Directional Deep Brain Stimulation of the Posteromedial Hypothalamus for Refractory Intermittent Explosive Disorder: A Case Series Using a Novel Neurostimulation Device and Intraoperative Microdialysis

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■ BACKGROUND: **Intermittent explosive disorder (IED) is a psychiatric disorder characterized by recurrent outbursts of aggressive behavior. Deep brain stimulation (DBS) in the posteromedial nucleus of the hypothalamus (pHyp) is an alternative therapy for extreme cases and shows promising results. Intraoperative microdialysis can help elucidate the neurobiological mechanism of pHyp-DBS. We sought to evaluate efficacy and safety of pHyp-DBS using 8-contact directional leads in patients with refractory IED (rIED) and the accompanying changes in neurotransmitters.**

■ METHODS: **This was a prospective study in which patients with a diagnosis of rIED were treated with pHyp-DBS for symptom alleviation. Bilateral pHyp-DBS was performed with 8-contact directional electrodes. Follow-up was performed at 3, 6, and 12 months after surgery.**

■ RESULTS: **Four patients (3 men, mean age 27 ± 2.8 years) were included. All patients were diagnosed with rIED and severe intellectual disability. Two patients had congenital rubella, one had a co-diagnosis of infantile autism, and the fourth presented with drug-resistant epilepsy. There was a marked increase in the levels of gamma-aminobutyric acid and glycine during intraoperative stimulation. The average improvement in aggressive behavior in the last follow-up was 6 points (Δ: 50%, $P = 0.003$) while also documenting an important improvement of the Short Form Health Survey in all domains except bodily pain. No adverse events associated with pHyp-DBS were observed.**

■ CONCLUSIONS: **This is the first study to show the safety and beneficial effect of directional lead pHyp-DBS in patients with rIED and to demonstrate the corresponding mechanism of action through increases in gamma-aminobutyric acid and glycine concentration in the pHyp.**

INTRODUCTION

Intermittent explosive disorder (IED) is a psychiatric disorder characterized by recurrent outbursts of aggressive behavior representing a failure to control impulses.[1] Aggressive behaviors are also observed frequently in multiple psychiatric and neurologic disorders and have a greater incidence among

Key words
- Aggressive behavior
- Deep brain stimulation
- Hypothalamus
- Intermittent explosive disorder
- Neuromodulation

Abbreviations and Acronyms
CT: Computed tomography
DBS: Deep brain stimulation
DLF: Dorsal longitudinal fasciculus
GABA: Gamma-aminobutyric acid
HFS: High-frequency stimulation
IED: Intermittent explosive disorder
MFB: Medial forebrain bundle
MRI: Magnetic resonance imaging
OAS: Overt Aggression Scale
pHyp: Posteromedial nucleus of the hypothalamus
rIED: Refractory intermittent explosive disorder
SF-36: Short Form Health Survey
SIB: Self-injury behavior

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younger individuals (i.e., <40 years old). It is estimated to affect 45% of patients with intellectual disability[2,3] and more than 50% of children with autism.[4] Treatment of IED and several aspects of aggressive behavior involves the use of pharmacotherapy (e.g., mood stabilizers, anticonvulsants, and neuroleptics) and behavioral therapy.[5] Although these treatments are largely efficacious, some individuals present drug-resistant aggressive behavior and are not capable of purposefully participating in behavioral therapies.[6,7] For patients with refractory aggressive behavior, functional neurosurgeries have been proposed with a high rate of success.[8-13]

In the 1960s, Sano et al.[14-16] reported on a surgical technique to treat pathologic aggression through the ablation of the posteromedial hypothalamus. The optimal area for ablation was called the "ergotropic triangle" and defined as the area in which electrical stimulation results in rise in blood pressure, tachycardia, and pupillary dilation.[16] Patients treated with ablations to the posterior hypothalamus (pHyp) presented with a significant improvement in aggressive behavior[11,14,17]; however, this technique has stagnated at a low level in the late 1980s, and it is currently scarcely conducted.[18] Franzini et al.[10] reported on the use of deep brain stimulation (DBS) of pHyp for the treatment of patients with refractory aggressive behaviors, leading to marked symptom reduction that was sustained throughout the 1-year follow-up. This study paved the way for a new era in the treatment of aggressive disorders targeting the hypothalamus and, in the following years, several other groups reported on pHyp-DBS to treat similar patient populations with positive outcomes.[9,19-21]

DBS is a neuromodulation therapy that involves the implantation of electrodes in discrete deep brain structures to deliver adjustable electric stimulation to modulate neuronal activity related to dysfunctional circuitry, also allowing for changes in neurotransmitter dynamics and protein expression.[22,23] DBS has the advantage of being a technique that does not create a lesion, in addition as having a wide range of possible stimulation parameters to maximize symptom relief and reduce adverse events.[23,24] Recently, DBS electrode design was improved with directional leads that allow for the current to be adjusted in the horizontal plane in addition to the vertical plane, minimizing stimulation of unwanted areas.[25,26] The evaluation of neurotransmitter release during DBS surgery is possible with the use of intraoperative microdialysis, a sampling technique capable of measuring the concentration of substances in the interstitial space.[27,28]

Here we report, for the first time, the outcomes of pHyp-DBS with directional leads for reducing aggressive behavior in patients with refractory intermittent explosive disorder (rIED) and the changes in amino acids neurotransmitter concentration in the pHyp during intraoperative high-frequency stimulation (HFS). The primary outcome was longitudinal changes in aggressive behavior measured by the Overt Aggression Scale (OAS). Secondary outcomes were as follows: 1) safety, measured by clinical observation of adverse events during surgery, on postoperative care and on follow-up visits; 2) longitudinal changes in quality of life measured by the Short Form Health Survey (SF-36) questionnaire; and 3) changes in neurotransmitter concentration in the pHyp, measured by intraoperative microdialysis under HFS.

Table 1. Inclusion and Exclusion Criteria

Inclusion Criteria	Exclusion Criteria
1. Diagnosis of intermittent explosive disorder 2. Unsatisfactory response to pharmacotherapy 3. Unsatisfactory response to behavioral therapy focused on reducing aggressive behavior 4. Adult men or women of all ethnical groups (≥18 years old) 5. Score ≥8 on the Overt Aggression Scale 6. No previous surgery for aggressive behavior	1. Pregnancy 2. Structural brain abnormalities that contraindicate surgery, as detected by magnetic resonance imaging examination 3. Chronic or acute commodities considered to be a contraindication to surgery

METHODS

Cases Presented

We report on a single-center, single-cohort, open-label, and nonmasked prospective case series study conducted between 2017 and 2019 (Table 1 describes inclusion and exclusion criteria). This study is composed of 4 consecutive cases (3 males, aged 22–26 years) diagnosed with IED (*Diagnostic and Statistical Manual of Mental Disorders*, Fifth Edition, code 312.34; F63.81), intellectual disability, and impoverished quality of life who were treated with pHyp-DBS for symptom alleviation (demographics in Table 2). All cases presented high risk for self-injury behavior (SIB) and intense heteroaggressive behavior (OAS score ≥10 points). Refractoriness was defined by the persistence of aggressive behavior despite the use of at least 2 antipsychotics and 1 mood stabilizer, unsatisfactory response to behavioral therapy focused on reducing aggressive behavior, and adequate control of other medical, neurologic, or psychiatric pathologies. Each case was carefully evaluated by the Research Ethics Board of the International FOSCAL Clinic-Department of Functional Neurosurgery, Colombia, in accordance with national scientific and technical standards for human research,[29] assessing the impact of rIED on patients' physical and mental well-being, the humanitarian aspects of preserving the safety and physical integrity of the patient and caregivers, and the need to prevent self-harm. Informed consent was obtained from the patients' legal representatives, who approved the surgical treatment and the use of the patients' data for research purposes and scientific publications. All patients were treated and followed in the International FOSCAL Clinic-Department of Functional Neurosurgery, Colombia.

