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EC NEUROLOGY
Review Article

The Essentials in Deep Brain Stimulation

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Received: May 19, 2020; **Published:** June 30, 2020

Abstract

Over the last 3 decades, deep brain stimulation (DBS) has become the mayor growth area for the treatment of patients with severe Parkinson disease with motor complications (PD), dystonia and refractory tremors. More recently, interest has begun to focus on the clinical application of DBS to psychiatric disorders, particularly Tourette syndrome (TS), obsessive compulsive disorders (OCD), and depression. In this article, we reviewed seminal and currently ongoing clinical trials that support our field of knowledge in DBS. The increasing therapeutic use of DBS has created opportunities to study the physiology and pathophysiology of these diseases, by allowing intra-cerebral micro electrode recordings (MER) to be made from patients and permitting electrical stimulation of various targets (regions) within the brain to be undertaken. We review the neurophysiological techniques involved in this process and the complex issue of programming the implanted stimulator in order to optimize therapeutic efficacy and minimize stimulation induced adverse effects. This paper is intended to provide an overview of the use of DBS for movement disorders and provide an introduction to the developing area of DBS for psychiatric diseases and covers the varying surgical techniques involved in implanting electrodes into various deep nuclei within the brain. This paper describes how to select appropriate patients for DBS and the results of DBS treatment for PD, dystonia and refractory tremors, as well as psychiatric conditions like TS and OCD; finally, we consider the future of DBS in patients with refractory mayor depression.

Keywords: *DBS; Parkinson; Dystonia; Tremor; OCD; Tourette; Depression*

Introduction

In 1987, A.L. Benabid surgically intervenes a patient with chronic pain carrying a tremor. During the surgery he notices that the tremor subsides when performing the high-frequency stimulation test on the contralateral thalamus and decides to stimulate said patient chronically. The latter leads to the birth of deep brain stimulation (DBS) as an instance of treatment of neurological conditions [1]. Based on the work of Mahlon DeLong and Crossman, Luys' subthalamic nucleus (STN) has been shown to play a crucial role in neuromodulation of abnormal movements, thus opening up new horizons for DBS. Starting in 1993, STN DBS became a standard neurosurgical procedure in the treatment of patients with PD. Currently more than 100,000 patients have been implanted with DBS devices, using different types of electrodes in different targets, intended to alleviate the symptoms of various neurological conditions [2].

General considerations

DBS on basal nuclei modifies neuronal corticostriatopallido-thalamocortical (CSPTC) network and produces changes within connectivity on said level [3]. Clinical benefits of DBS are accomplished by the effect of a locally generated electric field, which modifies synaptic transmission, although it wouldn't be the only mechanism of action and, in consequence, other (chemical, physiological and/or vascular) factors should be considered [4]. In animal models, DBS has shown an increase in extracellular glutamate, GABA, adenosine and dopamine concentrations [5]. DBS consists on the implantation of a cuadripolar (four contacts) or octopolar (eight contacts) electrode in a defined and predetermined target, by the previous colocation of a stereotactic frame (Figure 1). Activation of the best located contact in the target modifies local neuronal circuit. The electrode is connected by a connector cable to a neuro-stimulator (battery) located in subcutaneous cellular tissue below the clavicle or in other selected region (abdominal wall). Three weeks after the implant, we proceed to turn on and program the neuro-stimulator by telemetry or bluetooth, according to stimulation parameters obtained during surgery (frequency, pulse width, and current voltage).There are different stimulation parameters for each target, according to the initial clinical response and the subsequent evolution of the patient, thus constituting a dynamic instance. Consequently, patients must be frequently reprogrammed until a stable clinical response is obtained. Later the changes in the programming are more spaced out. The therapeutic effect of DBS must be considered in conjunction with pharmacological therapy. DBS produces a stable clinical response, while the response to pharmacological treatment is variable, depending on the half-life of each drug. The beneficial and adverse effects of each therapeutic strategy (DBS and pharmacological) must be known and adapted to each patient, according to the severity of the clinical profile [6]. Prior to surgery, the symptoms that characterize the neurological or psychiatric condition that will undergo DBS are evaluated. The selection of a patient for DBS involves careful multidisciplinary work involving a neurologist, psychiatrist, psychologist and neurosurgeon. Each case should be debated considering the benefits and possible adverse effects of DBS and the associated intercurrences that may compromise postoperative management. The expectations of the patient and the family must be in line with the real expectations that can be achieved with the DBS procedure. The target must be carefully chosen and also the need of an uni or bilateral stimulation should be taken into account [7]. The implantation of the DBS device can be performed in a single procedure (implantation of the neurostimulator, the electrode (s) and connecting cable) or in two neuro-surgical procedures. Difficulties in implanting the electrodes have been reported, namely: migration, fracture, erosion, infection or malfunction. Likewise, adverse effects due to the surgical procedure or related to DBS have been described (hemorrhages, infections, ischemia, seizures, paresthesias, dysarthria, hypophonia, dystonia, changes in mood, depression, apathy or attempted suicide) [9].

