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Neuromodulation of the inferior thalamic peduncle for major depression and obsessive compulsive disorder

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Summary

Neuromodulation of the inferior thalamic peduncle is a new surgical treatment for major depression and obsessive-compulsive disorder. The inferior thalamic peduncle is a bundle of fibers connecting the orbitofrontal cortex with the non-specific thalamic system in a small area behind the fornix and anterior to the polar reticular thalamic nucleus. Electrical stimulation elicits characteristic frontal cortical responses (recruiting responses and direct current (DC)-shift) that confirm correct localization of this anatomical structure. A female with depression for 23 years and a male with obsessive-compulsive disorder for 9 years had stereotactic implantation of electrodes in the inferior thalamic peduncle and were evaluated over a long-term period. Initial OFF stimulation period (1 month) showed no consistent changes in the Hamilton Depression Scale (HAM-D), Yale Brown Obsessive Compulsive Scale (YBOCS), or Global Assessment of Functioning scale (GAF). The ON stimulation period (3–5 V, 130-Hz frequency, 450-msec pulse width in a continuous program) showed significant decrease in depression, obsession, and compulsion symptoms. GAF improved significantly in both cases. The neuropsychological tests battery showed no significant changes except from a reduction in the perseverative response of the obsessive-compulsive patient and better performance in manual praxias of the female depressive patient. Moderate increase in weight (5 kg on average) was observed in both cases.

Keywords: Neuromodulation; psychosurgery; major depression; obsessive compulsive disorder; electrical stimulation; thalamus.

Introduction

The majority of neurosurgical procedures to treat psychiatric disorders have been directed toward disconnecting the frontal lobe from its connections with the basal ganglia [3, 4, 6] or interrupting anatomic pathways within the limbic system [3, 4]. Neurosurgical procedures have been conducted in anatomic structures on which experience has indicated that the procedure can be more effective or cause fewer side effects.

The inferior thalamic peduncle (ITP) is a bundle of fibers connecting the non-specific thalamic system (Non-STS) and orbito-frontal cortex [8, 13–15]. This is a neural inhibitory system that has several advantages over other targets [15]. Neuromodulation has been shown to be an efficient and safe therapeutic method for psychiatric illnesses such as major depression disorder (MDD) and obsessive compulsive disorder (OCD) [1, 7, 9, 11, 12]. Neuromodulation in ITP is based on the following considerations: 1) High-frequency electrical stimulation of ITP elicits specific electrophysiological responses in prefrontal cortex [13, 14]. Recruiting responses (RR) have been defined by negative, waxing and waning form with long-term latency. These characteristics allow exact localization of the target, 2) Subcaudate tractotomy has been used successfully in the treatment of depression disorders, and this lesion involves ITP and orbitofrontal cortex [3], 3) Experimental models with lesion or cryoprobe have showed effects in the thalamo-orbitofrontal system producing a perseverative and stereotypical behavior [14, 15], and 4) Positron emission tomography (PET) scans in patients with major depression disorder and obsessive compulsive disorder have shown hypermetabolism in the orbitofrontal cortex and the anterior polar thalamic nuclei [2, 5].

A team consisting of a psychiatrist, neurosurgeons, a neurophysiologist, and a neuropsychologist at the General Hospital of México in Mexico City carried out a prospective pilot research protocol of electrical stimulation of ITP in patients with MDD and OCD. The Ethics Committee of our Institution and external reviewers approved the final protocol and two patients were initially included. In this chapter, we will describe our selection criteria, surgical and neurophysiological procedures and the results of the treatment in these cases.

Case 1

LZO was 49 years old at the time of surgery. She was suffering from complete MDD according to the criteria of the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM IV-R) and additionally demonstrated border personality disorder and bulimia. The patient had suffered major depression episodes for 23 years and the last one was 2 years long with anhedonia, suicidal ideation, and two suicidal attempts. Several pharmacological combinations (selective serotoninergic inhibitor reuptakers, benzodiazepines, neuroleptics, and mood modulators) and two series of 10 sessions of electroconvulsive therapy (ECT) had been unsuccessful or associated with relapses after 1 month. Global assessment of functioning scale (GAF) score was 20. One month prior to surgery, medication was withdrawn due to several side effects. Hamilton depression scale (HAM-D) showed fluctuations ranging from 20 to 40.