Pre- and Postoperative Evaluations

A preoperative evaluation was performed by a multidisciplinary team and included 1) a full clinical and medical record evaluation; 2) magnetic resonance imaging (MRI); 3) assessment of aggressive behavior (OAS); 4) quality of life measured with the SF-36; and 5) blood laboratory tests, including karyotype. Since patients presented with severe intellectual disability, neuropsychologic evaluations were deferred and all scales were reported by parents/caregivers. Postoperative follow-up included preoperative

Table 2. Demographics and Clinical Characteristics

Variable	Case 1	Case 2	Case 3	Case 4
Age at time of surgery, years	22	26	28	28
Sex	Female	Male	Male	Male
BMI, kg/m^2	30	22	20	21
Medical history	Congenital rubella and hearing disability	Congenital rubella, hearing disability, and decrease in visual acuity	Resistant epilepsy	Infantile autism
Intellectual disability	Severe	Severe	Severe	Severe
Baseline OAS score	12	12	11	12
Institutionalization	Yes	Yes	None	None
Preoperative medication	Valproate sodium Olanzapine Levomepromazine Sertraline	Escitalopram Quetiapine Valproate sodium Clonazepam	Valproate sodium Carbamazepine Levomepromazine Clozapine Sertraline	Clonazepam Clozapine Carbamazepine Risperidone Biperiden
Blood glucose, mg/dL	98	101	95	105
Morning cortisol, µg/dL	12.99	12.08	10.5	6.7
hCG, mUI/mL	0.27	0.1	0.35	0.19
Progesterone, ng/mL	0.206	0.258	0.090	0.169
LH, mUI/mL	12.0	5.1	5.9	2.9
Total T3, ng/mL	99.15	83.2	95.23	87.69
Free T3, pmol/L	4.2	4.3	4.0	5.7
Total T4, µg/dL	6.4	6.9	7.3	5.9
Free T4, ng/mL	1.13	1.5	1.09	1.4
TSH, mUI/mL	2.4	1.3	3	
Free testosterone, pg/dL	0.28	3.32	4.0	20
Total testosterone, ng/dL	0.3	2.8	3.4	2.99
SHBG, nmol/L	109	13.4	18.3	23.09
Karyotype	46XX	46XY	46XY	46XY

BMI, body mass index; OAS, Overt Aggression Scale; hCG, human chorionic gonadotropin; LH, luteinizing hormone; T3, triiodothyronine; T4, thyroxine; TSH, thyroid-stimulating hormone; SHBG, sex hormone binding globulin.

measures and was performed at 3, 6, and 12 months. An additional computed tomography examination (CT) was performed after surgery to confirm accurate lead placement and rule out complications. There was no loss to follow-up. Figure 1 shows the study timeline.

DBS Surgery and Intraoperative Microdialysis

Surgeries were conducted at the International FOSCAL Clinic (Bucaramanga, Colombia) by the senior neurosurgeon (W.O.C.L.). A brain volumetric MRI was acquired 1 week before the surgery for trajectory planning. On the surgery day and with the patient under general anesthesia, a stereotactic Leksell frame (Leksell G; Elekta Instruments AB, Stockholm, Sweden) was attached to the patient's head and a volumetric CT was obtained in stereotactic conditions. The acquired images (MRI and CT) were merged using WayPoint Navigator (FHC Inc., Bowdoin, Maine, USA) for stereotactic coordinates (2 mm lateral to the lateral wall of the third ventricle, 3 mm

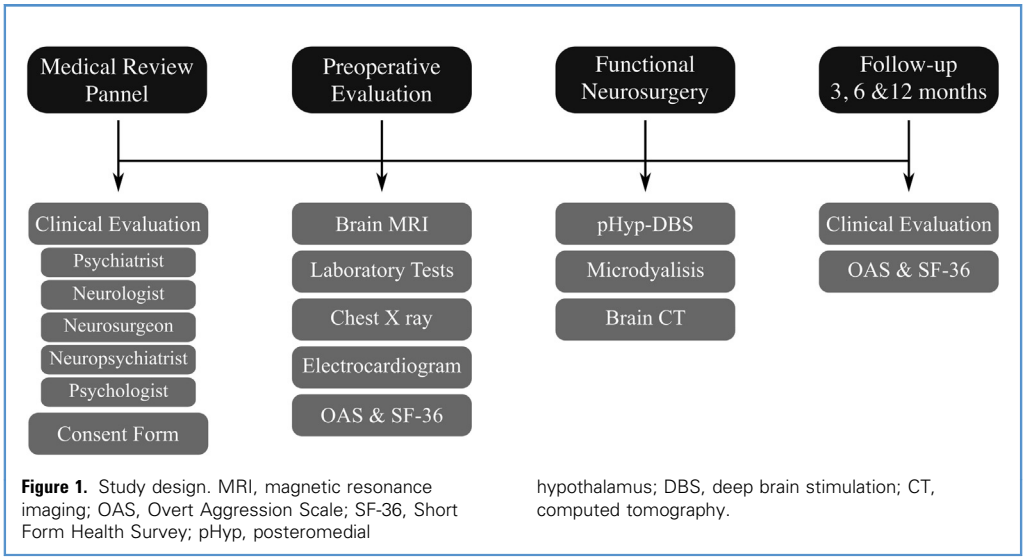

Figure 1. Study design. MRI, magnetic resonance imaging; OAS, Overt Aggression Scale; SF-36, Short Form Health Survey; pHyp, posteromedial hypothalamus; DBS, deep brain stimulation; CT, computed tomography.

posterior and 5 mm inferior to the mid-commissural anterior commissure–posterior commissure point) following previously described studies.[21,30] The trajectory through the brain was set at 40° from the anterior commissure–posterior commissure line in the sagittal projection and 15° from the vertical in the coronal projection. Intraoperative microelectrode mapping/stimulation was performed with a high impedance electrode (250-µm tip; impedance 1–1.5 MΩ; FHC Inc.) to confirm optimal targeting on a region that presented neuronal activity consistent with a nucleus and elicit a discrete increase in heart rate accompanied by ipsilateral eye deviation. Intraoperative microdialysis was performed in 2 cases as previously described.[28] To summarize, the probe was inserted 2 mm anteriorly to the microelectrode and positioned at the same dorsal–ventral level before being attached to a portable pump and to a collection vial and perfused with a sterile Ringer's lactate solution. Following an equilibration period of 10 minutes, 4 baseline samples were collected every 10 minutes, followed by collection of a 15-minute HFS sample and 3 poststimulation samples collected every 10 minutes. The 8-contact directional DBS lead (Cartesia TM Directional Lead; Boston Scientific, Marlborough, Massachusetts, USA) was implanted bilaterally and fixed onto the skull using Histoacryl (B. Braun, Melsungen, Germany).[31] Leads were connected to a multiple independent current control system (Vercise PC; Boston Scientific) and implanted subpectoral.[32,33] Stimulation started 15 days after pHyp-DBS surgery using monopolar stimulation with an amplitude of 1.5 mA, 90-µs pulse width, and frequency of 119 Hz. Stimulation parameters were adjusted individually if/when necessary. Dialysate analysis was performed in a blinded fashion with anonymized samples (patient and time of collection). Using high-performance liquid chromatography (Prominence UFLC; Shimadzu, Kyoto, Japan), we analyzed samples for quantification of extracellular aspartate, glutamate, glycine, and gamma-aminobutyric acid (GABA), as previously described.[27,34]

Statistical Analysis

The JASP 0.11.1 software was used for descriptive and statistical analysis. We used t tests to compare OAS and SF-36 between baseline and 12 months with level of significance set at $P < 0.05$. Owing to the exploratory nature of the study, we did not make multiple test adjustments.

