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.

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) \cite{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 \cite{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 inappropriate generalize an emotional response of fear, across multiple contexts [41].

DOI: 10.1159/000521130
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.

**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 and baseline 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

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**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. Blues boxes show the HIP, HIP, hippocampus; OFC, orbitofrontal cortex; dmPFC, dorsomedial prefrontal cortex.
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 μA.

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

Fig. 2. Flow diagram of review strategy and number of publications.
### Table 1. Details of PTSD in animal models

| Authors          | Rats, n | PTSD animal paradigm | Brain targets | Theoretical rationale for target | DBS parameters | Stimulation parameters | Stimulation onset | Outcome                                                                 |
|------------------|---------|----------------------|---------------|----------------------------------|----------------|------------------------|------------------|--------------------------------------------------------------------------|
| Vidal-Gonzalez et al. [48] | 40      | Fear conditioning    | PFC           | vmPFC role in extinction of fear response | 10 or 130 Hz; 90 μs; 100 or 300 μA 10 Hz; bilateral IL Chronic DBS 4 h/ day for 14 days, testing 2 h before and after DBS | 100 Hz; 100 μA for PL or IL | During extinction recall and DBS to PL, had the opposite effect on freezing behavior | DBS applied to PL increased freezing behavior during extinction recall and DBS to IL, had the opposite effect on freezing behavior |
| Reznikov et al. [49] | 40      | Fear conditioning    | vmPFC, PFC    | Fear conditioning and extinction | 10 Hz; 130 μA; 90 μs; 100 or 300 μA 100 Hz; bilateral IL Chronic DBS 4 h/ day for 14 days, testing 2 h before and after DBS | 100 Hz; 100 μA for PL or IL | During extinction recall and DBS to IL had the opposite effect on freezing behavior | No difference in freezing behavior between weak extinction type mice and strong extinction type mice for acute DBS. Weak extinction type freezing behavior reduced after chronic DBS |
| Bentefour et al. [50] | 47      | Fear conditioning    | PFC           | Prior research into PFC DBS and human imaging research | 10 Hz; 100 μA; 90 μs; 100 or 300 μA 100 Hz; bilateral IL Chronic DBS 8 h/day for 14 days, testing 2 h before and after DBS | 100 Hz; 100 μA for PL or IL | During extinction recall and DBS to IL had the opposite effect on freezing behavior | DBS applied to PL increased freezing behavior during extinction recall and DBS to IL, had the opposite effect on freezing behavior |
| Milad et al. [51, 52] | Not known | Fear conditioning, conditioned taste, aversion, fear extinction, and reconditioning | PFC | Two trains of 100 Hz pulses with 200 ms intertrain interval, total time 10 min, 250 Hz, bilateral mPFC | 100 Hz; 100 μA; 100 μA DBS | 100 Hz; 100 μA for PL or IL | During extinction recall and DBS to IL had the opposite effect on freezing behavior | Reduction in freezing behavior when stimulation administered between 100 and 400 μA after tone in extinction recall |
| Maroun et al. [53] | Not known | Fear conditioning, conditioned taste, aversion, fear extinction, and reconditioning | PFC | Two trains of 100 Hz pulses with 200 ms intertrain interval, total time 10 min, bilateral mPFC | 100 Hz; 100 μA; 100 μA DBS | 100 Hz; 100 μA for PL or IL | During extinction recall and DBS to IL had the opposite effect on freezing behavior | Decrease in freezing behavior only observed when stimulation administered between 100 and 400 μA after tone in extinction recall |
| Zheng et al. [54] | 57      | Fear conditioning    | mPFC          | Fear conditioning | 100 Hz; 100 μA; 100 μA DBS | 100 Hz; 100 μA for PL or IL | During extinction recall and DBS to IL had the opposite effect on freezing behavior | DBS applied to PL increased freezing behavior during extinction recall and DBS to IL, had the opposite effect on freezing behavior |
| Nachon et al. [55] | 39      | Fear conditioning    | mPFC          | Fear conditioning | 100 Hz; 100 μA; 100 μA DBS | 100 Hz; 100 μA for PL or IL | During extinction recall and DBS to IL had the opposite effect on freezing behavior | DBS applied to PL increased freezing behavior during extinction recall and DBS to IL, had the opposite effect on freezing behavior |
| Deschaux et al. [56] | Not known | Fear conditioning    | mPFC, PFC    | Fear conditioning and extinction | 100 Hz; 100 μA; 100 μA DBS | 100 Hz; 100 μA for PL or IL | During extinction recall and DBS to IL had the opposite effect on freezing behavior | DBS applied to PL increased freezing behavior during extinction recall and DBS to IL, had the opposite effect on freezing behavior |
| Deschaux et al. [57] | Not known | Fear conditioning    | HPC, mPFC    | Fear conditioning and extinction | 100 Hz; 100 μA; 100 μA DBS | 100 Hz; 100 μA for PL or IL | During extinction recall and DBS to IL had the opposite effect on freezing behavior | DBS applied to PL increased freezing behavior during extinction recall and DBS to IL, had the opposite effect on freezing behavior |
| Garcia et al. [58] | 25      | Fear conditioning    | HPC           | Fear conditioning and extinction | 100 Hz; 100 μA; 100 μA DBS | 100 Hz; 100 μA for PL or IL | During extinction recall and DBS to IL had the opposite effect on freezing behavior | DBS applied to PL increased freezing behavior during extinction recall and DBS to IL, had the opposite effect on freezing behavior |
| Authors                      | Rats, n | Theoretical rationale for target | PTSD animal paradigm | Brain targets | Stimulation parameters | Stimulation onset | Outcome                                                                 |
|------------------------------|---------|---------------------------------|----------------------|--------------|------------------------|------------------|-------------------------------------------------------------------------|
| Cleren et al. [60]           | Not known | Hippocampal dysfunction in animal and human imaging research | Contextual fear conditioning | HPC | 2 Hz; 100 μs; 500 μA for 25 min bilateral ventral CA1 DBS | 6 or 24 h after conditioning | Reduced freezing during extinction                                      |
| Rodriguez-Romaguera et al. [61, 62] | 129 and 55 | Existing research into DBS of VS in OCD | Fear conditioning | VS | 130 Hz; 100 μs; 100 μA 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 Rodriguez-Romaguera et al. [12] | Fear conditioning | VS | 130 Hz; 100 μs; 100 μA 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 μs; 100 μA 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 μA DBS bilateral BLa | Single session prior to behavioral testing at 3 different intensities | Decrease in burying time at 150 and 300 μs. Decrease number of crossing in elevated plus maze at 150 μs |
| Langevin et al. [66]         | 10      | Amygdala hyperactivity in PTSD from human imaging research | Defensive burying | Right BLa | 160 Hz; 120 μs; 2.5 V right DBS | 4 h/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 μs; 2.5 V right DBS | 4 h/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 μs; 3 V right DBS | 4 h/day for 7 days following conditioning | Decrease in freezing response to tone but not context |
| Hashtrjini 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 μs; 2.5 V right DBS | 1 h/day for 7 days following conditioning | Decrease in freezing behavior compared to controls. No effect on elevated plus maze |
| Hashtrjini 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 μs; 2.5 V right DBS | 1 h/day for 7 days following conditioning | Decrease in freezing behavior when combined with saffron treatment. No effect for DBS on own |
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-

