Deep Brain Stimulation for Post-Traumatic Stress Disorder: A Review of the Experimental and Clinical Literature

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Keywords

Deep brain stimulation · Post-traumatic stress disorder · Basolateral amygdala · Hippocampus · Prefrontal cortex

Abstract

Introduction: Up to 30% of patients with post-traumatic stress disorder (PTSD), especially combat veterans, remain refractory to conventional treatment. For them, deep brain stimulation (DBS) has been suggested. Here, we review the literature on animal models of PTSD in which DBS has been used to treat PTSD-type behavior, and we review and discuss patient reports of DBS for PTSD. **Methods:** A broad search was performed to find experimental animal articles and clinical reports on PubMed, Ovid MEDLINE, Cochrane Library, and PsycINFO, using combinations and variations of search words pertinent to DBS and PTSD. **Results:** The search yielded 30 articles, 24 on DBS in rat models of PTSD, and 6 publications between 2016 and 2020 reporting on a total of 3 patients. DBS in rat models targeted 4 brain areas: medial prefrontal cortex (mPFC), ventral striatum, amygdala, and hippocampus. Clinical publications reported on 2 male combat veterans who received DBS in basolateral amygdala, and 1 female with PTSD due to domestic abuse, who received DBS of mPFC. All 3 patients benefitted to various extents from DBS, at follow-ups of 4 years, 6 months, and 7 months,

respectively. **Conclusions:** PTSD is the only potential clinical indication for DBS that shows extensive animal research *prior* to human applications. Nevertheless, DBS for PTSD remains highly investigational. Despite several years of government funding of DBS research in view of treating severe PTSD in combat veterans, ethical dilemmas, recruitment difficulties, and issues related to use of DBS in such a complex and heterogenous disorder remain prevalent.

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Introduction

Post-traumatic stress disorder (PTSD) emerged after the Vietnam War as a clinical diagnosis in the 1980 Diagnostic and Statistical Manual of Mental Disorders (DSM-III) [1]. It is related to persons who were exposed to life-threatening events, such as combat, rape, or confinement to a concentration camp and who showed symptoms such as tormenting flashbacks and hypervigilance. In the DSM-IV, the diagnosis was broadened and was defined as an anxiety disorder that can develop after exposure to traumatic events, such as threat of death, serious injury, or a serious threat to an individual's bodily integrity. This could lead to individuals experiencing reoccurring intense fear, nightmares, horror, and helplessness [2].

It is estimated that PTSD has a prevalence of about 7% of the population in the USA and 5% in other high-income countries, making it the fourth most common psychiatric disorder, and a major global health problem [3–5]. PTSD has the highest comorbidity rates for developing other psychiatric disorders such as depression and has a 15 times higher risk for suicide attempt compared to other psychiatric conditions [6]. The estimated lifetime prevalence is between 5 and 8% for men and 10–14% for women [7]. In combat veterans, this is almost doubled [8, 9]. PTSD results in substantial economic costs through losses in productivity at work, and healthcare costs are estimated to be in the billions of dollars [10].

The symptoms of PTSD are clustered into 3 main categories: (i) the traumatic event is persistently and intrusively re-experienced, triggering flashbacks, and/or hallucinations, with intense psychological and physiological reactivity; (ii) individuals persistently avoid stimuli associated with the trauma, displaying anhedonia; and (iii) individuals display enduring symptoms of increased arousal such as insomnia, irritability, hypervigilance, and an exaggerated startle response [2].

Current treatment for PTSD consists of pharmacological (such as selective serotonin reuptake inhibitors) and/or psychological interventions (cognitive behavioral therapy, exposure therapy, and eye movement desensitization and reprocessing) [11]. Although research demonstrates clinical efficacy for these treatments [12], 30% of individuals are still debilitated by this condition 10 years after initial diagnosis and are considered treatment refractory [13, 14], and may suffer from low life satisfaction, marital problems, psychiatric disorders such as depression and higher suicide risk [15–17]. Johnson et al. [18] found a sobering 17% mortality rate in 51 PTSD combat veterans over 6 years. Combat-related PTSD compared to civilian PTSD is associated with more severe symptoms [19–21] and is more likely to be treatment refractory [14, 22, 23].

Neurocircuitry of PTSD

Evidence from brain imaging studies on people with PTSD indicate abnormalities in specific brain regions that may either contribute to, or result from, PTSD [24]. These abnormalities concern the hippocampus (HPC), amygdala, medial prefrontal cortex (mPFC), anterior cingulate cortex (ACC), and ventral striatum (VS) [11].

Structural neuroimaging studies of PTSD have focused on hippocampal volume, due to findings from animal research demonstrating the destructive nature of stress on the HPC [25]. Human studies frequently report

reduced hippocampal volume in individuals with PTSD [26–28] and abnormal hippocampi are argued to mediate specific PTSD symptoms [24]. It is suggested that under extreme stress the HPC is unable to encode reliably, leading to dysfunction in memory retrieval, specifically in relation to safe spaces and context [29].

The prefrontal cortex (PFC) has been found to be abnormal in structure and function in patients with PTSD, especially the mPFC and ACC. Abnormalities in these regions are associated with deficits in emotional regulation in PTSD. Patients with PTSD have been demonstrated to show diminished hemodynamic responses in both ventromedial PFC (vmPFC) and ACC [30, 31], and this hypoactivation correlates with PTSD symptom severity [32]. Furthermore, a reduction of PTSD symptoms following successful treatment is associated with increased vmPFC activation [33].

The most consistent finding in human functional imaging research is hyperactivity of the amygdala. Hyperactive amygdalae are associated with heightened fear and hyperarousal in individuals with PTSD. Specifically, the basolateral nucleus of the amygdala (BLA) is thought to be critical in acquisition and expression of fear. Several researchers [34–36] used single-photon emission computed tomography in veterans with PTSD and found that the amygdala had increased activation to combat sounds compared to controls. A meta-analysis of functional neuroimaging studies established the focus of this hyperactivity within the BLA [37]. Research in combat veterans with traumatic brain injury found that lesions to the amygdala and vmPFC were protective against the development of PTSD relative to other brain injury locations [38]. Furthermore, functional MRI studies have shown that PTSD patients who have improved with CBT showed a reduction in amygdala hyperactivity [39].

The PFC can inhibit amygdala activation and decrease its responsivity, and the hyporesponsiveness of the vmPFC in PTSD is argued to give rise to amygdala overactivation [40]. The BLA receives afferents from the mPFC and the HPC; the input from the mPFC is suggested to mediate fear extinction and its underactivity in PTSD is suggested to lead to a failure in fear extinction [41]. The input from the HPC is thought to relate to contextual information regarding events, allowing emotional responses to develop. During stressful events, it is suggested that neutral contextual information is not encoded reliably [42]. Overall, the lack of regulation of the amygdala by the PFC may allow the amygdala to inappropriately generalize an emotional response of fear, across multiple contexts [41].

Additionally, autonomic responses from the hypothalamic-pituitary-adrenal axis are regulated by the amygdala and HPC, controlling the release of corticotrophin-releasing hormones [43]. HPC degradation found in PTSD may result in a more pronounced stress response leading to greater cortisol release and therefore more HPC damage [43]. Thus, the amygdala is responsible for the generation of exaggerated fear responses in PTSD, the hypothalamus produces the autonomic responses, and the vmPFC provides inhibitory regulation of the amygdala. Since the vmPFC is found to be underactive in PTSD, the amygdala is insufficiently inhibited which drives exaggerated fear response, resulting in PTSD symptomology [43] (Fig. 1).