RESULTS

There were no surgical complications. No adverse events were observed during follow-up, and stimulation was well tolerated by all patients (see **Figure 2** for electrode placement and **Table 3**, **Figure 3** for individual stimulation parameters). A marked reduction in aggressive behavior was observed in all cases (reduction in OAS from baseline to last time point: Case 1: 50%; Case 2: 58.4%; Case 3: 36.7%; Case 4: 58.4%; $t_{(1,3)} = 8.4$, $P < 0.003$; **Figure 4A**), with evident improvement in quality of life (increase in SF-36 score from baseline to last time point: Case 1: 250%; Case 2: 223%; Case 3: 267%; Case 4: 339%; $t_{(1,3)} = 7.4$, $P < 0.002$, **Table 4**). Intraoperative microdialysis was performed in 2 cases (cases 2 and 3) for evaluation of extracellular concentration of aspartate, glutamate, glycine, and GABA during HFS of the pHyp. Case 2 showed an average increase in all neurotransmitters during HFS (aspartate: 177.05%, glutamate: 204.42%, glycine: 191.61%, GABA: 407.30%, in relation to baseline measure) and an average decrease during the post-stimulation period (aspartate: 62.33%, glutamate: 70.52%, glycine: 87.13%, GABA: 65.60%, in relation to HFS measure). Case 3 showed an average reduction in aspartate and glutamate and an average increase in glycine and GABA during HFS (aspartate: 69.34%, glutamate: 32.13%, glycine: 115.64%, GABA: 3550.35%, in relation to baseline measure) followed by an average increase in all neurotransmitter during the post-stimulation period (aspartate: 105.41%, glutamate: 156.39%, glycine: 118.69%, GABA: 108.32%, in relation to HFS measure). Interestingly, GABA and glycine

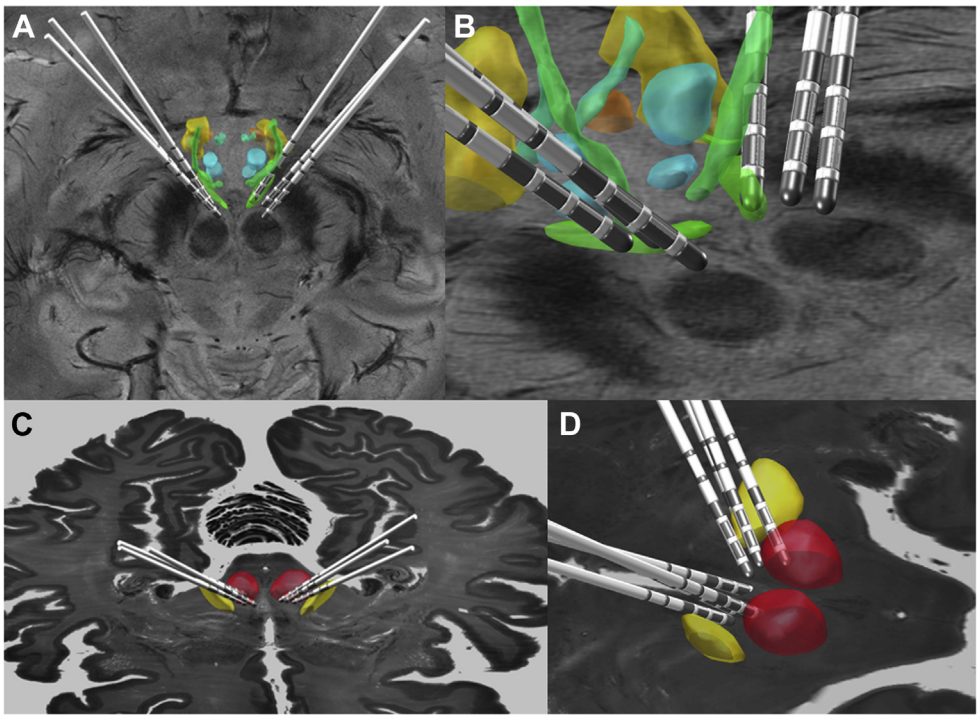

Figure 2. Axial views of the 3-dimensional reconstruction of lead placement and surrounding nuclei for 3 patients. In (**A**), the leads are shown together with a 7T cardiac gated FLASH (fast low-angle shot) magnetic resonance imaging (MRI)[35] and the anterior hypothalamic nuclei segmented from the São Paulo-Würzburg histologic atlas.[36] In (**B**), the region can be seen in detail, with medial forebrain bundle (in *green*). In (**C**) and (**D**), the relationship of the electrodes with the red nucleus (in *red*) and subthalamic nucleus (in *yellow*) can be seen, with histologic backdrop. Lead localization and postoperative fusion images (brain MRI and computed tomography) were registered in lead-DBS[35] to the São Paulo-Würzburg histologic atlas.[36]

concentrations were higher in both cases during HFS compared with baseline measures (Figure 4B-C, Supplementary Table 1).

Case 1

The patient presents a medical history of congenital rubella, diagnosis of IED, severe intellectual disability, hearing impairment, and obesity associated with compulsive eating disorder (demographics in Table 2). Chief complaints included severe outbursts of SIB and heteroaggressive behavior (2–3 episodes/day), hyperphagia, and anxiety. Patient is care dependent for self-care and daily-life activities and has been institutionalized in a therapeutic residence for eight years. Presurgical treatment strategy included pharmacologic (valproate sodium 1250 mg/day, olanzapine 20 mg/day, levomepromazine 100 drops/day, sertraline 50 mg/day) and behavioral therapy with no improvement in aggressive behavior. At age 22 years, the patient underwent pHyp-DBS implant without side effects. After surgery, there was an important reduction in aggressive behavior that was sustained throughout the 1-year follow-up. Reduction in hyperphagia and anxiety also was observed after surgery along with reduction in BMI (30–27 kg/m^2). The patient is living part-time with the family, and the relatives reported improvement in quality of life and daily life activities.

Case 2

The patient presents a medical history of congenital rubella, diagnosis of IED, severe intellectual disability, hearing impairment, and decrease in visual acuity (demographics in Table 2). Chief complaints included severe outbursts of SIB and heteroaggressive behavior (1–2 episodes/day) and hypersexuality. Patient presented a low pain threshold and onychophagia resulting in severe damage to the cuticles and nails. Patient is care dependent for self-care and daily-life activities and has been institutionalized in a therapeutic residence for 5 years. Presurgical treatment strategy included pharmacological (escitalopram 20 mg/day, quetiapine 400 mg/day, valproate sodium 2000 mg/day, clonazepam 4 mg/day) and behavioral therapy with no behavioral improvement. At age 26 years, the patient underwent pHyp-DBS surgery, without complications. There was substantial reduction in aggressive and sexual behaviors that was sustained throughout the 1-year follow-up. The patient continues to live in the

Table 3. Individual Stimulation Parameters

	Amplitude, mA	Pulse Width, μs	Frequency, Hz	Lead Parameters
Case 1	1.2	120	113	Left: Contacts -3 (40%) and -1 (60%) case + Right: Contacts -12 (40%) and -9 (60%) case +
Case 2	1.0	70	170	Left: Contacts -4 (40%) and -1 (60%) case + Right: Contacts -11 (40%) and -9 (60%) case +
Case 3	1.0	90	185	Left: Contacts -1 (50%) and -2 (50%) case + Right: Contacts -12 (40%) and -9 (60%) case +
Case 4	3.0	60	185	Left: Contact -1 (100%) case + Right: Contacts -12 (6%), -11 (6%), -10 (8%) and -9 (8%) case +

therapeutic residence and often visits the family home. The relatives reported improvement in quality of life and daily life activities.

Case 3

A patient born with intestinal malformation resulting in severe intestinal obstruction that was corrected at 30 days of age. The patient presented the first episode of generalized seizure at 45 days of age, and continued presenting 1–2 episodes/day despite antiepileptic treatment through life. Currently, the patient is diagnosed with IED, severe intellectual disability and epilepsy (demographics in Table 2). The patient was care dependent for self-care and daily-life activities. Chief complaints included severe SIB, leading to major head/skull damage (Supplementary

