

# Deep brain stimulation of the orbitofrontal projections for the treatment of intermittent explosive disorder

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Intermittent explosive disorder (IED) is characterized by a dysfunction in the greater limbic system leading an individual to experience sudden aggressive behavior with little or no environmental perturbation. This report describes a procedure for the treatment of IED in a 19-year-old woman with a history of IED, having had episodes of severe violent attacks against family, dating to early childhood. Due to the severity and intractability of the illness, deep brain stimulation was performed, targeting the orbitofrontal projections to the hypothalamus. The patient's history and the procedure, management, and rationale are described in detail. (DOI: 10.3171/2010.5.FOCUS10102)

**KEY WORDS** • **deep brain stimulation** • **orbitofrontal cortex** • **intermittent explosive disorder**

**I**NTERMITTENT explosive disorder is a psychological illness characterized by episodes of impulsive aggression that are disproportionate to the provocation.<sup>5</sup> The root of such behavior involves a disturbance to the emotional circuitry of the brain. This includes the anterior cingulate cortex, orbitofrontal cortex, amygdala, insular cortex, ventral striatum, and other interconnected circuitry throughout the limbic system that combine to form the emotional brain.<sup>7</sup> The orbitofrontal cortex, the amygdala, and anterior cingulate cortex have been implicated as key regions in impulsive behavioral control, while the anterior cingulate cortex has also been shown to recruit regions of the prefrontal cortex during periods of threat and aggression.<sup>2</sup> The right frontobasal cortex has recently been understood to be an integral part of the limbic system involved in modulating an individual's level of anger.<sup>4,7,15</sup> Almost all patients with IED have brain damage, which is usually traumatic in nature and occurs in the right frontobasal cortex. This damage is associated with a reduction in serotonin binding in the region.<sup>9</sup> In this report, we describe DBS targeted to the projections between the hypothalamus and orbitofrontal cortex as a useful means of treating intractable IED and providing the patient with the ability to control her aggressive behavior and suppress violent outbursts.

*Abbreviations used in this paper:* DBS = deep brain stimulation; IED = intermittent explosive disorder.

## Case Report

**History and Examination.** This 19-year-old woman was born of a traumatic birth and has moderate mental retardation. She was referred to our clinic for the possible treatment of her IED with stereotactic surgery. Intermittent explosive disorder had been diagnosed when the patient was a child. Throughout her life, the patient had experienced episodes in which she lost control of her emotions and engaged in violent attacks against individuals including her mother and grandmother. As she aged, she became increasingly difficult to control during these attacks and required heavy sedation to live at home and avoid institutional commitment. She also experienced depression, was diagnosed with bipolar disorder at one time, and MR imaging demonstrated bilateral atrophy of the hippocampus and hippocampal gyri. As part of her current treatment, the patient was taking Zyprexa (20 mg) at bedtime, Tegretol (200 mg) twice a day, Klonopin (1 mg) every morning, and Lunesta at bedtime. Aside from the previously stated issues, her examination and studies, including the results of her 24-hour electroencephalography, were normal. Therefore, the decision was made to proceed with a DBS procedure targeting the projections between the orbitofrontal cortex and the hypothalamus.

**Operation.** Under stereotactic guidance, with merged MR and CT images, a paramedian incision was made,

and the entry point extended along the coronal suture. The stereotactic electrode was directed just lateral to the lateral ventricle. Proceeding primarily through white matter tract, the electrode was guided into the region below the stria terminalis in the most inferior corona radiata projections from the frontobasal cortex to the hypothalamus. Both our preoperative planning and intraoperative guidance target selection confirmed that the electrode was correctly located at final coordinates of 15 mm anterior to the midcommissural plane, 5 mm lateral to the midsagittal plane, and with contacts level to the plane connecting the anterior and posterior commissures and traversing up to 3 mm ventral to anterior and posterior commissures (Schaltenbrand-Wahren Atlas). When satisfied with the accuracy of the placement, a Lucite lockdown device secured the device, and the electrode extension was brought down to the pulse generator in the subclavicular area. The Soletra neurostimulation system (Medtronic) was used for this patient. The location of the electrode was later confirmed on MR imaging (Fig. 1).