Deep Brain Stimulation

Deep brain stimulation (DBS) is an established treatment in Parkinson's disease, tremor, and dystonia, and a promising – albeit still investigatory – procedure in psychiatric disorders, especially in obsessive-compulsive disorder (OCD), Gilles de la Tourette's syndrome and depression [44]. From these promising results, the potential role of DBS in treating refractory PTSD has been proposed [41, 45]. It is in this context that the USA Government's Defense Advanced Research Projects Agency (DARPA) granted in 2003 seventy-million USD to support development of therapeutic brain stimulation technologies [46].

DBS as a treatment for PTSD is in its infancy [47], and comprehensive surveys of the rationale for this potential treatment, its applicability and efficacy are lacking. The present review aims to address this by examining animal model research and published case reports from ongoing clinical trials. Overall, the review aims to provide a comprehensive overview of the research area and discuss current debates within the field.

Methods

A broad search was performed using the following databases: PubMed, Ovid MEDLINE, Cochrane Library, and PsycINFO. A combination of words was used: "Deep Brain Stimulation," "DBS," "Functional Neurosurgery," "Neuromodulation" and "Post Traumatic Stress Disorder," "PTSD," "Post-traumatic stress disorder," "treatment resistant," "treatment resistant post-traumatic stress disorder," "treatment resistant post-traumatic stress disorder," "anxiety disorder." Bibliographies of relevant journal articles were then searched to retrieve additional articles not obtained in the initial search. References were excluded if they were not in the English language and did not specifically refer to DBS and psychiatric disorders.

Fig. 1. Hyperactive (in red) and hypoactive (in blue) brain areas in PTSD. Red boxes show the amygdala including its BLn and the dACC which are hyperactive in PTSD. Blue boxes show the HIP, and PFC, including the OFC, and the mPFC, dmPFC and vmPFC. BLn, basolateral nucleus; dACC, dorsal anterior cingulate cortex; HIP, hippocampus; OFC, orbitofrontal cortex; dmPFC, dorsomedial prefrontal cortex.

Results

Following search methodology, articles were combined, and duplicates removed. This resulted in 87 articles that met the search criteria; 57 articles were excluded since they did not meet the inclusion criteria (Fig. 2). The 30 included publications were grouped into 2 areas: animal models ($n = 24$) and human clinical reports ($n = 6$).

Animal Models

Table 1 details DBS for PTSD in animal models according to brain region stimulated: PFC including mPFC and vmPFC, HPC, VS, and basolateral amygdala (BLA). These articles are summarized below.

PFC Animal Models

Fear conditioning and extinction paradigms have been utilized to explore the role of PFC structures. Vidal-Gonzales et al. [48] found that subdivisions of the mPFC into prelimbic and infralimbic (IL) regions gave opposing results to DBS. Stimulation applied to prelimbic during extinction increased freezing behavior during extinction recall, whereas stimulation to the IL decreased freezing behavior, indicating an anxiolytic effect – a result also found by others [49, 50]. Research by Milad and Quirk [51] and Milad et al. [52] only observed these effects of IL stimulation when it was administered 100–400 ms after tone presentation. Others applied high-frequency stimulation to IL for 10 min after fear conditioning and extinction, and

Fig. 2. Flow diagram of review strategy and number of publications.

when rats were reexposed to the fear-conditioned context, freezing behavior was reduced [53–56]. DBS for PFC may thus depend on the PFC region and stimulation parameters.

HPC Animal Models

High-frequency stimulation to the HPC after fear extinction resulted in reduced freezing behavior during recall sessions [56, 57]. Research by Deschaux et al. [58] and Garcia et al. [59] using similar methodology but applying DBS at low frequencies (2 Hz) for 25 min to dorsal Cornu Ammonis 1 and Cornu Ammonis 2 regions found that this increased freezing behavior during retention training. However, Cleren et al. [60], delivered low frequency stimulation for 25 min to ventral Cornu Ammonis 1 instead, at either 6 or 14-h after fear conditioning and found freezing behavior was reduced during extinction. Hence, hippocampal studies suggest that the improvements in anxiety-like behavior may depend on the target regions and stimulation protocols.

Ventral Striatal Animal Models

Rodriguez-Romaguera et al. [61, 62] and Do-Monte et al. [63] showed that rats with electrodes implanted in the VS dorsal to the anterior commissure (AC) demonstrated significantly less freezing behavior than sham controls. The opposite effect was observed in those with electrodes implanted in the VS ventral to the anterior commissure.

Whittle et al. [64] used a fear-conditioning paradigm in mice to measure the effect of DBS to the VS core. DBS was administered during fear conditioning, during extinction training and extinction retrieval. DBS during conditioning and extinction was found to not affect freezing behavior compared to sham controls. However, DBS during extinction retrieval significantly reduced freezing behavior.

Amygdala Animal Models

Research into BLA DBS has mainly used the defensive burying paradigm. This is an innate behavior observed in rats, whereby objects that are threatening, dangerous, or associated with unpleasant experiences are buried. Treatments reducing an animal's tendency to defensively bury objects are seen as anxiolytic. Saldivar-Gonzalez et al. [65] used this paradigm in which rats were to bury a shocking rod. DBS was delivered in a single session prior to behavioral testing, at 3 different intensities. Animals were reported to show reduced burying at 150 and 300 μ A.

Langevin et al. [66] and Stidd et al. [67] used defensive burying paradigms, exposing rats to a ball (the conspicuous object), and giving them a series of inescapable shocks. DBS to the right BLA or sham treatment was administered for 4 h a day over 7 days, prior to defensive burying. Rats treated with right BLA DBS, spent significantly less time burying the ball than sham controls. Additionally, Sui et al. [68] used same protocol of right BLA DBS following fear conditioning and found significant