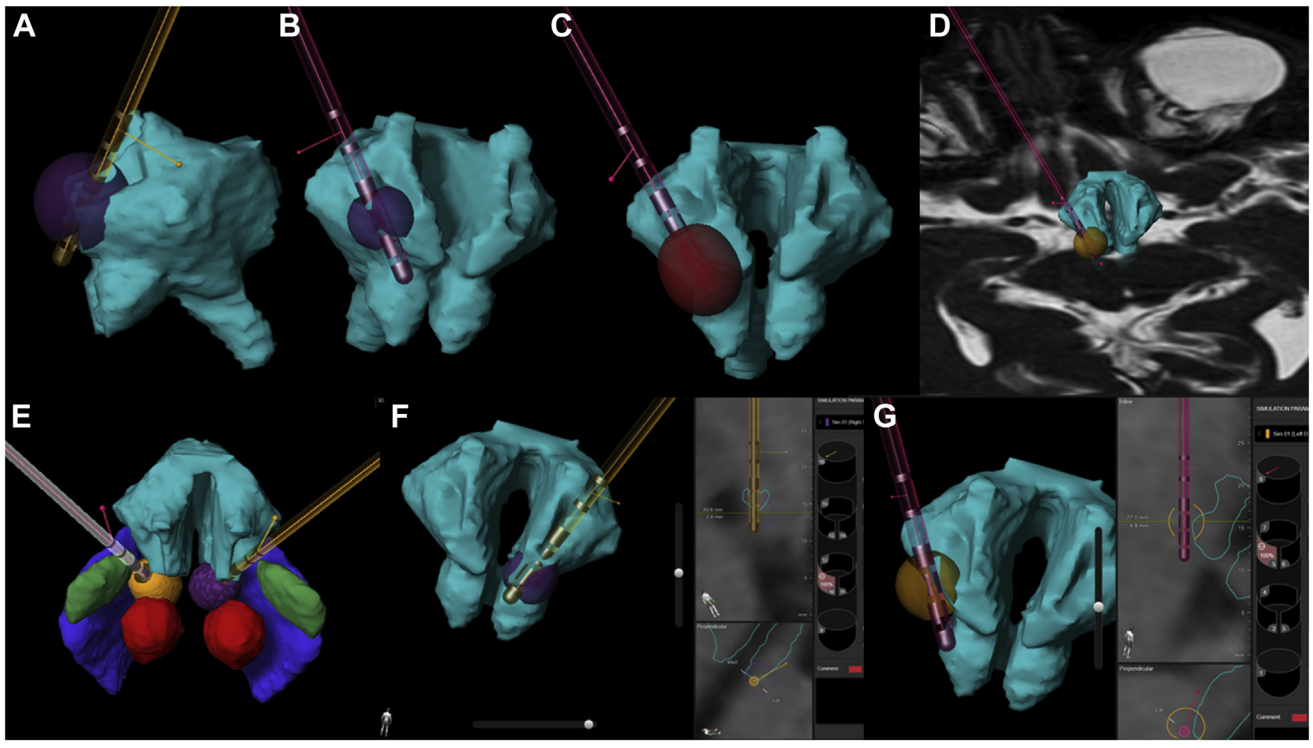

Figure 3. (**A**–**G**) Magnification of axial 3-dimensional FIESTA (fast imaging employing steady-state acquisition) illustrations of active electrodes showing different settings including focused settings, illustrating multiple independent current control (MICC), directionality and current steering. In these patient anatomy-specific images: left lead (*pink*), right lead (*yellow*), hypothalamus (*turquoise*), subthalamic nucleus (*green*), red nucleus (*red*), and substantia nigra (*blue*). Stimulation models are in *purple*, *red*, or *yellow*. In this figure, all settings correspond to: bipolar stimulation with 80 milliseconds, 198 Hz. (**A**) 2.6 mA Contact 14 (100%); (**B**) 1 mA Contact 5 (50%), Contact 7 (50%); (**C**) 2 mA Contact 1 (60%), Contact 2 (13%), Contact 3 (13%), Contact 4 (14%); (**D**) 2 mA Contact 2 (50%), Contact 4 (50%); (**E**) Right lead, 2 mA, Contact 9 (60%), Contact 10 (14%), Contact 11 (13%), Contact 12 (13%); (**F**) 0.9 mA, Contact 10 (100%); G: 1 mA Contact 5 (100%).

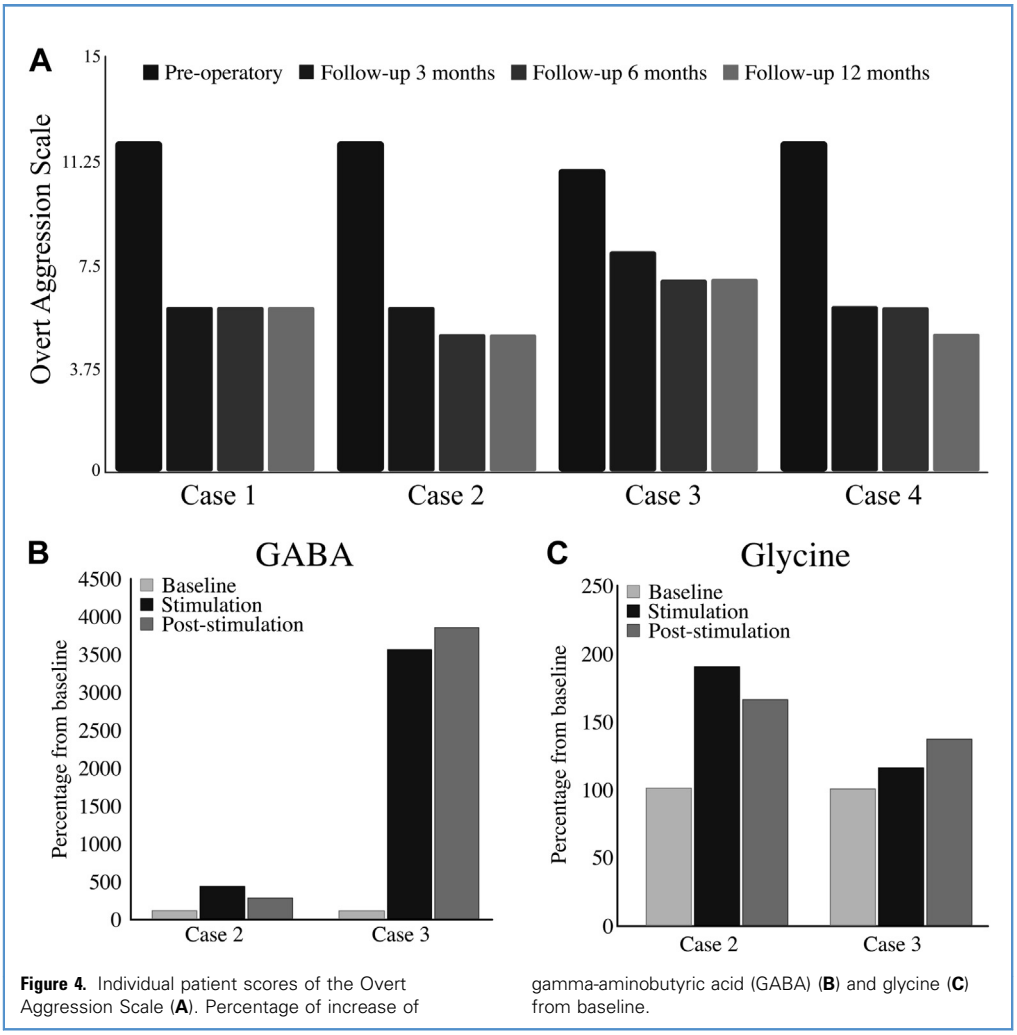

Figure 4. Individual patient scores of the Overt Aggression Scale (**A**). Percentage of increase of gamma-aminobutyric acid (GABA) (**B**) and glycine (**C**) from baseline.

Figure 1) and frequent outbursts of aggressive behavior towards relatives. Presurgical pharmacologic treatment (valproate sodium 1250 mg/day, carbamazepine 600 mg/day, levomepromazine 100 drops/day, clozapine 450 mg/day and sertraline 50 mg/day) was not successful in reducing SIB and epilepsy. At age 28 years, the patient underwent a pHyp-DBS implant without side effects. After surgery, there was a major reduction in SIB and the patient was free from generalized seizures with seldom episodes of focal seizures (<1 episode/week). The relatives reported improvement in quality of life and daily life activities.

Case 4

A patient diagnosed with IED, infantile autism and severe intellectual disability (demographics in Table 2). Chief complaints included severe SIB and heteroaggressive behavior (4–5 episodes/day). Patient was hospitalized multiple times for uncontrollable aggressive behavior, with minimal and transient symptom alleviation. The patient was dependent on self-care and daily-life activities. Presurgical pharmacologic treatment (clonazepam 2 mg/day, clozapine 300 mg/day, carbamazepine 600 mg/day, risperidone 9 mg/day, biperiden 6 mg/day) was not successful in reducing SIB and heteroaggressive behavior. At age 28 years, the patient underwent pHyp-DBS without side effects. There was an important reduction in SIB and heteroaggressive behavior after surgery. The relatives report the patient being calmer and allowing family approach along with an improvement in quality of life.