Figure 1: *A. DBS devices. B. Stereotactic frame. C. Implanted device.*

Parkinson's disease

PD results from extensive neuronal loss and its projections within the motor and non-motor networks at the level of the basal nuclei, which include the nigro-striated, meso-limbic and meso-cortical views [10]. Currently 6 million patients worldwide suffer from PD, a figure that will be doubled in the next generation. The pathophysiological model proposed in PD implies a degeneration and loss of dopaminergic neurons at the level of the pars compact of the substantia nigra (SN) associated with the intracellular accumulation of an abnormal protein, called alpha-synuclein (ASN) within the Lewy bodies (Figure 2). Neuronal depopulation is associated with a decrease in dopaminergic transmission at this level, which justifies some, but not all, of the clinical findings of PD, indicating the necessary abnormal activity of other neuronal circuits (norepinephrine, serotonin, and acetylcholine). With the advancement of PD, the Lewy bodies extend throughout the central nervous system (CNS) and involve other structures, namely: 1-dorsal nucleus of the vagus nerve (responsible for autonomic manifestations), 2-olfactory structures, 3-brainstem (SN and locus coeruleus) and 4-limbic cerebral cortex and neocortex. During the first years of pharmacological treatment, a true honeymoon is established, where the patient notes marked well-being with the medication [11]. PD progresses and consequently motor and non-motor medically resistant complications occur. The most frequent motor complications to observe are 1-fluctuations (wearing-off deterioration, on/off phenomena, akinesia or morning foot dystonia) and/or 2-dyskinesias (peak dose dyskinesias, start and end dose biphasic dyskinesias) [12]. The subthalamic nucleus (STN), the globus pallidus internus (GPi) and to a lesser extent, the ventrointermedius nucleus of the thalamus (VIM) are the targets of choice. The pedunculopontine nucleus (PPN) can be considered as targets in an exceptional way to reverse axial symptoms. To date, STN and GPi have been the most widely used targets and have shown similar clinical responses. STN DBS allows a significant reduction in the daily dose of medication, while GPi DBS suppresses dystonia and/or dyskinesias, although high doses of dopaminomimetic medication must be maintained. The correct choice of target will depend on the clinical picture and degree of progression of the disease, nature and type of motor and non-motor complications, age, psychiatric evaluation, neurocognitive status and intercurrences. Those patients with PD that can undergo DBS must previously perform the L-dopa test. This test consists of completely suspending treatment with the different dopaminomimetic drugs (MAO B inhibitors, dopaminergic agonists and L-dopa preparations). Said suppression must be no less than 3 days due to the long half-life of some of the drugs currently available. The UPDRS III scale is performed in off state and after administration of a usual morning dose and a half of L-dopa. The patient is re-evaluated after 30/60 and 90 minutes in on state. Sometimes the best clinical response can be expected after two hours. An improvement equal to or greater than 33% in the on state with respect to that of the baseline off score is considered positive. It is determined which symptoms respond effectively to the medication. Symptoms that respond to the L-dopa test will respond to DBS, with the exception of tremor and dyskinesias that do not improve pharmacologically but will respond after doing DBS [13].