Table 1. Details of PTSD in animal models

Authors	Rats, <i>n</i>	Theoretical rationale for target	PTSD animal paradigm	Brain targets	Stimulation parameters	Stimulation onset	Outcome
Vidal-Gonzalez et al. [48]	Not known	Human imaging research	Fear conditioning	PFC	100 Hz; 100 μ A to PL or IL	During extinction	DBS applied to PL increased freezing behavior during extinction recall and DBS to IL had the opposite effect
Reznikov et al. [49]	40	vmPFC role in extinction of fear response	Fear conditioning and extinction	vmPFC	10 or 130 Hz; 90 μ s; 100 or 300 μ A. Acute DBS bilateral IL 130 Hz; 90 μ s; 100 μ A. Chronic DBS bilateral IL	Acute DBS following conditioning, prior and/or during extinction. Chronic DBS 8 h/ day for 14 days, testing days 2 h before and 4 h after assessed	No difference in freezing behavior between weak extinction type mice and strong extinction for acute DBS. Weak extinction mice freezing behavior reduced at chronic DBS
Bentfour et al. [50]	47	Prior research into PFC DBS and human imaging research	Fear conditioning	vmPFC	Two trains 60 s apart of 150 pulses at 250 Hz. DBS bilateral IL	DBS 30 min for 5 days	Decrease of avoidance behavior only after extinction training
Milad et al. [51, 52]	Not known	Human imaging research	Fear conditioning	PFC	300 ms train of 0.2 ms pulse width, 100 Hz; 100 μ A unilateral IL	During extinction	Decrease in freezing behavior only observed when stimulation administered between 100 and 400 ms after tone in extinction recall
Maroun et al. [53]	Not known	Human imaging research	Fear conditioning, conditioned taste, aversion, fear extinction, and reconditioning	PFC	Three sets of 10 trains of 100 Hz pulses with 200 ms intertrain intervals. Interval between sets was 120 s. Total time 10 min. Bilateral stim	Immediately or 3 h after retrieval/ short extinction or before reconditioning	Freezing behavior reduced when DBS is immediately applied. No effect for DBS 3 h after extinction, retrieval, or reconditioning. Same results found for conditioned taste aversion
Zheng et al. [54]	57	Human imaging research	Fear conditioning	mPFC	100 Hz; 500 μ A; 100 μ A DBS bilateral mPFC	After extinction	Reduction in freezing behavior
Nachon et al. [55]	39	Human imaging research	Fear conditioning	mPFC	100 Hz; 500 μ A; 100 μ A DBS bilateral mPFC	After extinction	Reduction in freezing behavior
Deschaux et al. [58]	Not known	Hippocampal dysfunction in animal and human imaging research	Fear conditioning	HPC	2 Hz; 100 μ s; 500 μ A for 25 min DBS dorsal CA1 bilaterally	After extinction	Increased freezing during retention tests
Farinelli et al. [57]	Not known	Hippocampal dysfunction in animal and human imaging research	Fear conditioning	HPC	2 Hz; 100 μ s; 500 μ A DBS dorsal CA1, bilaterally	After extinction	Reduced freezing during extinction recall
Deschaux et al. [56]	78	Replication of Farinelli et al. [57]	Fear conditioning	HPC and mPFC	100 Hz; 100 μ s; 500 μ A DBS to ventral CA1 or mPFC Bilateral implants	After extinction	Reduced freezing during extinction recall for both HPC and mPFC
Garcia et al. [59]	25	Hippocampal dysfunction in animal and human imaging research	Fear conditioning	HPC	2 Hz; 100 μ s; 500 μ A for 25 min unilateral right dorsal CA2 region in between ventral/ dorsal HPC	After extinction	Increased freezing during retention tests

Table 1 (continued)

Authors	Rats, <i>n</i>	Theoretical rationale for target	PTSD animal paradigm	Brain targets	Stimulation parameters	Stimulation onset	Outcome
Claren et al. [60]	Not known	Hippocampal dysfunction in animal and human imaging research	Contextual fear conditioning	HPC	2 Hz; 100 μ s; 500 μ A for 25 min bilateral ventral CA1 DBS	6 or 24 h after conditioning	Reduced freezing during extinction
Rodríguez-Romaguera et al. [61, 62]	129 and 55	Existing research into DBS of VS in OCD	Fear conditioning	VS	130 Hz; 100 μ s; 100 μ A bilateral DBS	1 h before, 1 h during, and 1 h after extinction	DBS dorsal to the AC decreased freezing behavior. The opposite effect was found for DBS ventral to the anterior commissure
Do-Monte et al. [63]	37	Replication of prior research by Rodríguez-Romaguera et al. [12]	Fear conditioning	VS	130 Hz; 100 μ s; 100 μ A bilateral DBS	1 h before, 1 h during, and 1 h after extinction	DBS dorsal to the AC decreased freezing behavior. The opposite effect was found for DBS ventral to the anterior commissure
Whittle et al. [64]	Not known	Existing research into DBS of VS for OCD	Fear conditioning/extinction	VS	130 Hz; 60 μ s; 100 μ A unilateral DBS	During conditioning, during extinction training, during extinction retrieval	Only DBS during extinction retrieval condition decreased freezing. DBS during conditioning/extinction had no effect on freezing behavior
Saldivar-Gonzalez et al. [65]	28	Role of the amygdala in fear and emotional processing	Defensive burying and elevated plus maze	BLA	60 Hz; 75, 150 or 300 μ A DBS bilateral BLA	Single session prior to behavioral testing at 3 different intensities	Decrease in burying time at 150 and 300 μ s. Decrease number of crossing in elevated plus maze at 150 μ s
Langevin et al. [66]	10	Amygdala hyperactivity in PTSD from human imaging research	Defensive burying	Right BLA	160 Hz; 120 μ s; 2.5 V right DBS	4h/day for 7 days prior to defensive burying	Decrease in burying time compared to sham controls
Stidd et al. [67]	20	Amygdala hyperactivity in PTSD from human imaging research	Defensive burying and elevated plus maze	Right BLA	160 Hz; 120 μ s; 2.5 V right DBS	4h/day for 7 days prior to defensive burying/elevated plus maze	Decrease in burying time compared to sham controls. No effect on elevated plus maze
Sui et al. [68]	Not known	Replication of prior research by Langevin et al. [66]	Tone/contextual fear conditioning	Right BLA	200 Hz; 200 μ s; 3 V right DBS	4h/day for 7 days following conditioning	Decrease in freezing response to tone but not context
Hashtjini et al. [69]	40	Amygdala hyperactivity in PTSD from human imaging research and prior research PTSD alleviation from DBS in Animal Models	Fear conditioning	Right BLA	160 Hz; 120 μ s; 2.5 V right DBS	1h/day for 7 days following conditioning	Decrease in freezing behavior compared to controls. No effect on elevated plus maze
Hashtjini et al. [70]	56	Amygdala hyperactivity in PTSD from human imaging research and prior research PTSD alleviation from DBS in Animal Models	Fear conditioning	Right BLA	160 Hz; 120 μ s; 2.5 V right DBS	1h/day for 7 days following conditioning	Decrease in freezing behavior when combined with saffron treatment. No effect for DBS on own

Table 1 (continued)

Authors	Rats, <i>n</i>	Theoretical rationale for target	PTSD animal paradigm	Brain targets	Stimulation parameters	Stimulation onset	Outcome
Dengler et al. [71]	78	Amygdala hyperactivity in PTSD from human imaging research	Avoidance predator scent paradigm	BLA	160 Hz; 120 μ s; 3 V right DBS and bilateral DBS	4h/day 7 days following	Significant decrease in avoidance behavior for bilateral group. Decrease for unilateral group
PTSD Animal model paradigm explanations: conditioning is a behavioral paradigm whereby animals learn to associate a neutral cue (the CS, a tone, or light) with an aversive stimulus (the US, for example, a foot shock). After repeated CS-US pairing, the CS is presented alone and elicits a CR. This is commonly measured as the time an animal spends in a freezing state. Freezing can also be measured in relation to an animal's environment or context. Fear conditioning is suggested to be fundamental in the pathogenesis of PTSD; individuals with PTSD are hypersensitive to adverse stimuli and present strong fear learning. The extinction of fear conditioning is a gradual reduction of the CR after presenting the CS alone, and this process involves the learning of new memories that suppress the CR. Individuals with treatment-resistant PTSD are argued to show deficits in extinction. CA1, Cornu Ammonis 1; CA2, Cornu Ammonis 2; PL, prelimbic; CS, conditioned stimulus; US, unconditioned stimulus; CR, conditioned response.							

decrease of rats' freezing behavior in response to tone. Hashtjini et al. [69] used a fear-conditioning paradigm and found that DBS to right BLA significantly decreased rats' freezing. In a follow-up study [70], a combination of DBS to the right BLA with saffron treatment reduced freezing behavior but not with DBS alone. Recently, Dengler et al. [71] reported that bilateral DBS to the BLA decreases avoidance behavior when using a predator scent avoidance paradigm – which is argued to more closely replicate human PTSD as this is a life-threatening stressor for the rat.