Case 2

RRA was a 21-year-old male at the time of surgery. He had a diagnosis of OCD made 12 years ago and comorbidity of drug abuse with cocaine for 16 years. He suffered from obsessive ideation concerning the law of gravity loss and fear of flying out of the planet. His compulsion consisted of remaining indoors full time and writing during several hours daily on this obsession. YBOCS score fluctuated from 35 to 40. Baseline (BL) GAF was 10–20 because the patient depended on his relatives in nearly all activities. Medication with selective serotoninergic inhibitor reuptakers, benzodiazepines, neuroleptics, and mood modulators was inefficient and a continuous contention environment was necessary during 1 year. He received 6 months of cognitive behavioral therapy (CBT) without results.

Inclusion criteria

1. DSM IV R Diagnostic Criteria of MDD or OCD.
2. HAM-D score >30 in MDD and YBOCS >23 in OCD. Refractoriness to conventional treatment evaluated by two independent psychiatrists.
3. Awareness of the prospects of the disorder and the protocol conditions and ability to probe the informed consent form.
4. Illness chronicity for at least 5 years.

Exclusion criteria

1. Neurological disease confirmed by clinical examination, electroencephalography (EEG), or brain imaging.
2. Age < 18 years.
3. Anesthetic or surgical risk of grade II or greater according to the American Society of Anesthesiology.

Study design

In addition to the psychiatric scales (HAM-D and YBOCS), both patients were studied by neuropsychological test batteries (Wisconsin Cart Sorting Test, Token Test, Corsi Cube Test). The baseline evaluation was followed by an 1-month evaluation without stimulation in double-blind conditions, and subsequently, by a 12-month ON period with follow-up evaluation every 3 months.

Surgical procedure

Prior to surgery, magnetic resonance imaging (MRI) is performed in T2 fast spin echo, TE 1112, TR 4070, field of view 16.0, 256×256 matrix, and pulse sequence 1,125 2.5-mm slices without space between sections, in axial coronal and sagittal sections without the stereotactic frame. Sections must cover the area from the base of the skull to the vertex. On the day of surgery, patients have the stereotactic frame applied using local anesthesia. Two and half-mm-thick cuts with 2.5-mm displacements are obtained in a contrasted computed tomography (CT) scan study. Sections are obtained parallel to the intercommisural line. Images in this study are transformed into stereotactic coordinates and fused with MRI images using the Praezis System, 3rd version (Tamed, Freiburg, Germany). This information is used to determine the position of the commisures, fornices, internal capsule, and the length and width of the 3rd ventricle. Coordinates for ITP are as follows: (X): 3.5 mm lateral to the wall of the 3rd ventricle, (Y): 5.0 mm behind the posterior edge of anterior commisure as seen in the mid-sagittal section of the MRI and (Z): 2.5 below the level of anterior commisure–posterior commisure line (AC–PC). These coordinates correspond to the cathode of the electrode, and bipolar stimulation is utilized. It is recommended to use tetrapolar electrodes with 1.5-mm contact-to-contact distance and 2.5-mm center-to-control distance. These coordinates intend to place two contacts of the electrode within the ITP and to avoid the fornix and hypothalamus that are located immediately anterior and medial. The electrode trajectory should be calculated on an angle of 80° with regard to the AC–PC line and no more than 25° in the coronal plane. It is possible for the trajectory to traverse the enlarged lateral ventricle in some patients. After planning the trajectory, patients are operated on under general anesthesia. Burr holes are guided stereotactically according to the selected trajectory. Electrodes are fixed with burr hole caps. One tetrapolar electrode is implanted on each side. Each electrode is directed to the center of the ITP, and its proximal end lies along the anterior border of the reticular nucleus of the thalamus. Intraoperative monitoring is performed and subsequently the electrodes are connected to a temporary extension that is externalized behind each ear and is used for stimulation and post-operative mapping.

