Neuromodulation for Treatment-Refractory PTSD

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Deep brain stimulation has been successful in treating Parkinson disease and essential tremor and is now reducing PTSD symptoms in the first patient enrolled in an early-phase safety trial.

Failure of fear extinction is a core feature of posttraumatic stress disorder (PTSD).[1] Recently, it was confirmed that the amygdala and the orbitofrontal cortex are crucial for both fear acquisition and fear extinction.[2] The amygdala was found to have neurons active only during fear acquisition, and other neurons active only during fear extinction.[3] In essence, the balance of activity between these 2 neuronal populations determines whether if an incoming stimulus is feared or not feared. This balance is under the influence of several cognitive domains, including memory, reward, and executive function.

In PTSD, the equilibrium is shifted heavily toward fear acquisition. The majority of patients spontaneously regain the capacity for fear extinction over time[4] or with the help of treatment.[5,6] Nonetheless, some patients with severe PTSD seem unable to recover the ability of fear extinction and remain refractory to both standard and novel psychotherapeutic or psychopharmacologic treatments.[7] For these patients, direct modulation of the neural activity in the amygdala may permit fear extinction. This article describes the rationale for using deep brain stimulation (DBS) and initial results from the first-ever clinical trial.

DEEP BRAIN STIMULATION

Deep brain stimulation involves inserting electrodes in precise cerebral targets and then connecting the leads to a pulse generator (similar to a pacemaker) inserted in a subclavicular pocket. The generator controls the electrical signal (amplitude, pulse width, pulse frequency) delivered to the brain target and can be adjusted with use of a noninvasive programmer. In 1997, the FDA approved DBS for patients with Parkinson disease or essential tremor. Since then, its efficacy in these movement disorders has been confirmed in several studies.[8,9]

The mechanism by which the small electrical pulses of DBS influence activity is not clear. Clinically, DBS functionally inhibits the activity of local neurons.[10] One theory describes "frequency jamming," a concept similar to cardiac overdrive pacing in which the resultant high-frequency neuronal signal is meaningless and discounted by the rest of the brain.[11]

Over the years, DBS has demonstrated a strong safety profile.[12] The risks of electrode insertion are mitigated with targeting based on high-quality magnetic resonance imaging (MRI) and computed tomography (Figure). Unlike a destructive lesion, DBS is reversible, and the implanted system can be removed in its entirety. Histologic analyses have shown only a small amount of scarring around the electrode tip.[13] In movement disorder treatment, clinical experience has shown that stimulation-related adverse effects (AEs) are reversible with readjustment of stimulation parameters by external programmer.[14]

Novel Applications of DBS

The advantageous safety profile of DBS has permitted its evaluation in the treatment of other conditions thought to have malfunctioning networks at their core—such as intractable epilepsy (in resective surgery noncandidates).[15,16]

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Although several trials have shown promising results of using DBS for treatment-resistant depression,[17] the results of pivotal sham-controlled trials have been mixed.[18,19] Obsessive-compulsive disorder, on the other hand, received the FDA humanitarian device exemption designation on the basis of positive long-term results.[20] In treatment-resistant depression and obsessive-compulsive disorder, functional neuroimaging has identified DBS targets.[21,22] Functional MRI or positron emission tomography (PET) images can be compared at resting state, at symptomatic state, and after treatment response. Nodes hyperactive during a symptomatic state and less active after successful treatment can be targeted with high-frequency DBS to directly reduce the hyperactivity and indirectly modulate or normalize the overall function of the circuit.[23]