Clinical Research Results

Table 2 details DBS for PTSD in human clinical research, comprising 6 publications on 3 individual patients, summarized below. One pilot trial of DBS of the BLA [72] has resulted so far in 2 published cases with 4 years follow-up for one of the 2 operated patients [73–77]. The authors' rationale for targeting the BLA was based on one hand on the reported rat model research, and on the other hand on human imaging studies using fMRI, positron emission tomography and single-photon emission computed tomography showing that when patients with PTSD are exposed to imagery or audio related to their trauma, the BLA is hyperactive compared to healthy controls [37].

Langevin et al. [73, 74] and Koek et al. [75, 76] described a combat veteran who despite 20 years of pharmacological and psychological treatment remained severely symptomatic. His baseline clinician-administered PTSD scale (CAPS) score was 119, classifying his PTSD as extremely severe. After enrollment, the patient underwent 2-fluorodeoxyglucose positron emission tomography scans, one during resting conditions and 1 during an activated condition consisting of the patient recalling the traumatic event. Images obtained during recall demonstrated higher amygdala metabolism, compared to at rest. Subsequently, bilateral DBS electrodes were implanted in the BLA. Targeting was performed on stereotactic 3T-MRI with gadolinium and with the help of the Schaltenbrand and Wahren Atlas, and the authors used microrecording and macrostimulation through the contacts of the 3,387 Medtronic electrode. The inferior limit of the BLA was located 16 mm lateral and 4 mm posterior to the AC, and 18 mm inferior to the AC-PC plane (although these coordinates may show variations between individuals). The authors used a rather steep trajectory at an angle of 0–10° from the midline and an anterior angle of 70–80° from the AC-PC plane, making sure to avoid the ambient cistern and the lenticulostriate vessels. This approach al-

Table 2. Details of DBS for PTSD in 3 published patients

Authors, year	Gender of patients, <i>n</i>	PTSD	Brain target	Follow-up	Stimulation parameters	Outcome
Langevin et al. [73] Langevin et al. [74] Koek et al. [75] Koek et al. [77] Koek et al. [76]	1 male (combat veteran)	Combat veteran	Bilateral BLA	4 yr	Right side 1.4 V, 60 μ s, 160 Hz Left side 0.7 V, 60 μ sec, 160 Hz	40% reduction in CAPS scores
Hamani et al. [78]	1 female (domestic abuse)	Domestic abuse	Bilateral mPFC and uncinate fasciculus	6 mo	6.5 mA, 90 μ s, 130 Hz	>30% reduction in CAPS scores 100% reduction in CAPS scores

lowed for a DBS lead placement that spanned the central nucleus of the amygdala, the BLA, and the head of the HPC [74]. Substantial clinical improvement was reported 8 months postoperatively, with a reduction in CAPS score to 74 (37.8% reduction) and at 15 months a reduction to 62 (48% reduction) [73, 75]. Stimulation parameters were 1.4 V, 60 μ s, 160 Hz on the right side and 0.7 V, 60 μ s, and 160 Hz on the left side. In a 2-year update Koek et al. [76] reported “over a year of essentially complete suppression of previously nightly severe combat nightmares,” but hospitalization at 17 months for suicidality. At 4 years, the patient had maintained a 40% reduction in CAPS scores [76]. Recently, Koek et al. [76, 77] presented the results of a second operated patient, a 40-year-old Iraq combat veteran, who showed >30% amelioration in CAPS scores at 7 months post-surgery.

In 2020, Hamani et al. [78] published the results of DBS in the mPFC and the uncinate fasciculus in a 46-year-old woman with a 17-year history of PTSD due to domestic abuse. For surgical targeting, the authors relied on a 3T-MRI scan using a T1-magnetization prepared rapid acquisition gradient-echo sequence and diffusion tensor imaging sequences. They centered the DBS lead on the subgenual cingulum with manual adjustments allowing to maximize contact with the uncinate fasciculus. They used Boston Scientific directional Vercise electrodes so that one of the 2 middle directional electrodes was placed near the uncinate fasciculus. They state that this allowed stimulation of the uncinate fasciculus as well as the cingulate bundle, forceps minor, and frontostriatal projections. Their rationale for using these brain targets were based on experiments on rat models of PTSD by Reznicov et al. [49]. At 6-month follow-up, the patient, who scored 56 on the CAPS before surgery, showed 100% improvement as well as substantial improvement in depression, global assessment of functioning, and quality of life [78].

Discussion

Several issues were revealed by this review of the literature on experimental and clinical DBS for PTSD. First, when compared to virtually all other human DBS applications – whether in movement disorders or in neuropsychiatric illness – PTSD is the only potential clinical indication of DBS that shows an extensive animal research background prior to pilot human applications. Indeed, our review revealed 24 published reports on DBS in hundreds of rat models of PTSD, compared to 3 published PTSD patients who received DBS.

In the rat models of PTSD, DBS has been trialed on various brain areas considered to be implicated in the circuitry underpinning fear and behavioral reactions to fear: amygdala, PFC including the anterodorsal cingulum, VS, and HPC. In the 3 published clinical cases of PTSD, the DBS targets included the BLA in 2 patients and the mPFC in one, both yielding encouraging results.

Animal Models versus Clinical PTSD

In translating animal models research to humans, several criteria must be met. The behavior observed must be analogous to that in humans, models should test predictions regarding the disorder’s mechanism and etiology, and must share comparable neural mechanisms [10]. Neural mechanisms in animals seem to agree with neuroimaging research in humans on the neurocircuitry involved. While structure and connectivity of the amygdala in rodents correlates well with human anatomy [79], comparisons between prefrontal and hippocampal structures in rodents and humans are controversial due to topological differences [80, 81].

Animal models typically study short-term fear/anxiety, rather than long-term symptomatology of PTSD [29]. To accurately reflect PTSD, animals should develop long-

lasting fear/anxiety responses when reexposed to cues [82, 83]. Contrary to patients with treatment refractory PTSD who have undergone many treatments, most animal models are administered DBS as an initial treatment. Furthermore, delivering short time intervals of DBS in animals does not adequately emulate the continuous (for years) application in humans, failing to explore chronic consequences of DBS [29]. As such, models used to mimic PTSD states in rodents fail to meet the above criteria and may need interpreting with caution [84].

Treatment refractory PTSD is a heterogenous and multifaceted complex disorder, with a multitude of cognitive and physiological symptomology including impact on individuals' disease presentation by variable social and environmental factors [29]. Animal models cannot replicate this complexity.

Deep Brain Stimulation for PTSD?