Intraoperative monitoring

In order to verify the ITP localization, bipolar macrostimulation at 6 Hz, 1.0-msec pulse width and from 1.0 to 4.0 mAmp is carried out using contiguous pairs of contacts in ITP to obtain bilateral frontal recruiting responses elicited by unilateral stimulation. Oscilloscopic and EEG recordings are simultaneously performed in a conventional 10–20 EEG system; bipolar macrostimulation at 60 Hz, 1.0 msec and 3.0–5.0 mA is performed to obtain DC-shift. In the case of not obtaining DC-shift, the electrode location is verified and replaced. This intraoperative study must be performed with the patient in the lightest level of anesthesia; muscular relaxants may be necessary.

Postoperative monitoring

Two days after surgery, MRI is repeated to confirm electrode placement, and deep brain stimulation (DBS) is applied by Itrel 3 (Medtronic, Inc.) at high frequency (130 Hz and 0.45-msec pulse width) at different paired contacts with voltage increases from 1 to 10 V to identify side effects. DBS at low frequency (6 Hz and 1.0-msec pulse widths) at different paired contacts with increases from 0.5 to 4.0 mA is used while EEG with conventional 10–20 montage is performed to obtain recruiting responses. Finally, chronic ES at 60 Hz is performed to obtain a regional DC-shift.

Pulse generator implantation

One day after postoperative monitoring, Itrel 3 Brain Stimulation Systems are implanted in a subcutaneous (s.c.) infraclavicular pocket and are connected to leads.

Stimulation parameters

Charge density is adjusted to elicit bilateral RR. In Case 1, stimulation parameters were 3.0 V, 450 msec, 130 Hz, and continuous program that applied 3.75 microCoulombs per square cm. In Case 2, parameters were 5.0 V, 450 msec, 130 Hz, and continuous program that applied 6.25 microCoulombs per square cm.

Results

Both patients were evaluated by a psychiatric team at the baseline period of 1 month after surgery in OFF stimulation period and during ON stimulation follow-up periods every 3 months during the first year. Throughout the follow-up period, the patients and the psychiatrists were blinded to OFF or ON stimulation.

Figure 1 shows the location of electrodes in electrical stimulation of ITP on axial section (Hv, −0.5 mm).

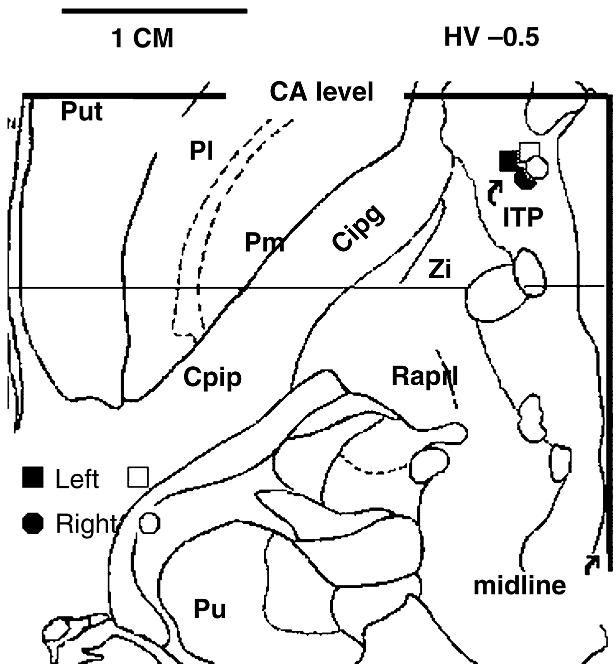

Fig. 1. Axial section from the Schaltenbrand and Warren Atlas in HV −0.5 mm. *ITP* Inferior thalamic peduncle (Pdthif in the Atlas); *Zi* zona incerta; *Raprl* prelemniscal radiations; *Put* putamen; *Pl* lateral pallidus; *Pm* medial pallidus; *Cpip* posterior branch of internal capsule; *Pu* pulvinar; *Cpig* genu of internal capsule; *circle* right electrodes, and *square* left electrodes

