

# Brain stimulation in posttraumatic stress disorder: animal studies

Leo SHER, Vladan NOVAKOVIC

Department of Psychiatry, Mount Sinai School of Medicine and Department of Psychiatry, James J. Peters Veterans' Administration Medical Center, New York City, USA

## The concept of posttraumatic stress disorder (PTSD)

Posttraumatic stress disorder (PTSD) is a severe, complex, heterogeneous disorder usually precipitated by psychological trauma, typically affecting vulnerable individuals, with many perceptual, cognitive, affective, physiological and psychological features [1,2]. According to the most recent edition of the Diagnostic and Statistical Manual of Psychiatric Disorders (DSM-IV-TR) [1], the essential feature of PTSD is the development of characteristic symptoms following exposure to an extreme traumatic stressor characterized by: direct personal experience of an event that involves actual or threatened death or serious injury, or other threat to one's physical integrity; or witnessing an event that involves death, injury, or a threat to the physical integrity of another person; or learning about unexpected or violent death, serious harm, or threat of death or injury experienced by a family member or other close associate. The person reacts to this event with fear and helplessness, and tries to avoid being reminded of it. The characteristic symptoms resulting from the exposure to a traumatic event include persistent reexperiencing of the traumatic event, persistent avoidance of stimuli associated with the trauma and numbing of general responsiveness, and persistent symptoms of increased arousal. Re-experiencing symptoms consist of intrusions of the traumatic memory in the form of distressing images, nightmares, or dissociative experiences, such as flashbacks. Avoidance symptoms include actively avoiding reminders of the traumatic event, including persons, places, or things associated with the trauma, and more passive behaviors reflecting emotional numbing and constriction. Hyperarousal symptoms include insomnia, irritability, impaired concentration, hypervigilance, and increased startle responses.

## Treatment of PTSD

Available pharmacological and psychological treatments for PTSD improve the depressive and anxiety-related aspects of PTSD more than the core symptoms that derive from an aberrant fear response, hyperarousal, and emotional dysregulation. Recently, researchers and clinicians pay an increasing attention to a possibility of using brain stimulation methods, such as Electroconvulsive Therapy (ECT), Deep Brain Stimulation (DBS), Direct (Epidural) Cortical Stimulation (DCS), Transcranial Magnetic Stimulation (TMS), Magnetic Seizure Therapy

(MST), Vagus Nerve Stimulation (VNS), transcranial Direct Current Stimulation (tDCS), Cranial Electrotherapy Stimulation (CES), and others for the treatment of PTSD. Given the diversity and heterogeneity of mechanisms of action of brain stimulating devices, and their ability to stimulate the central nervous system diffusely to locally, some brain stimulation interventions might address PTSD core symptoms in more targeted ways. It is important to note that data on brain stimulation for PTSD to date are limited. Therefore, animal studies may play an important role in understanding the biological mechanisms of the effects of brain stimulation on PTSD and developing new brain stimulation treatments for PTSD.

## Deep Brain Stimulation (DBS) and deep Transcranial Magnetic Stimulation (dTMS)

Recent functional neuroimaging and related studies suggest that amygdala hyperactivity may contribute to or be the primary cause of symptoms of PTSD [2]. Langevin et al. [3] tested whether DBS of the amygdala, to reduce its activation, could be used to treat PTSD symptoms. Rats traumatized by inescapable shocks in the presence of an unfamiliar object later tend to bury the object when re-exposed to it, an animal analog of some human PTSD symptoms such as stressful cue avoidance. An electrode was implanted in 10 rats in the right basolateral nucleus of the amygdala (BlN). Five rats received DBS treatment while the other 5 rats did not. After 7 days of treatment, rats treated with BlN DBS spent on average 13 times less time burying the ball than the sham control rats. The treated rats also spent 18 times more time exploring the ball than the sham control rats. The behavior of treated rats in reacting to a stimulus associated with an aversive event was nearly normal. Langevin et al. [3] believe these results have direct implications for treatment-resistant PTSD. DBS may be a useful new therapeutic strategy for PTSD.

