Closed-loop neuromodulation for Posttraumatic Stress Disorder

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Closed-loop neuromodulation is an emerging area of research, and its application for posttraumatic stress disorder (PTSD) is an active and evolving field. The concept involves real-time monitoring of neural activity, allowing for adaptive interventions tailored to an individual's specific neural dynamics. While research is ongoing, there have been some explorations into the potential use of closed-loop neuromodulation for PTSD.

Key points

Neural Circuits in PTSD:

PTSD is associated with alterations in neural circuits involved in fear processing, memory, and emotion regulation. Closed-loop neuromodulation aims to target and modulate these circuits to alleviate symptoms.

Electroencephalography (EEG) and Neurofeedback:

EEG-based closed-loop systems, combined with neurofeedback, have been investigated. These systems monitor brain activity in real-time, providing individuals with feedback on their own neural patterns. The goal is to help individuals learn to regulate their brain activity, potentially influencing

emotional responses and symptom severity.

Transcranial Magnetic Stimulation (TMS):

TMS is a non-invasive neuromodulation technique that uses magnetic fields to induce electrical currents in specific brain regions. Closed-loop TMS systems are being explored for conditions like depression and PTSD, where the stimulation parameters can be adjusted in response to ongoing brain activity.

Deep Brain Stimulation (DBS):

While invasive, deep brain stimulation has shown promise in other neuropsychiatric disorders. Research exploring closed-loop DBS for PTSD is in the early stages, with a focus on identifying specific neural targets and optimizing stimulation parameters.

Responsive Neurostimulation (RNS):

RNS involves the implantation of electrodes directly into the brain regions of interest. Closed-loop RNS systems, which monitor neural activity and deliver stimulation in response to specific patterns, have been investigated for epilepsy. This approach could potentially be adapted for PTSD.

Challenges and Considerations:

Implementing closed-loop neuromodulation for PTSD faces challenges related to the complexity of the disorder, the need for individualized treatment approaches, and ethical considerations, particularly in invasive interventions.

Research and Clinical Trials:

Ongoing research and clinical trials aim to better understand the neural mechanisms of PTSD and evaluate the safety and efficacy of closed-loop neuromodulation approaches. These studies often involve multidisciplinary collaboration between neuroscientists, clinicians, and engineers. While the field of closed-loop neuromodulation for PTSD is promising, it's important to note that this is an area of active research, and the development of effective interventions is still in the early stages. Future studies will be crucial for refining techniques, identifying optimal parameters, and establishing the safety and efficacy of closed-loop neuromodulation for PTSD.

Sierra et al. showed that closed-loop, SWR-triggered neuromodulation of the medial forebrain bundle (MFB) can enhance fear extinction consolidation in male rats. The modified fear memories became resistant to induced recall (i.e., 'renewal' and 'reinstatement') and did not reemerge spontaneously. These effects were mediated by D2 receptor signaling-induced synaptic remodeling in the basolateral amygdala. Our results demonstrate that SWR-triggered closed-loop stimulation of the MFB reward system enhances the extinction of fearful memories reducing fear expression across different contexts and preventing excessive and persistent fear responses. These findings highlight the potential of neuromodulation to augment extinction learning and provide a new avenue to develop treatments for anxiety disorders [1)].

Gill et al. recorded intracranial electroencephalographic data longitudinally (over one year) in two male individuals with amygdala electrodes implanted for the management of treatment-resistant posttraumatic stress disorder (TR-PTSD) under clinical trial NCT04152993. https://clinicaltrials.gov/study/NCT04152993

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To determine electrophysiological signatures related to emotionally aversive and clinically relevant states (trial primary endpoint), they characterized neural activity during unpleasant portions of three separate paradigms (negative emotional image viewing, listening to recordings of participant-specific trauma-related memories, and at-home-periods of symptom exacerbation). They found selective increases in amygdala theta band power (5-9 Hz) across all three negative experiences. Subsequent use of elevations in low-frequency amygdala band power as a trigger for closed-loop neuromodulation led to significant reductions in TR-PTSD symptoms (trial secondary endpoint) following one year of treatment as well as reductions in aversive-related amygdala theta activity. Altogether, the findings provide early evidence that elevated amygdala theta activity across a range of negative-related behavioral states may be a promising target for future closed-loop neuromodulation therapies in PTSD [2)].

Service members or veterans showed reductions in the symptomatology of PTS, insomnia, depressive mood, and anxiety that were durable through 6 months after the use of a closed-loop allostatic neurotechnology for the auto-calibration of neural oscillations. This study is the first to report increased HRV or BRS after the use of an intervention for service members or veterans with PTS. Ongoing investigations are strongly warranted [3)].

Neuromodulation for Posttraumatic Stress Disorder

- Antidepressant Medication Prescription and Incident Cardiovascular Disease in Women Veterans
- Self-compassion mediates treatment effects in MDMA-assisted therapy for posttraumatic stress disorder
- An Update on Psychotherapy for the Treatment of PTSD
- Negative Affect Circuit Subtypes and Neural, Behavioral, and Affective Responses to MDMA: A Randomized Clinical Trial
- Dopamine induces fear extinction by activating the reward-responding amygdala neurons
- Impact of Medical Comorbidities on Ketamine and Esketamine Treatment Effectiveness for Posttraumatic Stress Disorder and Depression: A Clinical Outcomes Analysis from the VA San Diego Healthcare System
- Treatment with psychedelics : potential benefits in Parkinson's disease
- Use of an Intraoral Neuroprosthesis for the Treatment of Posttraumatic Stress Disorder (PTSD)-Associated Nocturnal Behavior Disorder: Case Series of Four Patients

Although most patients often improve with medications and/or psychotherapy, approximately 20-30% are considered to be refractory to conventional treatments. In other psychiatric disorders, DBS has been investigated in treatment-refractory patients. To date, preclinical work suggests that stimulation at high frequency delivered at particular timeframes to different targets, including the amygdala, ventral striatum, hippocampus, and prefrontal cortex may improve fear extinction and anxiety-like behavior in rodents. In the only clinical report published so far, a patient implanted with electrodes in the amygdala has shown striking improvements in PTSD symptoms [4)].

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 [5].

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). Gouveia et al. 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 [6].

References

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