White geometric symbols (circles and squares) are located in the electrode implantation sites in the patient with MDD, while black symbols are located at the sites in the patient with OCD. Electrode coordinates ranged from 4 to 5 mm lateral at approximately midline, from 4 to 5 mm behind the posterior border of the anterior commisure in the axial plane that corresponds to intercommisural level, and from 1 to 2.5 mm behind the fornix.

Figure 2A shows the HAM-D score of the patient with MDD 24 months before, and Fig. 2B at 18 months after surgery. Point number 1 corresponds to the first trial of ECT that produced symptom remission for 1 month and a subsequent relapse. Points 2 and 3 depict good responses after medical treatment changes but of short duration. Poor response was observed in follow-up, with scores oscillating between 20 and 40. With regard to point 4, 1 day prior to surgery we were able to observe maximum HAM-D score, without medication, because multiple antidepressant drugs had produced serious side effects. Immediately after implantation, symptom remission was observed but electrical stimulation began 1 month afterwards. A score increase appeared within this period and the decrease of symptoms was related with turning ON the pulse generator and obtaining a good clinical response.

Figure 3 shows Yale Brown obsessive compulsive scale score in the preoperative period, 2 months and 1 week prior to implantation (BL), 1 month after implantation without stimulation (OFF), and the follow-up for 15 months. In the electrical stimulation period (black bar), an improvement of the symptoms was observed with a

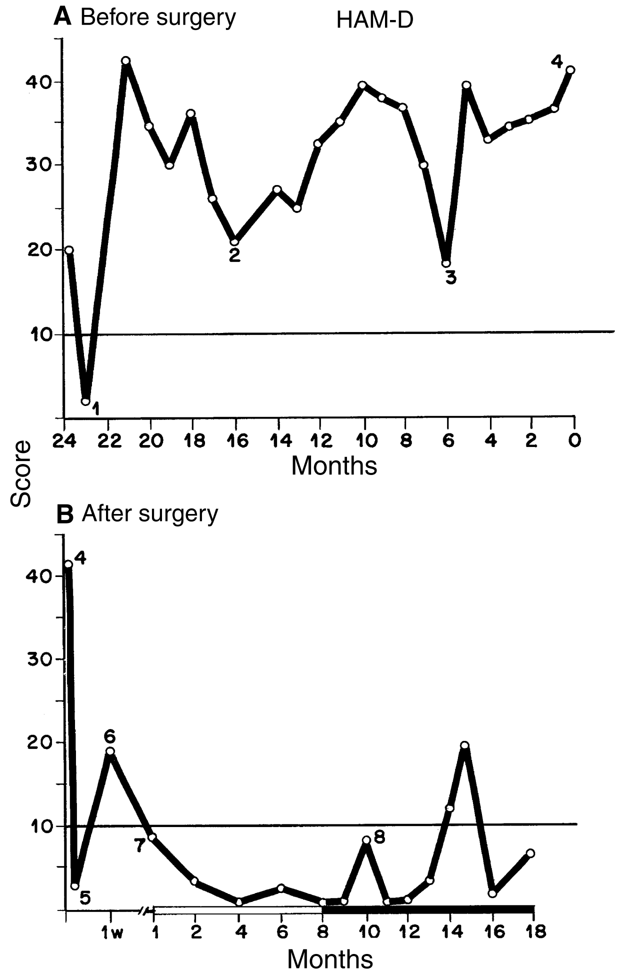

Fig. 2. In A, HAM-D scores 24 months prior to surgery. Number 1 shows responses to electroconvulsive therapy (*ECT*), numbers 2 and 3 show modification in medical treatment, and number 4 shows score on implantation day. In B, HAM-D score shows remarkable decrease after implantation without electrical stimulation. After a 1-month period in OFF, the patient underwent a double-blind period in ON (8 months) and OFF (10 months). An asymptomatic condition was observed in ON period, while a relapse and fluctuation appeared during OFF period