*Postoperative Course.* The patient recovered postoperatively without complications and was discharged home. She was then seen 1 month later, after her wounds had healed well, so that we could activate the stimulator. The visit took place with family, who stated that the patient was continuing with violent episodes and was completely uncooperative at times. The stimulation setting plan was to consist of high- and low-frequency stimulation trial periods with adjustments made during each period as needed. The DBS system was activated with contact settings of 0–2 negative and 3 positive. Stimulation was set to a high frequency of 130 Hz, amplitude of 4 V, with a 120- $\mu$ sec peak width to block the pathway. This resulted in immediate elimination of agitation and aggression. The patient was instantly cooperative, and at this point she turned to her family and described a sudden change in her emotions, stating that she “felt much better.” Her facial expression was calmed. Her motor skills were examined and her handwriting had markedly improved, likely because she previously had difficulty

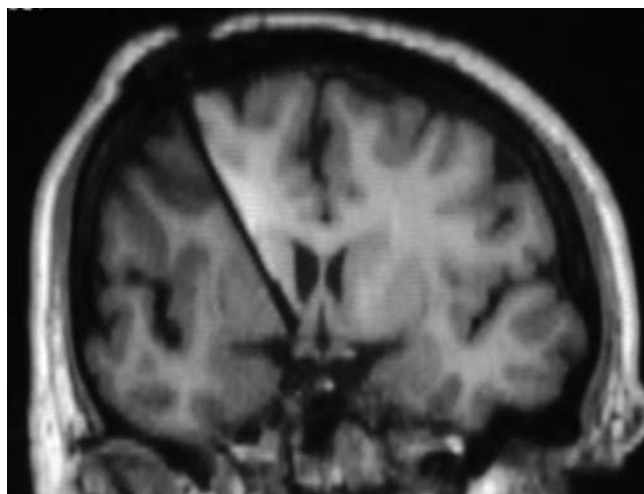


Fig. 1. Postoperative T1-weighted MR image demonstrating electrode placement in the basal projections from the orbitofrontal cortex.

forming letters in an agitated state. Several hours after stimulation began, her family reported that her memory had improved and she was fully compliant with instructions. The patient's Zyprexa was therefore ceased, but the other medications were continued. The family returned 1 week later, stating that her agitation and “acting out” had markedly increased, and they asked that the stimulation be turned off. She was described as being quite irritable at times and had run away from home. Her family did, however, report a more outgoing, talkative demeanor, and they believed for the first time that the patient was vocalizing her feelings. She had taken on some independence at home, albeit little. She was described as much less lethargic, was not sleeping throughout the day, and her memory and handwriting had improved. Despite these changes, during this period she had experienced outbursts of anger that prompted psychiatric hospitalization. Klonopin was discontinued, and the Tegretol dose was reduced. We discontinued blocking stimulation and went to activation levels of stimulation. Low-frequency stimulation was then tested with initial settings at 2.8-V amplitude, 55 Hz, 270- $\mu$ sec peak width, and with a cycle in which stimulation was on for 3 minutes and off for 5 minutes.

*Follow-Up and DBS Adjustments.* After 6 weeks with the aforementioned stimulation settings, the patient's performance in school had improved significantly, and there had been no violent outbursts. She had been able to attend church and was socializing better, but she remained argumentative at times, though this was always provoked. She returned to clinic and her stimulation settings were adjusted to a cycle of 3 minutes on and 3 minutes off.

At the 5-month evaluation, the family reported a violent verbal outburst directed toward a teacher. The patient was also admitted to the hospital with pneumonia during this period. When her stimulation was turned off during testing in the hospital, she attacked the technician and was immediately calmed with restoration of stimulation. At this visit, her peak width was increased to 360  $\mu$ sec and frequency reduced to 40 Hz.

At the 7-month follow-up, the patient was becoming increasingly argumentative, displayed some obsessive-compulsive behavior, and had experienced panic attacks. Once again, a reduction in her IED drugs was attempted. Six weeks following this adjustment, however, the patient became severely depressed. She overdosed on her medication and spent the next 3 months in a psychiatric ward.

Following this episode, the patient reported for her 12-month follow-up visit. Her DBS settings were adjusted to a 2.5-V amplitude, 40 Hz, and 360- $\mu$ sec peak width. These settings produced agitation and were therefore adjusted to 20 Hz, 2-V amplitude, with cycling of 1 minute on and 1 minute off stimulation. The patient was immediately calmed following this adjustment. The family reported that in the weeks following this visit the patient socialized well, and marked improvements were seen in her memory, concentration, and performance in school.

Currently, 2 years out from the operation, the patient has had no other violent outbursts or physical altercations, and she continues to control any agitation through verbal interaction. The improvements in her performance in

school have been maintained, and she no longer requires heavy sedation or antipsychotic drugs. Her socialization continues to be markedly improved. The stimulator settings have remained unchanged since the 12-month follow-up visit. We have observed, through various adjustments to the neurostimulator, that a fine line exists between control of symptoms and depression in this individual. The effects of the adjustment are quickly evident, however, thus facilitating our finding of the optimal settings.

