paired with successful exposure-therapy sessions in order to boost the learning that took place. As of yet, mostly pharmacological compounds have been used [1–5]. Some of these have shown promise, and it seems preferable to administer the drug only after therapeutic sessions that were successful (where fear was significantly reduced) in order to obtain optimal results.

Neuromodulation Approaches for Augmenting Extinction Memory Consolidation

Here, we propose the use of neuromodulation techniques to augment the consolidation process of the learning that occurred during exposure-based therapies for individuals suffering from PTSD. By identifying the nodes of the fear extinction

circuit that are either hypo- or hyperactivated in individuals suffering from this psychopathology, we can then use device-based brain stimulation techniques to either activate or inhibit the activity in these key nodes in order to restore homeostasis [32•].

Neuroimaging findings have shown that when compared to trauma-exposed healthy controls, individuals suffering from PTSD exhibit higher activation in the amygdala as well as lower activations of the ventromedial prefrontal cortex (vmPFC) during late phases of extinction learning [30•]. Moreover, when later tested for extinction memory recall, PTSD individuals show deficient recall relative to trauma-exposed healthy controls [29, 31]. This behavioral deficit correlates with distinct brain activation patterns. In general, when compared to trauma-exposed healthy controls, PTSD individuals exhibit hyperactivations of the amygdala and dorsal anterior cingulate cortex (dACC) along with hypoactivations of the hippocampus and the vmPFC when recalling the extinction memory trace [29, 30•, 33]. At a broader level, without focusing on extinction learning and recall tasks, the imbalanced cortico-limbic system is well established in the psychopathology of PTSD [34–36, 37•, 38, 39]. In fact, the various studies that have used brain-stimulation methods to improve symptoms and well-being in PTSD and anxiety disorders have aimed at reestablishing the equilibrium of this system.

Given that the vmPFC is hypoactivated during the late phases of extinction learning and at the time of recalling the extinction memory trace, one could think that stimulation of that region at the end of a successful therapy session could optimize the consolidation and the later retrieval of the safety memory trace acquired during the therapy. On the other hand, the reverse is true for the amygdala. Therefore, inhibition of that brain region could also yield promising results.

Both of these brain regions have a deeper location in the brain and are therefore not a direct target for stimulation techniques requiring superficial areas to be targeted, such as TMS or tDCS. We propose to seed the vmPFC or the amygdala region, which have both been shown to be dysregulated in PTSD populations, and to use psychophysiological interaction methods in order to determine a specific target at the dorsolateral prefrontal cortex (dlPFC) level, which is a common site for stimulation in TMS studies. Therefore, the area to be stimulated is determined at a group level and each individual to be treated undergoes a structural scan in order to optimize the accuracy of the location to be targeted for stimulation. Using a group approach certainly carries some advantages in terms of applicability and generalization of the results, especially at the early stages of research in this field. One should keep in mind, however, that favoring a more individual-based approach could eventually lead to more refined and accurate results. On the other hand, more invasive methods such as DBS could provide greater accuracy in terms of stimulation target.

Not only it is important to determine and refine the location for stimulation but also it is also crucial to optimize the

stimulation parameters. Stimulating at a set frequency for all individuals could inform initial studies, but this type of open-loop stimulation has its drawbacks. Importantly, one could take an approach based on closed-loop stimulation principles in order to guide the optimal parameters of stimulation [40–42]. For example, recordings in the regions that are known to be hyperactivated, such as the dACC or the amygdala, could guide the stimulation that should be applied to regions known to be hypoactivated, such as the vmPFC. In other words, rather than stimulating the vmPFC with set parameters for all individuals suffering from PTSD with the hope that this will result in optimal results, the vmPFC stimulation would be guided by signals recorded from hyperactivated regions in each individual. One of the advantages of this technique relative to open-loop stimulation is the constant adjustment of the stimulation based on the needs and the evolution of each individual's brain activity patterns [43]. This technique could not only guide optimal stimulation parameters following therapy sessions but it could also be used for general treatment of core PTSD symptoms. In fact, although this review focuses on pairing brain stimulation with therapy sessions, the current efforts that are currently taken to stimulate the brain of individuals suffering from PTSD to reestablish the homeostasis could benefit from closed-loop stimulations to guide and refine the therapeutic approaches.

Empirical Findings Supporting Brain Stimulation Following Therapy in PTSD

Importantly, few studies have used this approach. One study tested nine PTSD patients and administered 1 Hz TMS (or sham control) to the right dlPFC in conjunction with exposure therapy for 20 sessions. There were no statistical differences between the two groups [44]. The stimulation frequency might have been a key issue in yielding these negative findings. Isserles and colleagues [45•] have used deep TMS (dTMS), 20 Hz, to target the medial prefrontal cortex in PTSD patients that were divided in three groups: stimulation following brief exposure to the traumatic event, stimulation following brief exposure to a nontraumatic event, and sham stimulation after brief exposure to the traumatic event. The authors reported a significant improvement of the intrusive symptoms in patients who received the active stimulation following exposure to the traumatic event. This same group also showed reduced reactivity, measured by heart rate, when later exposed to the traumatic script [45•].

Conclusions

This review proposed the use of a combined approach in which exposure-based therapy and device-based brain

stimulation techniques, which are currently used in isolation for the treatment of PTSD, could be used in conjunction to yield better clinical outcomes. More validation studies are needed to have a better understanding of the optimal parameters that should be used. For example, should brain stimulation occur only following successful therapy sessions? Which frequency should be used? Should we target only refractory PTSD patients? Should non-PTSD anxious individuals also be studied with a similar approach? Hopefully, the next few years will provide more scientific findings that will answer some of these questions, which would guide clinicians and scientists towards improved treatments for PTSD.

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Compliance with Ethics Guidelines

Conflict of Interest Marie-France Marin reports a fellowship from Banting Postdoctoral Fellowship, during the conduct of the study. Mohammed Milad reports grants from NIMH and grants from DoD during the conduct of the study.

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

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