Stehberg et al. [4] studied localized intracranial electrical stimulation in a rat model of aversive memory. Ordinarily, in the rat, the induction of an amnesia by blocking reconsolidation of long-term memory could ameliorate traumatic memories and phobias. However, the pharmacological approach used – macromolecular synthesis inhibitors – is toxic and cannot be used in humans. Stehberg et al. [4] studied conditioned taste aversion in the rat and reported that reconsolidation of the conditioned response is impaired by localized intracranial electrical

Address for correspondence: Leo Sher, M.D.; JJP VA Medical Center, 130 West Kingsbridge Road, Bronx, New York 10468, USA; E-mail: drleosher@gmail.com

stimulation. Lasting impairment was obtained only when stimulation was applied during memory reactivation and only to the dysgranular insular cortex bilaterally. The same method blocked new memory consolidation, but produced anterograde amnesia, reminiscent of the known effect of non-localized electroconvulsive therapy. They concluded that localized electrical microstimulation, such as produced by deep-brain stimulation or deep transcranial magnetic stimulation [5] could be used to impair long-term memory if applied during memory reactivation, and could lead to the development of a novel treatment for intractable post-traumatic stress disorder.

#### Electroconvulsive Therapy (ECT)

Manion et al. [6] raise the possibility that ECT might be effective in the treatment of PTSD. They investigated the effects of electroconvulsive shocks (ECS) on the acoustic startle response (ASR), in a rat model of traumatic stress. A characteristic symptom of PTSD is an exaggerated reactivity to startling sounds. A restraint/tailshock paradigm was followed by administration of ECS to the rats. ASR measurements were obtained at several time points following ECS. Although ECS had no effect in control rats, ECS significantly exacerbated the already potentiated ASR in the stressed group. The authors conclude that although ECT may be an effective treatment for certain symptoms of

co-occurring major depressive disorder and PTSD or PTSD alone, it may exacerbate heightened arousal associated with PTSD.

#### DISCUSSION

The two brief animal model results for DBS are intriguingly suggestive of potential human benefit. There are no human DBS for PTSD studies to date; the possibility exists that eventually it may be safe and relevant to modulate the human amygdala using DBS. DBS would be a very invasive, expensive, ethically and scientifically challenging therapy for the complex and often fragile PTSD population, particularly in that we are only beginning to know the functional brain circuitry of PTSD. It is not yet clear where a DBS electrode might go, although the minimal animal research points to possible human analogs of the right basolateral nucleus of the rat amygdala [3], or the rat dysgranular insular cortex, bilaterally [4]. PTSD researchers might productively study the work of Mayberg and colleagues [7,8], and try to identify an over- or under-active focal brain region that might be stimulated using DBS, to reduce its adverse effects on any proposed key brain functional network underlying PTSD. Further animal and human studies of the effects of brain stimulation in PTSD are merited.

#### REFERENCES:

1. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision. Washington DC, American Psychiatric Association, 2000: 463–468.
2. Heim C, Nemeroff CB. Neurobiology of posttraumatic stress disorder. *CNS Spectr* 2009;14(1 Suppl 1):13–24.
3. Langevin JP, De Salles AA, Kosoyan HP, Krahl SE (in press). Deep brain stimulation of the amygdala alleviates post-traumatic stress disorder symptoms in a rat model. *J Psychiatr Res*.
4. Stehberg J, Levy D, Zangen A (2009). Impairment of aversive memory reconsolidation by localized intracranial electrical stimulation. *Eur J Neurosci*. Mar 2009; 29(5):964–9.
5. Deng ZD, Peterchev AV, Lisanby SH. Coil design considerations for deep-brain transcranial magnetic stimulation (dTMS). *Conf Proc IEEE Eng Med Biol Soc*. 2008:5675–9.
6. Manion ST, Figueiredo TH, Aroniadou-Anderjaska V, Braga MF. Electroconvulsive shocks exacerbate the heightened acoustic startle response in stressed rats. *Behav Neurosci*. 2010;124(1):170–4.
7. Mayberg HS, Lozano AM, Voon V, McNeely HE, Seminowicz D, Hamani C, Schwab JM, Kennedy SH. Deep brain stimulation for treatment-resistant depression. *Neuron* 2005;45(5):651–60.
8. Hamani C, Mayberg H, Snyder B, Giacobbe P, Kennedy S, Lozano AM. Deep brain stimulation of the subcallosal cingulate gyrus for depression: anatomical location of active contacts in clinical responders and a suggested guideline for targeting. *J Neurosurg* 2009;111(6):1209–15.