### Discussion

#### *Prevalence of IED*

Recent estimates have found shown IED may have a prevalence of 2–5% in the general population, a value that could exceed bipolar disorder or schizophrenia.<sup>6</sup> Furthermore, IED is associated with a high rate of lifetime bipolar disorder comorbidity.<sup>22</sup> The consequences for an individual with this disorder can be as severe as committing a violent crime, but it may involve more minor episodes, which remain highly detrimental to the quality of their professional and personal lives. A recent epidemiological survey found lifetime and 12-month prevalence estimates of DSM-IV IED to be 7.3% and 3.9%, with a mean of 43 lifetime attacks resulting in an average of \$1359 in property damage.<sup>17</sup>

#### *Surgical Approaches to Aggressive Disorders*

Current and historical approaches to the surgical treatment of aggressive disorders have included both lesioning and stimulation of structures involved in modulating aggression within the limbic system. Goltz,<sup>11</sup> in 1892, and Klüver and Bucy,<sup>19</sup> in the 1930s, demonstrated that bilateral temporal lobectomy in animals attenuated aggressiveness and fear responses, rendering the animals, as Klüver and Bucy stated, psychically blind.<sup>8</sup> This early exploration into the neuroanatomy of the limbic system, along with Papez's 1937 description<sup>27</sup> of the neural circuit involved in emotion, helped to shape modern surgical approaches to treat aggressive disorders. Due to its well-defined involvement in emotion and aggression, the amygdala became the first major surgical target for aggressive disorder treatment. In 1963, Narabayashi et al.<sup>24</sup> published the first large series of patients treated with amygdalotomy for severe aggressive disorders, reporting that surgery reduced aggression and improved social behavior in 85% of the cases. More recently, Mpakopoulou et al.<sup>23</sup> described historical and current perspectives on amygdalotomy. They concluded that although the procedure was used frequently since its initial description for the treatment of aggressive disorders, advances in pharmacotherapies and a growing stigma associated with psychosurgery have led to a decrease in its use. They felt, however, that with modern stereotactic surgical techniques, the procedure should still be considered for patients with severe aggressive disorders refractory to current therapies. In 2002, Kim et al.<sup>18</sup> reported long-term follow-up of 2 patients with aggressive disorders in whom they performed bilateral amygdalotomy and subcaudate tractotomy. A stereotactic approach and a radiofrequency

lesion generator were used to target these regions. Aggression was measured pre- and postoperatively with the Overt Aggression Scale, which assigns points based on various physical and verbal behaviors.<sup>13</sup> The authors found a decline in aggression at 2-weeks and at 7-year follow-up visits with improvement in social behavior.<sup>18</sup>

Deep brain stimulation of the hypothalamus has also been described as a means of controlling intractable aggressive disorders.<sup>10,14,20</sup> Hernando and colleagues<sup>14</sup> described one such case of a young man with mental retardation and intractable aggressive disorder in whom bilateral electrodes were implanted in the medial posterior hypothalamus. The authors employed low-frequency stimulation and stated that a positive behavioral response was sustained at the time of reporting, 18 months postoperatively. Similarly, Kuhn et al.<sup>20</sup> reported a case involving bilateral stimulation of the posterior hypothalamus for the treatment of severe self-mutilation in a mentally retarded young woman. The authors used high-frequency (130-Hz) stimulation and achieved sustained elimination of self-mutilating behavior.

#### *Nonsurgical Therapies for IED*

Serotonin (5-hydroxytryptamine) is believed to be the critical neurotransmitter in modulating violent impulsive behavior.<sup>9</sup> Studies examining inhibition of serotonin biosynthesis, either in individuals with tryptophan hydroxylase enzyme polymorphism<sup>26</sup> or in those in whom tryptophan is removed from the diet,<sup>3</sup> have found significant increases in aggressive behavior associated with low levels of serotonin. Traditional treatment for IED may include behavioral therapy, pharmacotherapy, or a combination. Pharmacotherapy includes selective serotonin reuptake inhibitors, mood stabilizers, and beta-blockers, all meant to modulate the level of emotional arousal or inhibition within the limbic system. However, because controlled trials for IED pharmacotherapies are absent, the efficacy of these treatments is largely anecdotal.<sup>1</sup> Although these treatments are part of the standard of care, in our case the patient's condition remained refractory to such pharmacological therapies and her behavior had progressed to a point where more aggressive treatment was necessary.