For over 30 years DBS has been used to treat >208,000 patients worldwide, the majority suffering from Parkinson's disease, tremor, and dystonia [47]. Although modern DBS in neuropsychiatry was inaugurated in 1999 with DBS for OCD [85], and DBS for Gilles de la Tourette syndrome [86], then in 2005 with DBS for depression [87], so far DBS in these conditions has not made a dent, nor has it reached the level of routine surgical treatment as has been the case since long time for DBS in movement disorders [88]. However, the mere probing of DBS as a treatment of severe refractory neuropsychiatric conditions has extended the potential applications of DBS to new "indications," one of which is thus PTSD. It is in this perspective that one can understand the interest of DARPA in late 2013 to finance research in DBS with 70 million USD over 5 years [46]. However, a consultation of registered clinical trial on <https://clinicaltrials.gov/>, (accessed September 19, 2021), using search words "deep brain stimulation" rendered a total of 563 trials, of which 50 are for DBS in OCD and 152 for DBS in depression. For DBS and PTSD, the site lists had only 3 trials, of which one is "Active not recruiting," one "Withdrawn," and one "Recruiting." The latter trial indicates a "study start date" in 2014, aims at recruiting 6 patients, and indicates an "Estimated study completion date" by December 31, 2025. The brief summary provided for this trial states that PTSD "affects 30% of American veterans returning from Iraq and Afghanistan" and that "combat PTSD has a tendency to be resistant to current treatments." Hence, the authors propose to trial "DBS of the basolateral nucleus of the amygdala." As shown in Table 2, the authors of this trial have presented the 4 years

results of the first patient and the 7 months results of the second patient.

The most recently registered trial (<https://clinicaltrials.gov/ct2/show/NCT04152993>) deals with responsive DBS for PTSD and aims to enroll 6 participant veterans with severe PTSD. It proposes to target the BLA, and based on the fact that in PTSD, local field potentials recordings from the BLA reveal a pattern of signals that correspond to an exaggerated state of fear, the trial aims at using these local field potentials signals as a biomarker in order to program the DBS device to detect them and deliver the stimulation when needed, that is, on demand, instead of using continuous stimulation.

Although neurocircuitry of OCD is well studied in animal and in man [89], and data from pilot patients arguably demonstrate a potential for DBS to improve PTSD in combat veterans, over the last 7 years only 2 patients were recruited and published. Experience in these 2 patients has shown that DBS should be carefully monitored because it may yield different and conflicting clinical responses dependent on the strength of stimulation and exact location of the electrode within the BLA [90]. Although Langevin et al. and Koek et al. found significant improvements in their first patient following BLA DBS, a CAPS score of 62 is still deemed as rather severe PTSD [91]. Additionally, as in DBS for other neuropsychiatric disorders, there is a frequent need for battery changes and battery depletion or accidental disconnections may result in rebound of symptoms and even suicidal crisis [92, 93]. PTSD in humans is further complicated in this respect as differences in trauma type can differentially affect responsiveness, as well as sleep disturbances, hyperarousal, and dissociation [11], and symptoms involved are not only limited to extinction deficits and anxiety, but also disturbances in cognition, difficulties with affect regulation, self-perception, and interpersonal relationships.

Ethical Issues

Importantly, there may be ethical issues in relation to obtaining full informed consent from individuals who are severely ill [94–96]. Within this, PTSD is related to changes in cognition and in affect, which can further exacerbate concerns around informed consent. Potential ethical concerns may also arise from clinical trial funded by the department of veteran affairs and the DARPA [97, 98]. In an article published in *Nature* in 2015 [98], Sara Reardon voiced concerns in relation to DARPA's involvement in some neurological research projects, stating that DARPA's program managers can fund projects without waiting for peer review, and researchers are often termed as

“performers” with projects axed if milestones are not on time. Be it as it may, ethical issues surrounding potential indications for DBS are not confined to use of DBS for PTSD, which after all is an illness and a highly relevant disorder in need of treatment. There may be other more debatable issues related to DBS “indications” such as reports showing support for the idea of using DBS to enhance memory in healthy people [99], or to treat “antisocial behavior,” and improve “morality” [100].

Conclusion

PTSD is a heterogenous disorder involving multiple brain circuitries. There is a solid wealth of data from DBS applied to various nodes in the brain circuitry of rodent models of PTSD, of which one is investigated in a clinical trial of DBS targeting the BLA. While the first 2 combat veterans who received BLA DBS for PTSD in a registered clinical trial have shown promising results, it seems that there are difficulties in recruitment of patients for this trial. This may be probably due to cautious interpretation of results for such a complex condition and perhaps to reluctance of combat veterans with severe PTSD to undergo such trial. Though DBS is shown to potentially help treat fear extinction and anxiety, it is as yet unclear whether other aspects of PTSD will improve, and whether patients are able to reintegrate in their social role and in the community. Despite initial enthusiasm and funding, and

despite the obvious need to address and treat the not so uncommon neuropsychiatric consequences of combat on veteran soldiers, it is uncertain as to what extent DBS will become a common, accepted, and efficient treatment of PTSD in the future. In this, DBS for PTSD shares even more the fate of all DBS in psychiatry, including DBS for OCD and DBS for depression which is still not considered “established” despite all reports and case series and clinical trials that have been published in the last 2 decades [101].

Conflict of Interest Statement

J.F. declares no conflicts of interest. M.H. received speaker honoraria from Boston Scientific.

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Author Contributions

J.F. contributed to study conduct; data collection; analysis and interpretation; first manuscript drafting, revision, and approval. M.H. contributed to study design; study conduct; data collection; analysis and interpretation; manuscript drafting, revision, and approval.

References

- 1 Tully J, Bhugra D, Lewis SJ, Drennan G, Markham S. Is PTSD overdiagnosed? *BMJ*. 2021;373:n787.
- 2 American Psychiatric Association. *Diagnostic and statistical manual of mental disorders, fourth edition*. Washington, DC: American Psychiatric Press; 1994.
- 3 Koenen KC, Ratanatharathorn A, Ng L, McLaughlin KA, Bromet EJ, Stein DJ, et al. Posttraumatic stress disorder in the world mental health surveys. *Psychol Med*. 2017; 47(13):2260–74.
- 4 Ayuso-Mateos JL. *Global burden of post-traumatic stress disorder in the year 2000. version 1 estimates*. World Health Organization; 2002.
- 5 Lopez AD, Mathers CD, Ezzati M, Jamison DT, Murray CJL. Measuring the global burden of disease and risk factors, 1990–2001. In: Lopez AD, Mathers CD, Ezzati M, editors. *Global burden of disease and risk factors*. Washington, DC: World Bank Group; 2006. p. 1–14.
- 6 Kessler RC, Berglund P, Demler O, Jin R, Merikangas KR, Walters EE. Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the national comorbidity survey replication. *Arch Gen Psychiatry*. 2005; 62(6):593–602.
- 7 Yehuda R. Post-traumatic stress disorder. *N Engl J Med*. 2002;346(2):108–14.
- 8 Hoge CW, Castro CA, Messer SC, McGurk D, Cotting DI, Koffman RL. Combat duty in Iraq and Afghanistan, mental health problems, and barriers to care. *N Engl J Med*. 2004; 351(1):13–22.
- 9 Kang HK, Natelson BH, Mahan CM, Lee KY, Murphy FM. Post-traumatic stress disorder and chronic fatigue syndrome-like illness among Gulf War veterans: a population-based survey of 30,000 veterans. *Am J Epidemiol*. 2003;157(2):141–8.
- 10 Reznikov R, Hamani C. Posttraumatic stress disorder: perspectives for the use of deep brain stimulation. *Neuromodulation*. 2017; 20(1):7–14.
- 11 Taghva A, Oluigbo C, Corrigan J, Rezai AR. Posttraumatic stress disorder: neurocircuitry and implications for potential deep brain stimulation. *Stereotact Funct Neurosurg*. 2013;91(4):207–19.
- 12 Watts BV, Schnurr PP, Mayo L, Young-Xu Y, Weeks WB, Friedman MJ. Meta-analysis of the efficacy of treatments for posttraumatic stress disorder. *J Clin Psychiatry*. 2013;74(6):e541–50.
- 13 Breslau N. Outcomes of posttraumatic stress disorder. *J C Psychiatry*. 2001;62 Suppl 17: 55–9.
- 14 Koek RJ, Schwartz HN, Scully S, Langevin J-P, Spangler S, Korotinsky A, et al. Treatment-refractory posttraumatic stress disorder (TRPTSD): a review and framework for the future. *Prog Neuropsychopharmacol Biol Psychiatry*. 2016;70:170–218.
- 15 Koenen KC, Stellman SD, Sommer JF Jr, Stellman JM. Persisting posttraumatic stress disorder symptoms and their relationship to functioning in Vietnam veterans: a 14-year follow-up. *J Trauma Stress*. 2008;21(1):49–57.