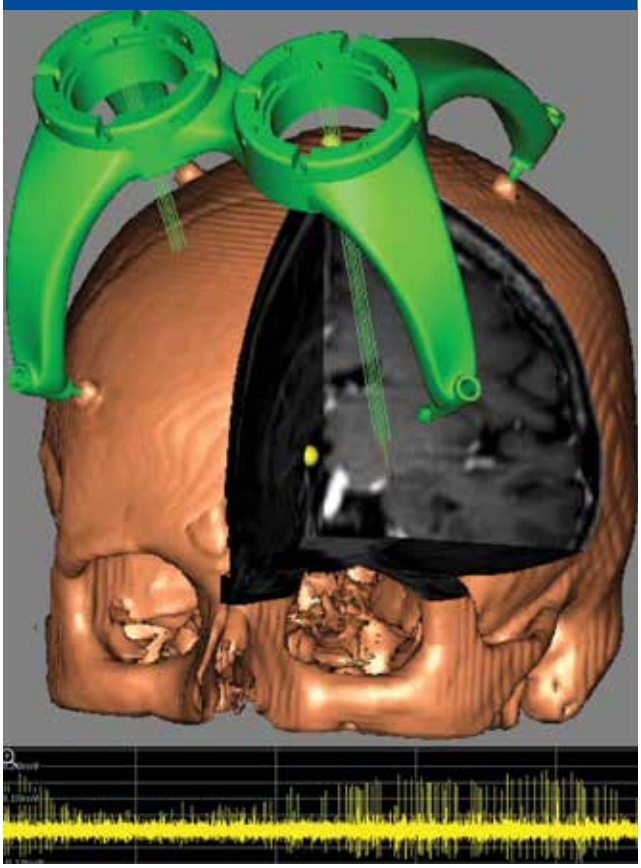
Given the functional MRI and O15 (oxygen-15) PET evidence of amygdala hyperactivity in patients with PTSD having core symptoms,[24-26] the authors hypothesized that high-frequency DBS targeting of the amygdala would improve PTSD-associated hyperarousal and reexperiencing symptoms in treatment-refractory patients. Indirect data supporting this hypothesis include a correlation between amygdala hyperactivity of increased intensity and symptom severity measured with the Clinician-Administered PTSD Scale (CAPS),[27] and a correlation between reduced pretreatment amygdala hyperactivity and successful cognitive-behavioral treatment.[28,29]

PRECLINICAL WORK

Using a rodent model in which a novel object serves as a cue reminder of foot shocks (traumatic event), the authors tested the hypothesis that amygdala DBS would reduce PTSD-like symptoms.[30] When untreated rats were presented with the object in their cage a week after the initial exposure, they immediately buried the object under bedding to avoid being reminded of the shocks. In contrast, rats treated with DBS did not bury the object. In most cases, in fact, they played with it.

The authors also replicated their results but with the addition of rats treated with paroxetine.[31] Using the same rodent model, they found DBS superior to paroxetine in treating PTSD-like symptoms. This study had a crossover design: DBS and sham DBS. Briefly, 20 rats received an electrode in the amygdala and were exposed to inescapable shocks in the presence of the cue object. The rats were then randomly assigned to a DBS group (10 rats) or a sham-DBS group (10 rats). After 1 week, behavioral testing showed fear extinction in the DBS group and no improvement in the sham-DBS group. Then the groups were switched: The rats originally treated with DBS received no treatment, and the rats that were originally sham-treated underwent DBS. One week later, behavioral testing showed acquisition of fear extinction in all the rats. These results suggested DBS can be effective even when delayed after establishment of fear persistence and PTSD symptoms. These results also showed that DBS effects persist even after therapy discontinuation.

Figure. Planned Electrode Trajectory as Seen on 3-Dimensional Reconstruction Using Magnetic Resonance Imaging and Computed Tomography Coregistration



Custom-made frameless system (STarFix; FHC, Inc.) guides electrode. Intraoperative single-unit neuronal recording is represented at inferior aspect of figure.

Table. DSM-IV CAPS21 Scores Over 18 Months for Amygdala Deep Brain Stimulation in a Patient With Combat PTSD

CAPS Score	Study Visit						
	Baseline[a]	3 mo	6 mo	9 mo	12 mo	15 mo	18 mo
Recurrence	39	21	25	23	24	17	21
Avoidance	46	40	37	28	30	28	28
Hyperarousal	34	25	27	26	24	17	23
Total	119	86	89	77	78	62	72

Abbreviations: CAPS, Clinician-Administered PTSD Scale; DSM-IV, *Diagnostic and Statistical Manual of Mental Disorders* (4th ed); PTSD, posttraumatic stress disorder.
[a]Mean of 4 separate assessments over 2-month period.

Similarly, other investigators have reported that the role of the amygdala is not limited to fear acquisition; it extends to fear expression. A lesion in the amygdala can prevent fear expression even if the disruption is performed subsequent to fear-conditioning training.[32] This finding is important for humans, as DBS would be initiated during the chronic phase of the disorder, after failure of less invasive treatment options, such as pharmacotherapy and psychotherapy.