| Authors | Rats, n | Theoretical rationale for target | STS 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 BLA paradigm | BLA | 160 Hz; 120 μs; 3 V right DBS | 4h/day 7 days following | Significant decrease in avoidance behavior for bilateral group. Decrease for unilateral group |

Table 1 (continued)
followed 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 μs, 160 Hz on the right side and 0.7 V, 60 μs, 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-
last duration 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

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Stereotact Funct Neurosurg 2022;100:143–155
DOI: 10.1159/000521130
“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 heterogeneous 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.

Funding Sources

The authors declare no funding sources.

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, Bhagra 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 posttraumatic 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 Remnikov R, Hamani C. Posttraumatic stress disorder: perspectives for the use of deep brain stimulation. Neuromodulation. 2017; 20(1):7–14.
11 Taghva A, Olugbog 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, Whoseley 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(9):652–8.

18 Johnson DR, Fontana A, Lubin H, Cern 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. 2001;128(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 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, Polizotto NR, Galli R, et al. Changes in hippocampal volume in patients with post-traumatic stress disorder after sertraline treatment. J Clin Psychopharmacol. 2007;27(2):233–5.

27 Gilbertson MW, Shenton M, Ciesielski 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, Petroopoulos 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):101–51.

32 Vasterling JJ, Brailey K, Constans JI, Putker PB. Attention and memory dysfunction in posttraumatic stress disorder. Neuropsychology. 1998;12:125–33.

33 Vasterling JJ, Duke LM, Brailey K, Constans JJ, 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 cerebrobral 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, Raymont V, Cheon B, Kamm M. 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.

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. 2006;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 Langenev JP. The amygdala as a target for behavioral 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, Langenev 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 prefrontal 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-Mhamed 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. Electrophysiological and microstimulation correlates of active fear extinction in the infralimbic cortex. J Neurosci. 2018;38:3555–62.
Cleren C, Tallarida I, Le Guiniec E, Janin F, Deschaux O, Thevenet A, Spennato G, Arnas-Vidal LE, Quirk GJ. Deep brain stimulation of the amygdala facilitates expression of previously acquired fear extinction with deep brain stimulation: a model. Neurosci. 2013; 44(16):1241–5.

Stidd DP, Zhang K, Krail 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.

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. J Neurotransm. 2014;121(7):773–82.

Hashitani MM, Jahromi GP, Sadr SS, Meftahi GH, Hatet B, Javidnazar D. Deep brain stimulation in a rat model of posttraumatic stress disorder modifies forebrain neuronal activity and serum corticosterone. Iran J Basic Med. Sci. 2018;21(4):370–5.

Hashitani MM, Jahromi GP, Meftahi GH. Aqueous extract of saffron administration along with amygdala deep brain stimulation promoted alleviation of symptoms in posttraumatic stress disorder (PTSD) in rats. Avicenna J Phymother. 2018;8:358–69.

Dengler BA, Haskowsh SA, Berardo L, McDougall I, Papathanassiou AM. Bilateral amygdala stimulation reduces avoidance behavior in a predator scent posttraumatic stress disorder model. Neurosurg Focus. 2018;45(2):E16.

Koek RJ, Langevin JP, Krail SE, Kosoyan HJ, Schwartz CHN, 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.

Langevin JP, Koek RJ, Schwartz CHN, Chen JW, Sultzter 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.

Koek RJ, Langevin JP, Krail SE, Kosoyan HJ, Schwartz CHN, Chen JW, et al. Deep brain stimulation of the basolateral amygdala targeting technique and electrodagnostic findings. Brain Sci. 2016;10(6):28.

Koek RJ, Langevin J-P, Krail SE, Chen JYW, Kulick AD, Schwartz CHN, et al. Amygdala DBS for PTSD: 2 years of observations on the first case. Brain Stimul. 2017;10:369.

Koek R, Langevin J, Krokh S, Chen J, Sultzter 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.
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 neuro-modulation. 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.