- 16 Cohen BE, Marmar CR, Neylan TC, Schiller NB, Ali S, Whooley MA. Posttraumatic stress disorder and health-related quality of life in patients with coronary heart disease: findings from the Heart and Soul Study. *Arch Gen Psychiatry*. 2009;66(11):1214–20.
- 17 Mills KL, Teesson M, Ross J, Peters L. Trauma, PTSD, and substance use disorders: findings from the Australian National Survey of Mental Health and Well-Being. *Am J Psychiatry*. 2006;163(49):652–8.
- 18 Johnson DR, Fontana A, Lubin H, Corn B, Rosenheck R. Long-term course of treatment-seeking Vietnam veterans with posttraumatic stress disorder: mortality, clinical condition, and life satisfaction. *J Nerv Ment Dis*. 2004;192(1):35–41.
- 19 Amir M, Kaplan Z, Kotler M. Type of trauma, severity of posttraumatic stress disorder core symptoms, and associated features. *J Gen Psychol*. 1996;123(4):341–51.
- 20 Elhai JD, Frueh BC, Gold PB, Gold SN, Hamner MB. Clinical presentations of posttraumatic stress disorder across trauma populations: a comparison of MMPI-2 profiles of combat veterans and adult survivors of child sexual abuse. *J Nerv Ment Dis*. 2000;188(10):708–13.
- 21 Naifeh JA, North TC, Davis JL, Reyes G, Logan CA, Elhai JD. Clinical profile differences between PTSD-diagnosed military veterans and crime victims. *J Trauma Dissociation*. 2008;9(3):321–34.
- 22 Zohar J, Amital D, Miodownik C, Kotler M, Bleich A, Lane RM, et al. Double-blind placebo-controlled pilot study of sertraline in military veterans with posttraumatic stress disorder. *J Clinical Psychopharmacol*. 2002;22(2):190–5.
- 23 Richardson JD, Contractor AA, Armour C, Cyr KS, Elhai JD, Sareen J. Predictors of long-term treatment outcome in combat and peacekeeping veterans with military-related PTSD. *J Clin Psychiatry*. 2014;75(14):e1299–305.
- 24 Admon R, Milad MR, Hendler T. A causal model of post-traumatic stress disorder: disentangling predisposed from acquired neural abnormalities. *Trends Cogn Sci*. 2013;17(7):337–47.
- 25 Conrad CD. What is the functional significance of chronic stress-induced CA3 dendritic retraction within the hippocampus? *Behav Cogn Neurosci Rev*. 2006;5(1):41–60.
- 26 Bossini L, Tavanti M, Lombardelli A, Calossi S, Polizzotto NR, Galli R, et al. Changes in hippocampal volume in patients with posttraumatic stress disorder after sertraline treatment. *J Clin Psychopharmacol*. 2007;27(2):233–5.
- 27 Gilbertson MW, Shenton M, Ciszewski A, Kasai K, Lasko NB, Orr SP, et al. Smaller hippocampal volume predicts pathologic vulnerability to psychological trauma. *Nat Neurosci*. 2002;5(11):1242–7.
- 28 Villarreal G, Hamilton DA, Petropoulos H, Driscoll I, Rowland LM, Griego JA, et al. Reduced hippocampal volume and total white matter volume in posttraumatic stress disorder. *Biol Psychiatry*. 2002;52(2):119–25.
- 29 Reznikov R, Binko M, Nobrega JN, Hamani C. Deep brain stimulation in animal models of fear, anxiety, and posttraumatic stress disorder. *Neuropsychopharmacology*. 2016;41(12):2810–7.
- 30 Hou C, Liu J, Wang K, Li L, Liang M, He Z, et al. Brain responses to symptom provocation and trauma-related short-term memory recall in coal mining accident survivors with acute severe PTSD. *Brain Res*. 2007;1144:165–74.
- 31 Milad MR, Pitman RK, Ellis CB, Gold AL, Shin LM, Lasko NB, et al. Neurobiological basis of failure to recall extinction memory in posttraumatic stress disorder. *Biol Psychiatry*. 2009;66(12):1075–82.
- 32 Vasterling JJ, Brailey K, Constans JI, Sutker PB. Attention and memory dysfunction in posttraumatic stress disorder. *Neuropsychology*. 1998;12:125–33.
- 33 Vasterling JJ, Duke LM, Brailey K, Constans JI, Allain AN, Sutker PB. Attention, learning, and memory performances and intellectual resources in Vietnam veterans: PTSD and no disorder comparisons. *Neuropsychology*. 2002;16(1):5–14.
- 34 Liberzon I, Taylor SF, Amdur R, Jung TD, Chamberlain KR, Minoshima S, et al. Brain activation in PTSD in response to trauma-related stimuli. *Biol Psychiatry*. 1999;45(7):817–26.
- 35 Pissiota A, Frans O, Fernandez M, von Knorring L, Fischer H, Fredrikson M. Neurofunctional correlates of posttraumatic stress disorder: a PET symptom provocation study. *Eur Arch Psychiatry Clin Neurosci*. 2002;252(2):68–75.
- 36 Shin LM, Orr SP, Carson MA, Rauch SL, Macklin ML, Lasko NB, et al. Regional cerebral blood flow in the amygdala and medial prefrontal cortex during traumatic imagery in male and female Vietnam veterans with PTSD. *Arch Gen Psychiatry*. 2004;61(2):168–76.
- 37 Etkin A, Wager TD. Functional neuroimaging of anxiety: a meta-analysis of emotional processing in PTSD, social anxiety disorder, and specific phobia. *Am J Psychiatry*. 2007;164(10):1476–88.
- 38 Koenigs M, Huey ED, Raymond V, Cheon B, Solomon J, Wassermann EM, et al. Focal brain damage protects against post-traumatic stress disorder in combat veterans. *Nat Neurosci*. 2008;11(2):232–7.
- 39 Bryant RA, Felmingham K, Kemp A, Das P, Hughes G, Peduto A, et al. Amygdala and ventral anterior cingulate activation predicts treatment response to cognitive behaviour therapy for post-traumatic stress disorder. *Psychol Med*. 2008;38(4):555–62.
- 40 Delgado MR, Olsson A, Phelps EA. Extending animal models of fear conditioning to humans. *Biol Psychol*. 2006;73(1):39–48.
- 41 Langevin JP. The amygdala as a target for behavior surgery. *Surg Neurol Int*. 2012;3(Suppl 1):S40–6.
- 42 Payne JD, Jackson ED, Ryan L, Hoscheidt S, Jacobs JW, Nadel L. The impact of stress on neutral and emotional aspects of episodic memory. *Memory*. 2006;14(1):1–16.
- 43 Bear M, Connors B, Paradiso MA. *Neuroscience: exploring the brain*. 4th ed. Philadelphia: Lippincott Williams & Wilkins; 2015.
- 44 Deeb W, Giordano JJ, Rossi PJ, Mogilner AY, Gunduz A, Judy JW, et al. Proceedings of the fourth annual deep brain stimulation think tank: a review of emerging issues and technologies. *Front Integr Neurosci*. 2016;10:38.
- 45 Bina RW, Langevin JP. Closed loop deep brain stimulation for PTSD, addiction, and disorders of affective facial interpretation: review and discussion of potential biomarkers and stimulation paradigms. *Front Neurosci*. 2018;12:300.
- 46 Shen H. Implants aim to track brain signals in real time. *Nature*. 2013. Accessed 2021 Sep 2.
- 47 Vedam-Mai V, Deisseroth K, Giordano J, Lazaro-Munoz G, Chiong W, Suthana N, et al. Proceedings of the eighth annual deep brain stimulation think tank: advances in optogenetics, ethical issues affecting DBS research, neuromodulatory approaches for depression, adaptive neurostimulation, and emerging DBS technologies. *Front Hum Neurosci*. 2021;15:644593.
- 48 Vidal-Gonzalez I, Vidal-Gonzalez B, Rauch SL, Quirk GJ. Microstimulation reveals opposing influences of prelimbic and infralimbic cortex on the expression of conditioned fear. *Learn Mem*. 2006;13(6):728–33.
- 49 Reznikov R, Bambico FR, Diwan M, Raymond RJ, Nashed MG, Nobrega JN, et al. Prefrontal cortex deep brain stimulation improves fear and anxiety-like behavior and reduces basolateral amygdala activity in a preclinical model of posttraumatic stress disorder. *Neuropsychopharmacology*. 2018;43(5):1099–106.
- 50 Bentefour Y, Bennis M, Garcia R, Ba-M'hamed S. High-frequency stimulation of the infralimbic cortex, following behavioral suppression of PTSD-like symptoms, prevents symptom relapse in mice. *Brain Stimul*. 2018;11(4):913–20.
- 51 Milad MR, Quirk GJ. Neurons in medial prefrontal cortex signal memory for fear extinction. *Nature*. 2002;420(6911):70–4.
- 52 Milad MR, Vidal-Gonzalez I, Quirk GJ. Electrical stimulation of medial prefrontal cortex reduces conditioned fear in a temporally specific manner. *Behav Neurosci*. 2004;118(2):389–94.
- 53 Maroun M, Kavushansky A, Holmes A, Wellman C, Motanis H. Enhanced extinction of aversive memories by high-frequency stimulation of the rat infralimbic cortex. *PLoS One*. 2012;7(5):e35853.