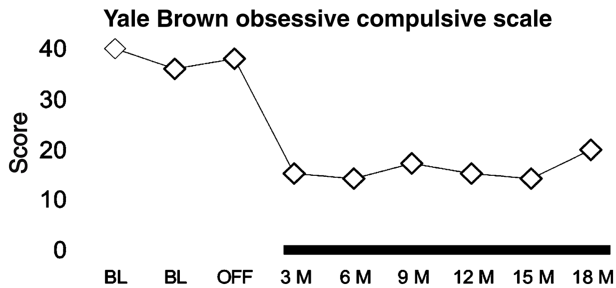

Fig. 3. It shows the Yale Brown obsessive compulsive scale score in the pre-operative period, 2 months and 1 week prior to implantation (*BL*), 1 month after implantation without stimulation (*OFF*), and follow-up during 15 months. In the electrical stimulation period (*black bar*), a decrease of the score was observed with scores ranging from 15 to 20 vs. scores compared to without stimulation ranging from 36 to 40

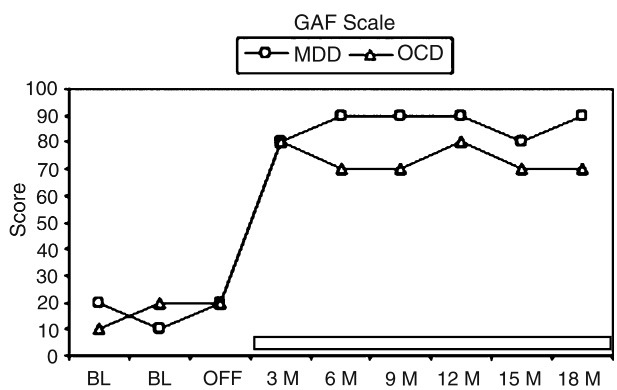

Fig. 4. Global assessment functioning scale (*GAF*) scores are shown in baseline, in OFF period (1 month), and ON period (3, 6, 9, 12, 15, and 18 months). After electrical stimulation, an improvement in functioning behavior was observed. Mild variations were documented in the case of the patient with MDD. After month 8, she was in OFF period; however, she did not show any serious relapse in GAF score. In the patient with OCD, we did not observe big score variations