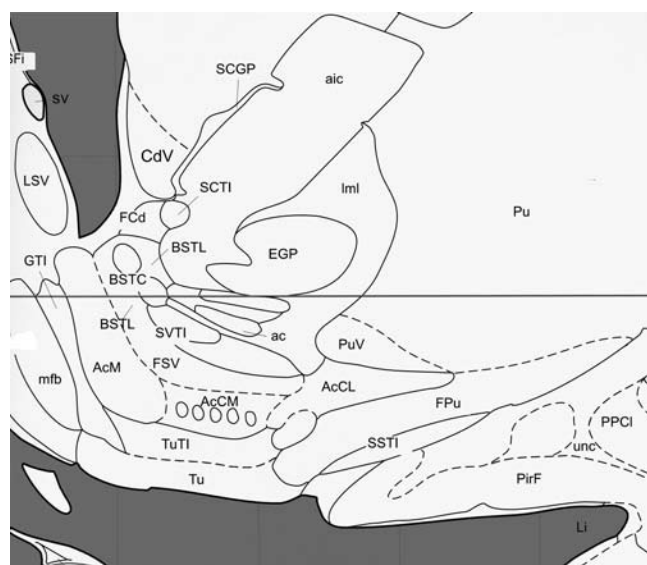
#### *Target and Procedure*

As discussed earlier, the inferior tracts from the orbitofrontal cortex were chosen as a target because of their role in the conduction of signals related to emotion and particularly aggression within the greater limbic system. Recently, PET and functional MR imaging studies have shown that individuals with loss of impulse control and explosive disorders have abnormal activity localized specifically to the right orbitofrontal cortex.<sup>4,7,28</sup> This interesting asymmetrical involvement of the regions related to aggressive behavior prompted our use of unilateral right-side stimulation. In our case, the location of the electrode within the stria terminalis and orbitofrontal cortical projections was confirmed intraoperatively with stereotactic instrumentation in concert with MR imaging and CT overlays. In our region of stimulation, the combination of

multiple small nuclei and tracts such as the stria terminalis, nucleus accumbens, and others, in proximity, makes defining a specific target difficult. Our definition of the right orbitofrontal cortical projections through the most inferior internal capsule as our primary target is based on imaging studies and symptom reduction. The predicted reduction in symptoms related to the orbitofrontal cortex, including proper modulation of defensive rage and aggression, was seen following stimulation.<sup>12,16,25</sup> Figure 2 is a diagrammatic coronal slice that demonstrates the proximity of the stria terminalis to the nucleus accumbens and anterior limb of the internal capsule at approximately 16 mm anterior to the midcommissural plane. The region traversed by our electrode leads involves each of these 3 structures, and it is therefore possible that each is affected by stimulation. It is difficult, however, to compare our results with studies examining DBS of the nucleus accumbens and internal capsule, as these studies have used different stimulator settings and were for the treatment different disorders, most notably obsessive-compulsive disorder.<sup>16,25</sup> Due to these differences, we cannot definitively state that any single nuclear region is the sole target of stimulation. However, through careful examination of postoperative MR imaging and analysis of our coordinates with multiple stereotactic atlases, we conclude that the orbitofrontal cortical tracts remain the primary target.

## Conclusions

In the case presented in this report, the goals of attenuating aggressive impulses and providing the patient with control over her emotions and violent outbursts were achieved. A significant improvement in the quality of life



**Fig. 2.** Diagrammatic coronal slice at approximately 16 mm rostral to the midcommissural plane, demonstrating the region traversed by the electrode array. The straight line denotes the plane connecting the anterior and posterior commissures. Ac = regions of nucleus accumbens; Aic = anterior internal capsule; BSTL = bed nucleus of stria terminalis; Pu = putamen. The image is reprinted from Mai JK, Assheuer J, Paxinos G: *Atlas of the Human Brain*, ed 2. San Diego: Elsevier Academic Press, 2004.

of both the patient and her family was seen almost immediately upon determining the proper settings of her stimulator. As mentioned previously, we found that there was a fine line between achieving control of symptoms and producing some depression as well as obsessive-compulsive disorder symptoms. The change in behavior was seen nearly instantly after adjusting stimulator settings, however, thus facilitating our determination of optimal settings at each clinic visit. While high-frequency settings appeared to stimulate defensive rage in this individual, our final low-frequency settings were successful in attenuating this pathway. This case demonstrates the vast potential that DBS holds for psychological disorders if the appropriate targets are chosen and the correct stimulation settings are achieved.

## Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author contributions to the study and manuscript preparation include the following. Conception and design: Alvernia, Maley, Richardson. Drafting the article: Maley. Critically revising the article: Alvernia, Maley, Valle.

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