- 54 Zheng X, Deschaux O, Lavigne J, Nachon O, Cleren C, Moreau JL, et al. Prefrontal high-frequency stimulation prevents sub-conditioning procedure-provoked, but not acute stress-provoked, reemergence of extinguished fear. *Neurobiol Learn Mem.* 2013; 101:33–8.
- 55 Nachon O, Cleren C, Husson S, Huguet C, Auclair J, Faure S, et al. Prefrontal tetanic stimulation, following fear reconditioning, facilitates expression of previously acquired extinction. *Neurobiol Learn Mem.* 2014;113: 62–8.
- 56 Deschaux O, Motanis H, Spennato G, Moreau JL, Garcia R. Re-emergence of extinguished auditory-cued conditioned fear following a sub-conditioning procedure: effects of hippocampal and prefrontal tetanic stimulations. *Neurobiol Learn Mem.* 2011;95(4):510–8.
- 57 Farinelli M, Deschaux O, Hugues S, Thevenet A, Garcia R. Hippocampal train stimulation modulates recall of fear extinction independently of prefrontal cortex synaptic plasticity and lesions. *Learn Mem.* 2006;13(3):329–34.
- 58 Deschaux O, Thevenet A, Spennato G, Arnau C, Moreau JL, Garcia R. Low-frequency stimulation of the hippocampus following fear extinction impairs both restoration of rapid eye movement sleep and retrieval of extinction memory. *Neuroscience.* 2010;170(1): 92–8.
- 59 Garcia R, Spennato G, Nilsson-Todd L, Moreau JL, Deschaux O. Hippocampal low-frequency stimulation and chronic mild stress similarly disrupt fear extinction memory in rats. *Neurobiol Learn Mem.* 2008;89(4):560–6.
- 60 Cleren C, Tallarida I, Le Guiniec E, Janin F, Nachon O, Canini F, et al. Low-frequency stimulation of the ventral hippocampus facilitates extinction of contextual fear. *Neurobiol Learn Mem.* 2013;101:39–45.
- 61 Rodriguez-Romaguera J, Do Monte FH, Quirk GJ. Deep brain stimulation of the ventral striatum enhances extinction of conditioned fear. *Proc Natl Acad Sci U S A.* 2012; 109(22):8764–9.
- 62 Rodriguez-Romaguera J, Do-Monte FH, Tanimura Y, Quirk GJ, Haber SN. Enhancement of fear extinction with deep brain stimulation: evidence for medial orbitofrontal involvement. *Neuropsychopharmacology.* 2015; 40(7):1726–33.
- 63 Do-Monte FH, Rodriguez-Romaguera J, Rosas-Vidal LE, Quirk GJ. Deep brain stimulation of the ventral striatum increases BDNF in the fear extinction circuit. *Front Behav Neurosci.* 2013;7:102.
- 64 Whittle N, Schmuckermair C, Cinar OG, Hauschild M, Ferraguti F, Holmes A, et al. Deep brain stimulation, histone deacetylase inhibitors and glutamatergic drugs rescue resistance to fear extinction in a genetic mouse model. *Neuropharmacology.* 2013;64(4): 414–23.
- 65 Saldívar-González JA, Posadas-Andrews A, Rodríguez R, Gómez C, Hernández-Manjarrez ME, Ortiz-León S, et al. Effect of electrical stimulation of the baso-lateral amygdala nucleus on defensive burying shock probe test and elevated plus maze in rats. *Life Sci.* 2003; 72(7):819–29.
- 66 Langevin JP, De Salles AA, Kosoyan HP, Krah SE. Deep brain stimulation of the amygdala alleviates post-traumatic stress disorder symptoms in a rat model. *J Psychiatr Res.* 2010;44(16):1241–5.
- 67 Stidd DA, Vogelsang K, Krah SE, Langevin JP, Fellous JM. Amygdala deep brain stimulation is superior to paroxetine treatment in a rat model of posttraumatic stress disorder. *Brain Stimul.* 2013;6(6):837–44.
- 68 Sui L, Huang S, Peng B, Ren J, Tian F, Wang Y. Deep brain stimulation of the amygdala alleviates fear conditioning-induced alterations in synaptic plasticity in the cortical-amygdala pathway and fear memory. *J Neural Transm.* 2014;121(7):773–82.
- 69 Hashtjini MM, Jahromi GP, Sadr SS, Meftahi GH, Hatf B, Javidnazar D. Deep brain stimulation in a rat model of post-traumatic stress disorder modifies forebrain neuronal activity and serum corticosterone. *Iran J Basic Med Sci.* 2018;21(4):370–5.
- 70 Hashtjini MM, Jahromi GP, Meftahi GH. Aqueous extract of saffron administration along with amygdala deep brain stimulation promoted alleviation of symptoms in post-traumatic stress disorder (PTSD) in rats. *Avicenna J Phytomed.* 2018;8:358–69.
- 71 Dengler BA, Hawksworth SA, Berardo L, McDougall I, Papanastassiou AM. Bilateral amygdala stimulation reduces avoidance behavior in a predator scent posttraumatic stress disorder model. *Neurosurg Focus.* 2018;45(2):E16.
- 72 Koek RJ, Langevin JP, Krah SE, Kosoyan HJ, Schwartz HN, Chen JW, et al. Deep brain stimulation of the basolateral amygdala for treatment-refractory combat post-traumatic stress disorder (PTSD): study protocol for a pilot randomized controlled trial with blinded, staggered onset of stimulation. *Trials.* 2014;15:356.
- 73 Langevin JP, Koek RJ, Schwartz HN, Chen JW, Sultz DL, Mandelkern MA, et al. Deep brain stimulation of the basolateral amygdala for treatment-refractory posttraumatic stress disorder. *Biol Psychiatry.* 2016;79(10):e82–4.
- 74 Langevin JP, Chen JW, Koek RJ, Sultz DL, Mandelkern MA, Schwartz HN, et al. Deep brain stimulation of the basolateral amygdala: targeting technique and electrodiagnostic findings. *Brain Sci.* 2016;106(3):28.
- 75 Koek RJ, Langevin J-P, Krah SE, Chen JWY, Kulick AD, Schwartz HN, et al. Amygdala DBS for PTSD: 2 years of observations on the first case. *Brain Stimul.* 2017;10:369.
- 76 Koek R, Langevin J, Krah S, Chen J, Sultz D, Mandelkern M, et al. Basolateral amygdala deep brain stimulation for treatment refractory combat PTSD: data from the first two cases. *Brain Stimul.* 2019;12:429–30.
- 77 Koek RJ, Roach J, Athanasiou N, van 't Wout-Frank M, Philip NS. Neuromodulatory treatments for post-traumatic stress disorder (PTSD). *Prog Neuropsychopharmacol Biol Psychiatry.* 2019;92:148–60.
- 78 Hamani C, Davidson B, Levitt A, Meng Y, Corchs F, Abrahao A, et al. Patient with post-traumatic stress disorder successfully treated with deep brain stimulation of the medial prefrontal cortex and uncinate fasciculus. *Biol Psychiatry.* 2020;88(11):e57–9.
- 79 Rosen JB, Donley MP. Animal studies of amygdala function in fear and uncertainty: relevance to human research. *Biol Psychol.* 2006;73(1):49–60.
- 80 Fanselow MS, Dong HW. Are the dorsal and ventral hippocampus functionally distinct structures? *Neuron.* 2010;65(1):7–19.
- 81 Uylings HB, Groenewegen HJ, Kolb B. Do rats have a prefrontal cortex? *Behav Brain Res.* 2003;146(1–29):3–17.
- 82 Siegmund A, Wotjak CT. Toward an animal model of posttraumatic stress disorder. *Ann N Y Acad Sci.* 2006;1071:324–34.
- 83 Yehuda R, Antelman SM. Criteria for rationally evaluating animal models of posttraumatic stress disorder. *Biol Psychiatry.* 1993; 33(7):479–86.
- 84 Hamani C, Temel Y. Deep brain stimulation for psychiatric disease: contributions and validity of animal models. *Sci Transl Med.* 2012; 4(142):142rv8.
- 85 Nuttin B, Cosyns P, Demeulemeester H, Gybels J, Meyerson B. Electrical stimulation in anterior limbs of internal capsules in patients with obsessive-compulsive disorder. *Lancet.* 1999;354(9189):1526.
- 86 Vandewalle V, van der Linden C, Groenewegen HJ, Caemaert J. Stereotactic treatment of Gilles de la Tourette syndrome by high frequency stimulation of thalamus. *Lancet.* 1999; 353(9154):724.
- 87 Mayberg HS, Lozano AM, Voon V, McNeely HE, Seminowicz D, Hamani C, et al. Deep brain stimulation for treatment-resistant depression. *Neuron.* 2005;45(5):651–60.
- 88 Hariz M, Blomstedt P, Zrinzo L. Future of brain stimulation: new targets, new indications, new technology. *Mov Disord.* 2013; 28(13):1784–92.
- 89 Fenster RJ, Lebois LAM, Ressler KJ, Suh J. Brain circuit dysfunction in post-traumatic stress disorder: from mouse to man. *Nat Rev Neurosci.* 2018;19(9):535–51.
- 90 Lai G, Langevin JP, Koek RJ, Krah SE, Bari AA, Chen JWY. Acute effects and the dreamy state evoked by deep brain electrical stimulation of the amygdala: associations of the amygdala in human dreaming, consciousness, emotions, and creativity. *Front Hum Neurosci.* 2020;14:61.
- 91 Weathers FW, Bovin MJ, Lee DJ, Sloan DM, Schnurr PP, Kaloupek DG, et al. The clinician-administered PTSD Scale for DSM-5 (CAPS-5): development and initial psychometric evaluation in military veterans. *Psychol Assess.* 2018;30(3):383–95.