EARLY CLINICAL EXPERIENCE

The authors have initiated the first ever clinical trial (NCT02091843) evaluating use of DBS for PTSD and are now recruiting patients. Enrollment is limited to 6 combat veterans with disabling PTSD that has not responded to pharmacotherapy and psychotherapy. This VA-funded single-site study, being conducted at the VA Greater Los Angeles Healthcare System (VAGLAHS), was approved by the VAGLAHS Institutional Review Board and the FDA. The authors have published the 2-year trial's protocol, which includes an active-versus-sham stimulation phase; continuous electroencephalogram monitoring; baseline and posttreatment ^{18}FDG (fluorodeoxyglucose) PET performed during a resting state vs during investigator-guided exposure to trauma reminders; and extensive psychological and neuropsychological assessments.[33] The literature includes only 1 case report on amygdala DBS.[34] The authors of that report used DBS of the basolateral nucleus of the amygdala to treat a teenaged boy with severe autism and found that the therapy was safe.

As of this writing, the authors have recruited and implanted 1 patient and reported on his clinical results (including baseline PET) over the first 8 months of stimulation[35] and on the electrophysiologic findings over the first year.[36] After experiencing extremely severe combat PTSD refractory to pharmacotherapy and psychotherapy treatments for more than 20 years, the patient treated with DBS is now experiencing substantial symptom relief, and his CAPS score (primary outcome measure) has improved by about 40%. He has tolerated continuous stimulation without any serious DBS-related AEs for up to 16 months. Notably, he has not had a single severe combat nightmare in a year—in stark contrast to nightly combat nightmares during the 20-year period leading to the trial. Furthermore, he has not been having any episodes of severe dissociation, which had been a common disabling problem before the trial. He has taken a second trip out of the country, improved his relationships with family, and made strides (albeit limited) in pursuing additional social interactions.

Avoidance remains a major problem. He recently left his job after 7 years, because he prefers a more nature-oriented rather than people-oriented environment. In addition, his interest in intensive psychotherapy has increased, and he has been considering options for spending more time working on his therapy.

Over 15 months of treatment, the patient's CAPS total and subscale scores have decreased—his symptoms have improved (Table).[21] He has had rapid and substantial reductions in recurrence and hyperarousal symptoms but slower improvement in avoidance. Improvements in emotional reactivity would be expected to occur before any change in behavior (eg, avoidance). Patients likely must first recognize changes in emotional reactivity to events before they can engage in a cognitive process to modify learned behavioral responses to those events.

After about 9 months of treatment, all of the study patient's symptoms were somewhat stabilized, and the authors began making gradual stimulation adjustments to the latest parameters—3.5 V, 60 μs, and 160 Hz for the right electrode and 1.5 V, 60 μs, and 160 Hz for the left electrode—using the contacts in the basolateral nucleus of the amygdala, per postoperative neuroimaging.[35] A thin cuts computed tomography (CT) scan of the brain was obtained postoperatively and merged to the preoperative MRI. The CT scan captured the location of the DBS electrode contacts and the MRI superimposition to determine the position of those contacts in the brain.

After 15 to 18 months, when improvement peaked at 48% symptom reduction from baseline, the patient experienced psychiatric decompensation (depression, suicide gesture) not attributable to changes in stimulation settings and not associated with exacerbation of PTSD symptoms. Treatment team members and independent psychiatric consultants attributed the decompensation to the patient's difficulty in changing a long-standing avoidant behavior routine, owing to severe recurrence and hyperarousal symptoms in the past. His persistent inability to overcome avoidance and isolation, despite core PTSD symptom improvement, had left him feeling worthless.

The patient remains in the study but also is participating in other medication and psychotherapy trials and is making a career change. Periodic decompensations may be part of the treatment course as patients reach a more complex and volatile phase of improvement that requires more intensive cognitive reprocessing. If this proves to be the case with other patients enrolling in the study, intensive psychotherapy that addresses cognitive and emotional PTSD symptoms may be needed once there is improvement in intrusive and hyperarousal symptoms.

CONCLUSION

Deep brain stimulation has been successful in treating Parkinson disease and essential tremor. Physiologically, DBS seems to inhibit specific brain regions' dysfunctional activity stemming from a disease process. Deep brain stimulation-induced inhibition of a dysfunctional node improves clinical outcomes in movement disorders.

Given the reversibility and positive safety profile of DBS, new applications are being studied. The authors propose that DBS may benefit patients with severe treatment-refractory PTSD. Their first patient's core PTSD symptoms have improved significantly, as expected, but as in other psychiatric DBS cases, the seriousness and chronicity of his illness may be complicating the course of recovery. The authors plan to recruit 6 patients for this early-phase safety trial. ●

Author disclosures

The authors report no actual or potential conflicts of interest with regard to this article.

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