DISCUSSION

The present study shows for the first time the use of directional leads for pHyp-DBS to alleviate symptoms of rIED and the use of intraoperative microdialysis to investigate the neurobiological mechanisms of treatment. The increase in extracellular concentration of inhibitory neurotransmitters during HFS of the pHyp suggests that a local inhibition is necessary for reducing both SIB and heteroagressive behaviors. Thus, the inhibition of local neuronal elements by DBS has a beneficial effect similar to the one observed in selective ablation of the pHyp.[14,37,38] The pHyp is an

Table 4. Short Form Health Survey (SF-36)

	Physical Functioning	Bodily Pain	Limitations: Physical Health Problems	Limitations: Personal or Emotional Problems	Emotional Well-Being	Social Functioning	Energy/Fatigue	General Health Perceptions	Total
Preoperative measures									
Case 1	10	50	0	0	20	0	40	40	160
Case 2	20	80	0	0	30	0	40	50	220
Case 3	10	60	0	0	20	0	60	30	180
Case 4	10	80	0	0	20	0	50	20	180
Mean ± SD	12.5 ± 5.0	67.5 ± 15.0	0.0	0.0	22.5 ± 5.0	0.0	47.5 ± 9.6	35.0 ± 12.9	185.0 ± 25.2
12-month follow-up measures									
Case 1	50	50	60	20	40	30	70	80	400
Case 2	60	80	40	20	50	70	80	90	490
Case 3	50	60	70	30	50	70	70	80	480
Case 4	80	80	80	40	50	90	90	100	610
Mean ± SD	60.0 ± 14.1	67.5 ± 15.0	62.5 ± 17.1	27.5 ± 9.6	47.5 ± 5.0	65.0 ± 25.2	77.5 ± 9.6	87.5 ± 9.6	495.0 ± 86.6

SD, standard deviation.

area posterior to the mammillary bodies in which sympathetic responses can be generated by electrical stimulation.[15] This region projects to the cingulate and insular cortices and to bed nucleus of stria terminalis and various amygdaloid nuclei.[39] Although targeting the pHyp with ablative techniques has shown to be effective in reducing aggressive behavior, this procedure can result in intolerable adverse effects such as tachycardia, high blood pressure, nonspecific pain, and worsening cluster headache due to sympathetic response.[40]

DBS is a reversible and adaptable technique that can be used to modulate dysfunctional brain circuits that gives rise to the behavioral deficits, thereby alleviating the individual's impairment.[23] Several studies have shown pHyp-DBS to be a safe and efficacious therapy to reduce aggressive behavior in patients who show unsatisfactory response to pharmacologic and behavioral therapy.[20,21,41,42] Importantly, a 19-year-old woman with rIED and moderate intellectual disability was treated with DBS targeting the orbitofrontal projections to the hypothalamus to reduce aggressive outbursts resulting in significant symptom improvement.[8] At 2-year follow-up, the patient had complete cessation of aggressive episodes and no longer required antipsychotic drugs.[8]

In his seminal work upon treating pathological aggresion by ablation of the posterior hypothalamus, Sano[14] postulated the hypothesis that this could be accomplished by the destruction of the dorsal longitudinal fasciculus (DLF) a white matter tract located in the dorsal brainstem tegmentum and comprised of visceral sensory and descending hypothalamic axons (**Supplementary Figure 1**). According to Ban et al.,[43] the DLF is the most important bundle connecting the sympathetic zone of the hypothalamus with other autonomic centers of the brainstem and the spinal cord. Therefore, Sano postulated that its destruction would result in a decrease of sympathicotonia and the related expression of rage or aggression, which is always accompanied by signs of sympathetic discharge (**Supplementary Figure 2**).[44] The neocortex is also influenced by the reticular system through the posterior hypothalamus. This influence is driven by impulses mediated in the somatic sensory system, exerting an effect upon emotional experience. Those influences are mediated by the medial forebrain bundle (MFB). The DLF lies in a more ventral and medial position with respect to MFB in the brainstem. The MFB lies, therefore, in a more lateral and superior position to the DLF when targeting of the posteromedial hypothalamus (**Supplementary Figures 3–4**). Using directional leads, it is possible to isolate the electric field by separately stimulating each of those tracts, depending on a patient's clinical features. Directional DBS (**Supplementary Figure 5**) was found to be beneficial in selecting which components the Clinician desired to inactivate (limbic, sympathetic, or both), using current steering. In our series, we found that stimulation side effects such as hypersexuality, hypomania, hyperphagia, and insomnia were resolved using directional current shaping, choosing the anterior and posteromedial contacts and, deactivating the posterolateral contacts, or using it as anodic neurostimulation. Directional current shaping provided an opportunity for a wider therapeutic window by steering the electrical field, to certain degree, avoiding undesired effects from stimulation of structures adjacent to the target. Another advantage of directional leads was to prevent stimulation of fibers from oculomotor nerve (CN III) due to the proximity of the electrodes to this region. By blocking the current in the direction

of the CN III, it is possible to achieve higher electric currents with less collateral effects in such a small region.

The observed increase in GABA and glycine during HFS suggests that by carefully titrating the electrical signals arising from pHyp-DBS, it is possible to use the intrinsic inhibitory potential of the pHyp to achieve the same beneficial results without ablating the tissue. Previous works have shown increased aggressive behavior following decreased GABAergic inhibitory control of the limbic system[45–47] and marked reduction of aggressive behaviors in subjects receiving GABA uptake inhibitors[48] and in animals receiving systemic doses of glycine.[49] Furthermore, aggressive behavior is commonly treated in the clinic with anticonvulsants that act on enhancing GABA function.[50,51] Also, it has to be mentioned that several factors could influence the microdialysis results, such as location of the electrode, impedance, general anesthesia, medication, or the original pathology. In this sense, the mechanisms of DBS effect are far more complex and different results[52] have been obtained regarding the original pathology, target, and the pattern of stimulation. In addictive disorders, acute low-frequency DBS activates glutamate neurotransmission modulating synaptic transmission. While a preclinical model of Parkinson disease showed that HFS increased the levels of glutamate and GABA.[53]

The limitations of this work are the following: 1) The small number of patients included limits its reliability and generalizability. However, most studies of DBS for novel indications include a small sample,[54–57] representing a balance between the search for efficacy with considerations of feasibility and safety. 2) The patients and the research team were aware of the stimulation parameters. Otherwise, the chronicity, the resistant nature of the participants' illness, and the durability of the clinical response is against the possibility of a placebo effect, although such an effect cannot be definitively excluded without sham stimulation, blind, and controlled study.

CONCLUSIONS

This is the first study to show the safety and beneficial effect of directional lead pHyp-DBS in patients with refractory IED and to demonstrate the corresponding mechanism of action through increases in GABA and glycine concentration in the pHyp.

CRediT AUTHORSHIP CONTRIBUTION STATEMENT

William Omar Contreras Lopez: Conceptualization, Methodology, Collected, and organized the database, Writing – original draft, Writing – review & editing. **Paula Alejandra Navarro:** Collected, and organized the database, Writing – original draft, Writing – review & editing. **Flavia Venetucci Gouveia:** Writing – original draft, Writing – review & editing. **Erich Talamoni Fonoff:** Conceptualization, Methodology, Writing – review & editing. **Ivo Lebrun:** Formal analysis, Writing – review & editing. **Aline V.V. Auada:** Formal analysis, Writing – review & editing. **Eduardo Joaquim Lopes Alho:** Conceptualization, Methodology, Writing – review & editing. **Raquel C.R. Martinez:** Conceptualization, Methodology, Collected, and organized the database, Writing – review & editing.