- 92 Holtzheimer PE, Kelley ME, Gross RE, Filkowski MM, Garlow SJ, Barrocas A, et al. Subcallosal cingulate deep brain stimulation for treatment-resistant unipolar and bipolar depression. *Arch Gen Psychiatry*. 2012;69(2): 150–8.
- 93 Lozano AM, Giacobbe P, Hamani C, Rizvi SJ, Kennedy SH, Kolivakis TT, et al. A multi-center pilot study of subcallosal cingulate area deep brain stimulation for treatment-resistant depression: clinical article. *J Neurosurg*. 2012;116(2):315–22.
- 94 Hariz M, Amadio JP. The new era of neuromodulation. *Virtual Mentor*. 2015;17(1):74–81.
- 95 Klaming L, Haselager P. Did my brain implant make me do it? Questions raised by DBS regarding psychological continuity, responsibility for action and mental competence. *Neuroethics*. 2013;6(3):527–39.
- 96 Stahl D, Cabrera L, Gibb T. Should DBS for psychiatric disorders be considered a form of psychosurgery? Ethical and legal considerations. *Sci Eng Ethics*. 2018;24(4):1119–42.
- 97 United States Veterans Affairs. *VA research on post-traumatic stress disorder*. 2016. Available from: <http://www.research.va.gov/topics/ptsd.cfm>.
- 98 Reardon S. The military-bioscience complex. *Nature*. 2015;522(7555):142–4.
- 99 Lipsman N, Mendelsohn D, Taira T, Bernstein M. The contemporary practice of psychiatric surgery: results from a survey of North American functional neurosurgeons. *Stereotact Funct Neurosurg*. 2011;89(2): 103–10.
- 100 Fumagalli M, Priori A. Functional and clinical neuroanatomy of morality. *Brain*. 2012; 135(Pt7):2006–21.
- 101 Elias GJB, Boutet A, Parmar R, Wong EHY, Germann J, Loh A, et al. Neuromodulatory treatments for psychiatric disease: a comprehensive survey of the clinical trial landscape. *Brain Stimul*. 2021;14(5):1393–403.