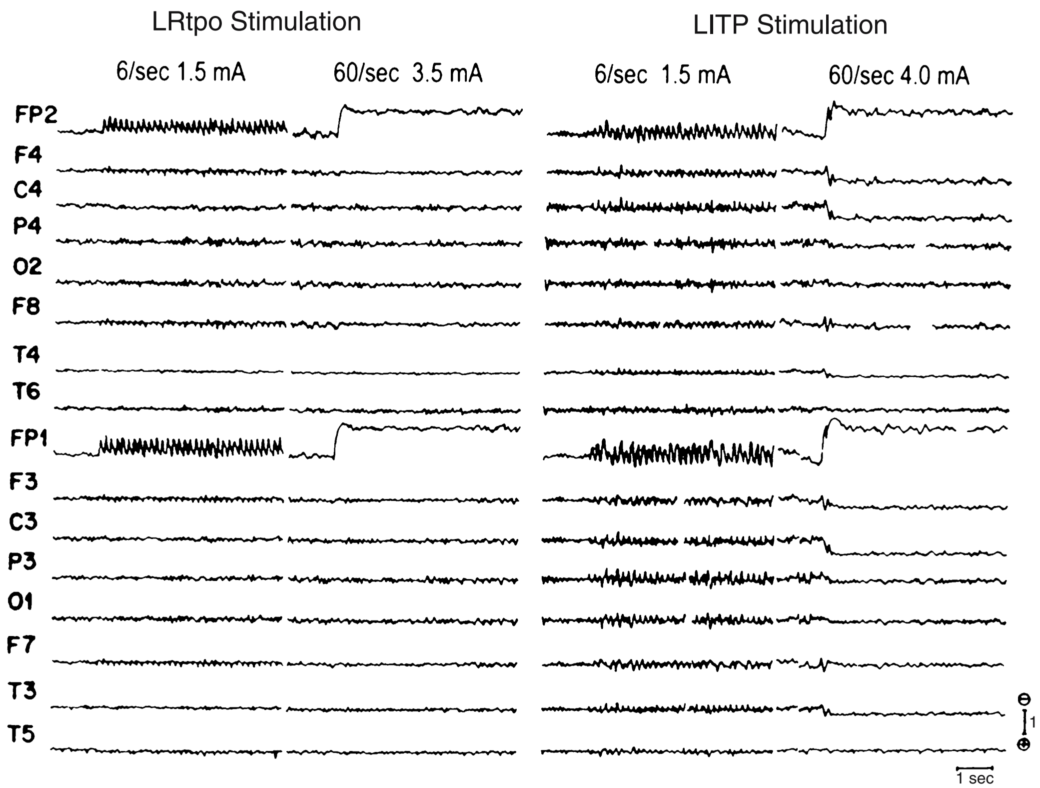

Fig. 5. Scalp distribution of electrocortical responses elicited by acute low- (6/sec) and high-frequency (60/sec) stimulation of the left reticulopolar thalamic nucleus (*L Rtpo*) and the left inferior thalamic peduncle (*LITP*). Conventional EEG recording from right and left frontopolar (*FP2, FP1*), frontal (*F4, F3*), central (*C4, C3*), parietal (*P4, P3*), occipital (*O2, O1*), frontotemporal (*F8, F7*), anterior temporal (*T4, T3*), and posterior temporal (*T6, T5*) scalp regions referred to ipsilateral ears (*A2, A1*). *Left*: Surface-negative recruiting-like responses produced by 6/sec unilateral supra-threshold stimulation of Rtpo and ITP predominantly at bilateral fronto-polar regions. *Right*: Surface-negative DC-shifts and desynchronization produced by 60/sec unilateral supra-threshold stimulation of Rtpo

decrease of the score from 15 to 20 vs; the scores without stimulation ranged from 36 to 40.

In Fig. 4, global assessment functioning (GAF) scale shows an increase of scores in both cases during electrical stimulation. Improvement in quality of life was more significant in MDD; however, the patient with OCD showed a score increase of approximately 50 points.

Figure 5 is a sample of characteristic neurophysiological responses elicited by low- or high-frequency electrical stimulation of the reticulopolar thalamic nucleus and ITP. In both anatomic areas, electrical stimulation on 6 Hertz produced recruiting responses (waxing-waning negative spikes in the frontal area). High-frequency stimulation (130 Hz) elicited a change in the level of direct current (DC-shift). These patterns of electrophysiological responses can be elicited solely by electrical stimulation of the thalamo-orbitofrontal system, but require an extra procedure to verify electrode location.

The neuropsychological tests did not show any differences. However, the Wisconsin Card Sorting Test showed decreased preservative responses in both cases and MDD manual praxias improved significantly. There were no objective chronic symptoms or serious adverse effects of ES. An increase in body weight was seen in both cases, with an average of 5 kg at the end of the study.

Conclusions

The two main advantages of ITP as a neurosurgical target in psychiatric disorders are the specific anatomic definition and the consistent neurophysiological responses. This preliminary report provides information with respect to the safe clinical use of this target. A decrease in MDD or OCD symptoms by applying neuromodulation offers a novel alternative to patients with such severe disabilities. Multicentered prospective double-blind protocols must be designed to provide valid results. The persistent neuropsychological deficit [10] observed after conventional treatment was not seen in neuromodulation of ITP, but an increase of weight by 5 kg was documented.

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