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REFERENCES

1. *Diagnostic and Statistical Manual of Mental Disorders: DSM-5*. Washington, DC: American Psychiatric Publishing, Inc.; 2013.
2. Rizzi M, Trezza A, Messina G, De Benedictis A, Franzini A, Marras CE. Exploring the brain through posterior hypothalamus surgery for aggressive behavior. *Neurosurg Focus*. 2017;43:E14.
3. Sopromadze S, Tsiskaridze A. Violent behavior. *Front Neurol Neurosci*. 2018;42:106-121.
4. Brentani H, de Paula CS, Bordini D, et al. Autism spectrum disorders: an overview on diagnosis and treatment. *Rev Bras Psiquiatr*. 2013;35:S62-S72.
5. Coccaro EF. The Overt Aggression Scale Modified (OAS-M) for clinical trials targeting impulsive aggression and intermittent explosive disorder: validity, reliability, and correlates. *J Psychiatr Res*. 2020;124:50-57.
6. Gouveia FV, Germann J, Devenyi GA, et al. Refractoriness of aggressive behaviour to pharmacological treatment: cortical thickness analysis in autism spectrum disorder. *BJPsych Open*. 2020;6:e85.
7. Adler BA, Wink LK, Early M, et al. Drug-refractory aggression, self-injurious behavior, and severe tantrums in autism spectrum disorders: a chart review study. *Autism*. 2015;19:102-106.
8. Maley JH, Alvernia JE, Valle EP, Richardson D. Deep brain stimulation of the orbitofrontal projections for the treatment of intermittent explosive disorder. *Neurosurg Focus*. 2010;29:E11.
9. Franzini A, Messina G, Cordella R, Marras C, Broggi G. Deep brain stimulation of the posteromedial hypothalamus: indications, long-term results, and neurophysiological considerations. *Neurosurg Focus*. 2010;29:E13.
10. Franzini A, Marras C, Ferroli P, Bugiani O, Broggi G. Stimulation of the posterior hypothalamus for medically intractable impulsive and violent behavior. *Stereotact Funct Neurosurg*. 2005;83:63-66.
11. Balasubramaniam V, Kanaka TS. Amygdalotomy and hypothalamotomya comparative study. *Confin Neurol*. 1975;37:195-201.
12. Gouveia FV, Germann J, de Morais R, et al. Longitudinal changes after amygdala surgery for intractable aggressive behavior: clinical, imaging genetics, and deformation-based morphometry study—a case series. *Neurosurgery*. 2020;35:S62.
13. Gouveia FV, Hamani C, Fonoff ET, et al. Amygdala and hypothalamus: historical overview with focus on aggression. *Neurosurgery*. 2019;85:11-30.
14. Sano K, Mayanagi Y. Posteromedial hypothalamotomy in the treatment of violent, aggressive behaviour. *Acta Neurochir Suppl (Wien)*. 1988;44:145-151.
15. Sano K. Sedative neurosurgery. *Neurol Med Chir*. 1962;4:112-142.
16. Sano K, Sekino H, Tsukamoto Y, Yoshimasu N, Ishijima B. Stimulation and destruction of the region of the interstitial nucleus in cases of torticollis and see-saw nystagmus. *Confin Neurol*. 1972;34:331-338.
17. Black P, Uematsu S, Walker AE. Stereotaxic hypothalamotomy for control of violent, aggressive behavior. *Stereotact Funct Neurosurg*. 1975;37:187-188.
18. Garcia-Munoz L, Carrillo-Ruiz JD, Favila-Bojorquez J, Lopez-Valdes JC, Jimenez-Ponce F. Treatment of refractory aggressiveness by amygdalotomy and posteromedial hypothalamotomy by radiofrequency. *Rev Neurol*. 2019;68:91-98 [in Spanish].
19. Hernando V, Pastor J, Pedrosa M, Peña E, Sola RG. Low-frequency bilateral hypothalamic stimulation for treatment of drug-resistant aggressiveness in a young man with mental retardation. *Stereotact Funct Neurosurg*. 2008;86:219-223.

20. Torres CV, Sola RG, Pastor J, et al. Long-term results of posteromedial hypothalamic deep brain stimulation for patients with resistant aggressiveness. *J Neurosurg*. 2013;119:277-287.

21. Benedetti-Isaac JC, Torres-Zambrano M, Vargas-Toscano A, et al. Seizure frequency reduction after posteromedial hypothalamus deep brain stimulation in drug-resistant epilepsy associated with intractable aggressive behavior. *Epilepsia*. 2015;56:1152-1161.

22. Jakobs M, Fomenko A, Lozano AM, Kiening KL. Cellular, molecular, and clinical mechanisms of action of deep brain stimulationa systematic review on established indications and outlook on future developments. *EMBO Mol Med*. 2019;11:11.

23. Lozano AM, Lipsman N, Bergman H, et al. Deep brain stimulation: current challenges and future directions. *Nat Rev Neurol*. 2019;15:148-160.

24. Harmsen IE, Elias GJB, Beyn ME, et al. Clinical trials for deep brain stimulation: current state of affairs. *Brain Stimul*. 2020;13:378-385.

25. Steigerwald F, Matthies C, Volkmann J. Directional deep brain stimulation. *Neurotherapeutics*. 2019;16:100-104.

26. Boutet A, Gramer R, Steele CJ, et al. Neuroimaging technological advancements for targeting in functional neurosurgery. *Curr Neurol Neurosci Rep*. 2019;19:42.

27. Lopez WOC, Fonoff ET, Hamani C, et al. Optimizing microdialysis for deep brain stimulation. *Front Biosci*. 2016;8:299-310.

28. Martinez RCR, Hamani C, de Carvalho MC, et al. Intraoperative dopamine release during globus pallidus internus stimulation in Parkinson's disease. *Mov Disord*. 2013;28:2027-2032.

29. World Medical Association. Declaration of Helsinki – Ethical Principles for Medical Research Involving Human Subjects. Available at: https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/. Accessed October 24, 2020.

30. Franzini A, Messina G, Marras C, Villani F, Cordella R, Broggi G. Deep brain stimulation of two unconventional targets in refractory non-resectable epilepsy. *Stereotact Funct Neurosurg*. 2008;86:373-381.

31. Fonoff ET, Teixeira MJ, Nascimento CNG, Lopez WO. Aesthetically optimal deep brain stimulation technique in patients with alopecia. *Neurocirugia (Astur)*. 2015;26:206-208.

32. Gillette PC, Edgerton J, Kratz J, Zeigler V. The subpectoral pocket: the preferred implant site for pediatric pacemakers. *Pacing Clin Electrophysiol*. 1991;14:1089-1092.

33. Kistler PM, Eizenberg N, Fynn SP, Mond HG. The subpectoral pacemaker implant. *Pacing Clin Electrophysiol*. 2004;27:361-364.

34. de Andrade EM, Martinez RCR, Pagano RL, et al. Neurochemical effects of motor cortex stimulation in the periaqueductal gray during neuropathic pain. *J Neurosurg*. 2019;132:239-251.

35. Horn A, Li N, Dembek TA, et al. Lead-DBS v2: towards a comprehensive pipeline for deep brain stimulation imaging. *Neuroimage*. 2019;184:293-316.

36. Alho EJL, Di Lorenzo Alho AT, Grinberg L, et al. High thickness histological sections as alternative to study the three-dimensional microscopic human sub-cortical neuroanatomy. *Brain Struct Funct*. 2018;223:1121-1132.

37. Sano K, Mayanagi Y, Sekino H, Ogashiwa M, Ishijima B. Results of stimulation and destruction of the posterior hypothalamus in man. *J Neurosurg*. 1970;33:689-707.

38. Sano K, Yoshioka M, Ogashiwa M, Ishijima B, Ohye C. Postero-medial hypothalamotomy in the treatment of aggressive behaviors. *Stereotact Funct Neurosurg*. 1966;27:164-167.

39. Cavdar S, Onat F, Aker R, Sehirli U, San T, Yananli HR. The afferent connections of the posterior hypothalamic nucleus in the rat using horseradish peroxidase. *J Anat*. 2001;198:463-472.

40. Seijo F, Saiz A, Lozano B, et al. Neuromodulation of the posterolateral hypothalamus for the treatment of chronic refractory cluster headache: experience in five patients with a modified anatomical target. *Cephalalgia*. 2011;31:1634-1641.

41. Kuhn J, Lenartz D, Mai JK, Huff W, Klosterkoetter J, Sturm V. Disappearance of self-aggressive behavior in a brain-injured patient after deep brain stimulation of the hypothalamus. *Neurosurgery*. 2008;62:E1182.

42. Franzini A, Broggi G, Cordella R, Dones I, Messina G. Deep-brain stimulation for aggressive and disruptive behavior. *World Neurosurg*. 2013;80:S29.e11-S29.e14.

43. Ban T. The septo-preoptico-hypothalamic system and its autonomic function. *Prog Brain Res*. 1966;21:1-43.

44. Schaltenbrand G. *Atlas for Stereotaxy of the Human Brain: With an Accompanying Guide*. Stuttgart: Thieme; 1977.

45. Mandel P, Ciesielski L, Maitre M, Simler S, Kempf E, Mack G. Inhibitory amino acids, aggressiveness, and convulsions. *Adv Biochem Psychopharmacol*. 1981;29:1-9.

46. Roeling TAP, Kruk MR, Schuurmans R, Veening JG. Behavioural responses of bicucculline methiodide injections into the ventral hypothalamus of freely moving, socially interacting rats. *Brain Research*. 1993;615:121-127.

47. Adams DB, Boudreau W, Cowan CW, Kokonowski C, Oberteuffer K, Yohay K. Offense produced by chemical stimulation of the anterior hypothalamus of the rat. *Physiol Behav*. 1993;53:1127-1132.

48. Lieving LM, Cherek DR, Lane SD, Tcheremissine OV, Nouvion SO. Effects of acute tiagabine administration on aggressive responses of adult male parolees. *J Psychopharmacol*. 2008;22:144-152.

49. Stern P, Ćatović S. Brain glycine and aggressive behavior. *Pharmacol Biochem Behav*. 1975;3:723-726.

50. Siegel A, Bhatt S, Bhatt R, Zalcman S. The neurobiological bases for development of pharmacological treatments of aggressive disorders. *Curr Neuropharmacol*. 2007;5:135-147.

51. Corrigan PW, Yudofsky SC, Silver JM. Pharmacological and behavioral treatments for aggressive psychiatric inpatients. *Hosp Community Psychiatry*. 1993;44:125-133.

52. Creed M, Pascoli VJ, Lüscher C. Addiction therapy. Refining deep brain stimulation to emulate optogenetic treatment of synaptic pathology. *Science*. 2015;347:659-664.

53. Lee KJ, Shim I, Sung JH, Hong JT, Kim IS, Cho CB. Striatal glutamate and GABA after high frequency subthalamic stimulation in parkinsonian rat. *J Korean Neurosurg Soc*. 2017;60:138-145.

54. Laxton AW, Tang-Wai DF, McAndrews MP, et al. A phase I trial of deep brain stimulation of memory circuits in Alzheimer's disease. *Ann Neurol*. 2010;68:521-534.

55. Mayberg HS, Lozano AM, Voon V, et al. Deep brain stimulation for treatment-resistant depression. *Neuron*. 2008;45:651-660.

56. Hodaie M, Wennberg RA, Dostrovsky JO, Lozano AM. Chronic anterior thalamus stimulation for intractable epilepsy. *Epilepsia*. 2002;43:603-608.

57. Lipsman N, Woodside DB, Giacobbe P, et al. Subcallosal cingulate deep brain stimulation for treatment-refractory anorexia nervosa: a phase 1 pilot trial. *Lancet*. 2013;381:1361-1370.

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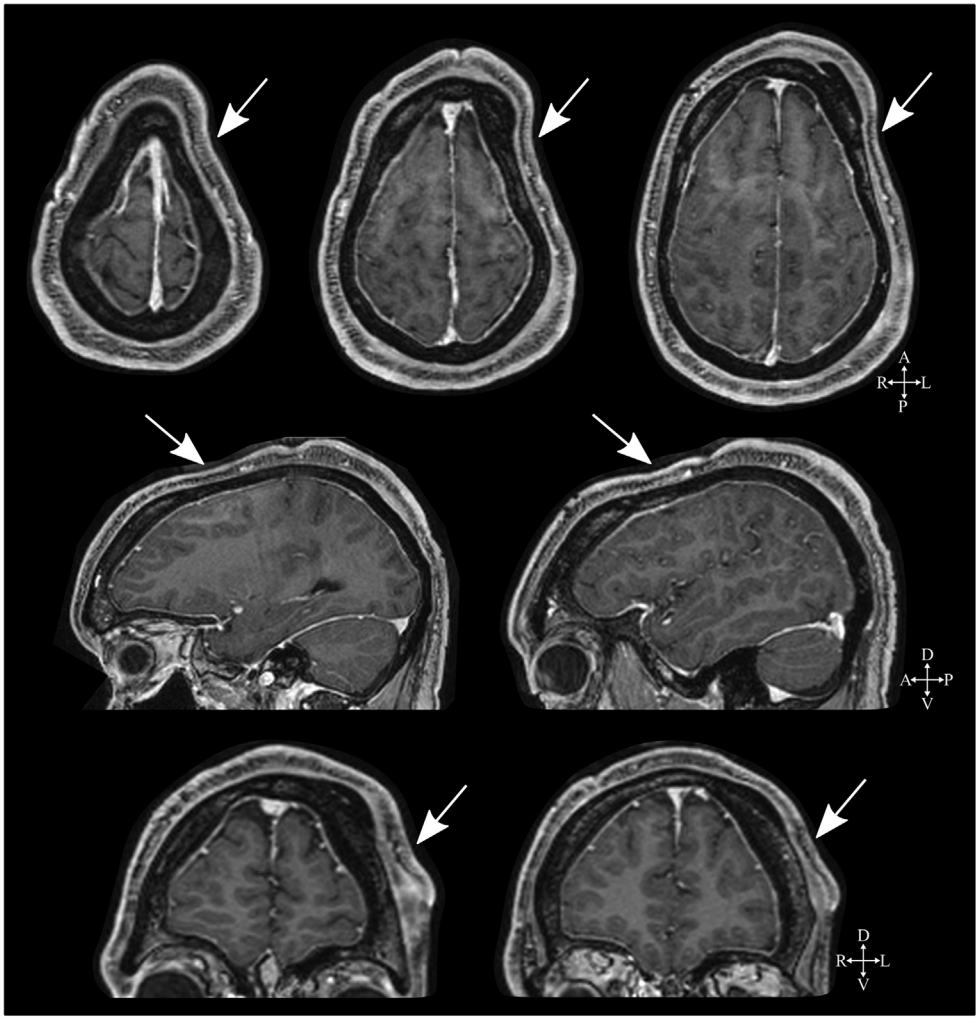
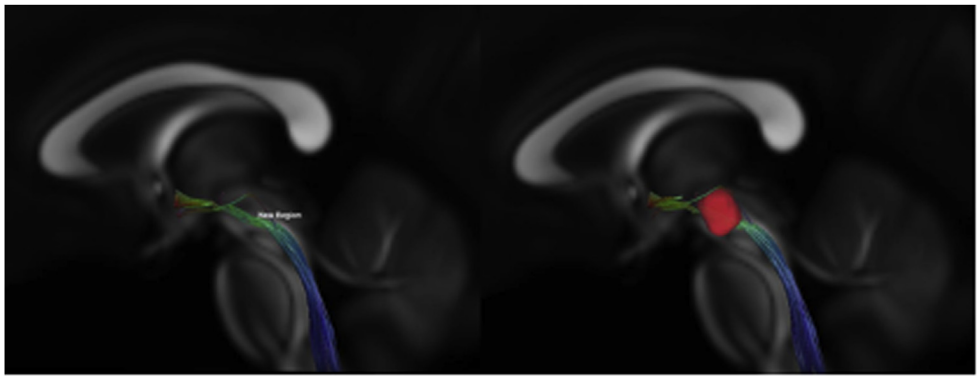
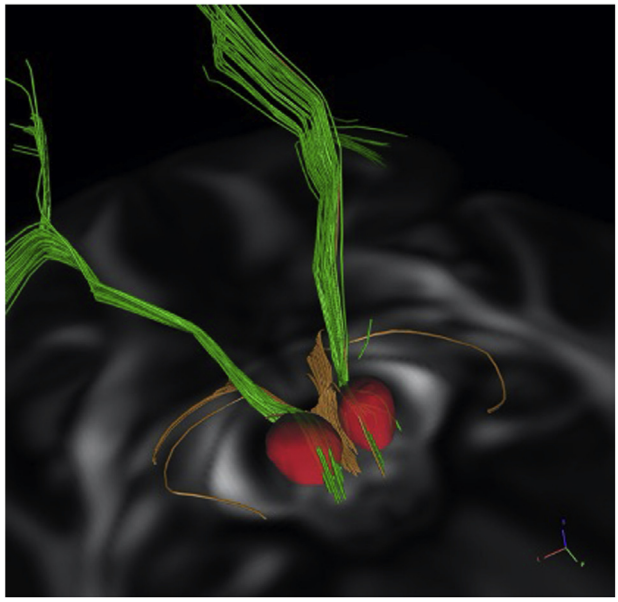


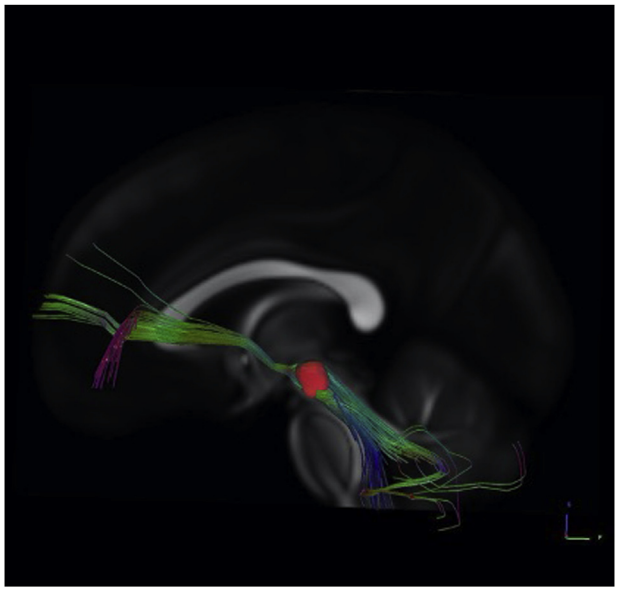
Supplementary Figure 1. Magnetic resonance images from Case 3 showing skull deformation caused by severe self-injury behavior (*white arrow*). *From top to bottom*: axial, sagittal, and coronal views.



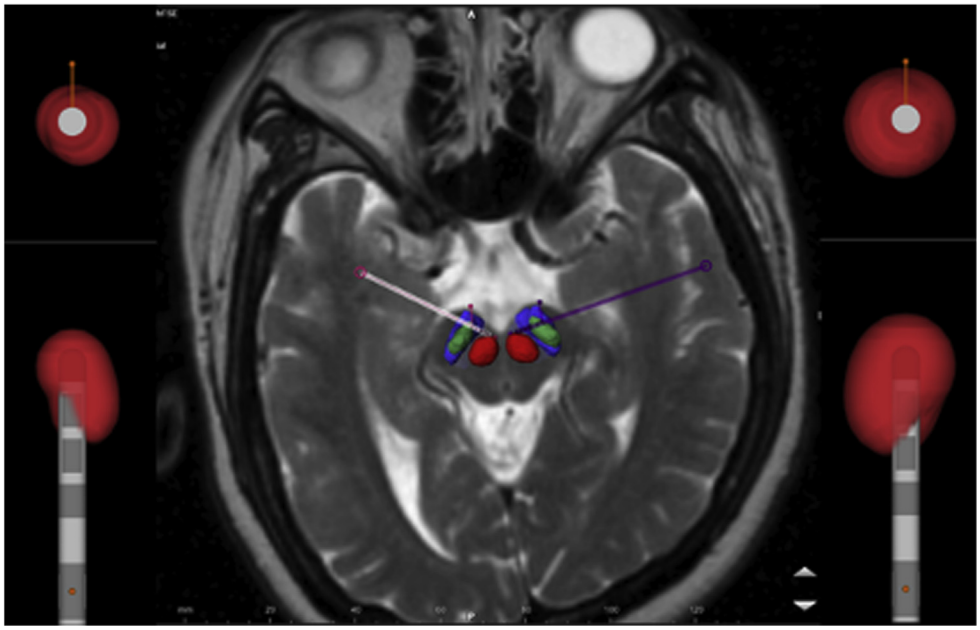
Supplementary Figure 2. Diffusion magnetic resonance image data in DSI Studio's SRC format with an HCP1065 normative connectome showing a sagittal projection of the dorsal longitudinal fasciculus (DLF) fiber tract reconstruction; at the *left* its relation with the red nucleus. The principal pathway of the hypothalamus in the central autonomic network is the DLF. The DLF originates in the region of the paraventricular nucleus and descends along the most medial aspect of the third ventricle through the periaqueductal gray and mesencephalic reticular formation. The DLF continues caudally in the midline near the floor of the fourth ventricle until the closure of the open medulla where it becomes internalized near the central canal remnant. Afferent inputs from the periaqueductal gray, parabrachial nucleus, and the locus coeruleus ascend through the DLF to the hypothalamus.



Supplementary Figure 3. Diffusion magnetic resonance image data in DSI Studio's SRC format with an HCP1065 normative connectome showing a fiber tract reconstruction. The dorsal longitudinal fasciculus (DLF) lies in a more ventral and medial position than the medial forebrain bundle (MFB) in the brainstem. The MFB is located laterally and superiorly (*green tract*) to the DLF (*brown tract*) in the target of the posteromedial hypothalamus. The medial forebrain bundle (MFB) is the primary route for input to the hypothalamus from the septal nuclei and basal forebrain limbic structures. The red nucleus (*red*) is a reference for those structures at the posterior hypothalamus level.



Supplementary Figure 4. Diffusion magnetic resonance image data in DSI Studio's SRC format with an HCP1065 normative connectome showing a fiber tract reconstruction of both the dorsal longitudinal fasciculus and medial forebrain bundle. The *red* nucleus also appears in this image.



Supplementary Figure 5. MRI+ postoperative CT fusion and reconstruction of definitive electrode position for posterior hypothalamus DBS in patient 4 using Brainlab Elements software (Brainlab AG-Germany). The marker detection shows the marker position. The STN is depicted in *green*, red nucleus in *red*, and Substantia Nigra in *blue*. Stimulation fields are in the right or left hemisphere respectively (Vercise-Boston Scientific, USA). The use of directional leads allowed to stimulate the DLF selectively, by steering the current medially and ventrally.

Supplementary Table 1. Concentration of Neurotransmitter Acquired During Intraoperative Microdialysis

	Baseline #1	Baseline #2	Baseline #3	Baseline #4	Average Baseline	STM	Post-STM #1	Post-STM #2	Post-STM #3	Average Post-STM
Aspartate, µg/mL										
Case 2	0.430347	0.403520	0.791956	0.304431	0.482563	0.854358	0.544711	0.521947	0.530920	0.532526
Case 3	1.033479	0.882097	0.807588	0.725167	0.862083	0.597742	0.615812	0.650716	0.623648	0.630059
Glutamate, µg/mL										
Case 2	0.017554	0.026380	0.057904	0.021353	0.030798	0.062957	0.033036	0.047356	0.0528092	0.044400
Case 3	0.095416	0.097583	0.059875	0.025485	0.079322	0.025485	0.029884	0.046737	0.042946	0.039856
Glycine, µg/mL										
Case 2	0.283010	0.434705	0.503372	0.305111	0.381550	0.731070	0.661931	0.574561	0.674451	0.636981
Case 3	1.103950	0.836784	0.750635	0.828586	0.879989	1.017656	0.929799	1.246481	1.447167	1.207816
GABA, µg/mL										
Case 2	0.145478	0.377523	0.172112	0.144487	0.209900	0.854916	0.568809	0.502262	0.611442	0.560838
Case 3	0.063573	0.223990	0.128382	0.095578	0.127881	4.540235	4.605651	4.441484	5.706874	4.918003

STM, stimulation; Post-STM, poststimulation; GABA, gamma-aminobutyric acid.