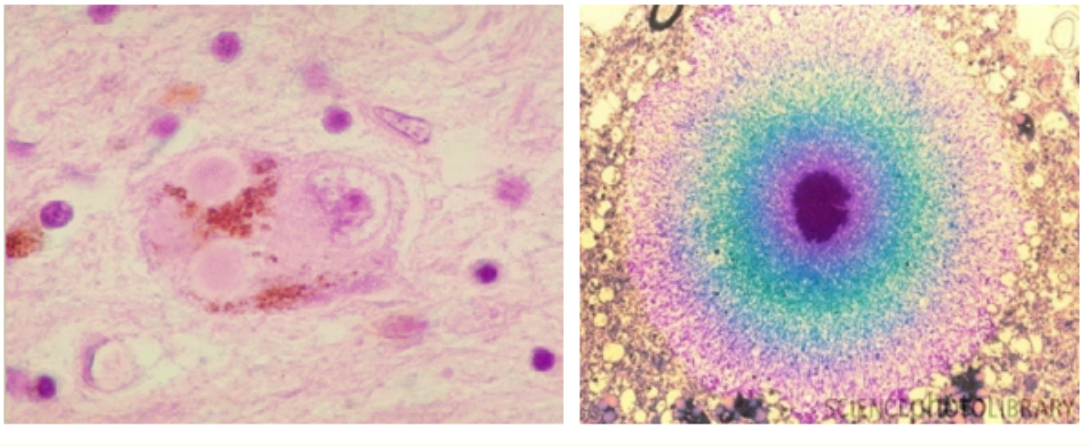


Figure 2: *A. Lewy bodies (LB). B. LB by Electron Microscopy.*

Relevant characteristics of STN as a target in PD

1- Since 1993, bilateral STN DBS has been considered the neurosurgical procedure of choice for the treatment of motor complications of PD (Figure 3). 2- The pre-operative L-dopa test responsiveness predicts the response to STN stimulation. 3- After five years of STN DBS, the Unificated Parkinson s Disease Rating Scale (UPDRS) part III score remains improved by 54%, with improvements of 75% for tremor, 71% for rigidity and 49% for bradykinesia. 4- The L-dopa equivalent daily dose decreased to 37% at 5 years [14]. 5- 57% of the STN stimulation patients had no adverse events, 42% had at least one, and of these 20% were severe, 30% significant and 45% benign.

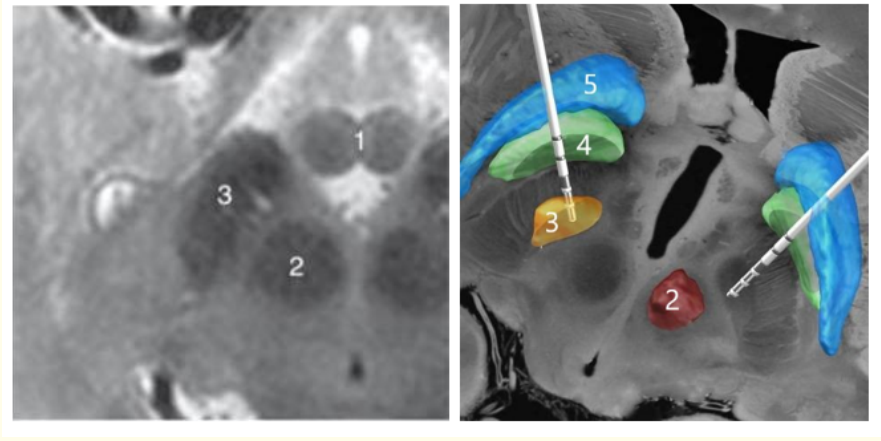
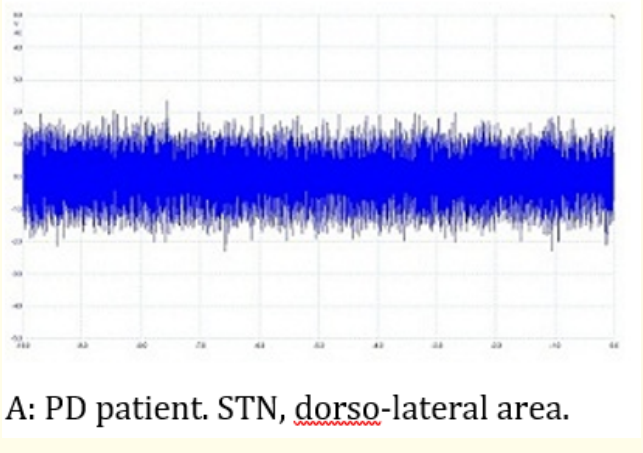


Figure 3: *.A. RM. T2 axial sequence. B. DBS electrodes on both STNs. 1: mammillary bodies 2: red nucleus 3: STN. 4: GPi. 5: GPe.*

Relevant characteristics of Gpi as a target in PD

1- The GPi is subdivided into three functional areas: the postero-ventral area of motor-sensory filiation, the ventro-medial area of limbic filiation and the remaining associative area (Figure 5). 2- The Gpi and its subdivisions can be clearly visualized on thin slice stereotactic MRI, especially in the axial plane, using Flair sequences. 3- The postero-ventral area of GPi is the target of choice for DBS in the treatment of motor complications of PD (dyskinesias and dystonia indoubted by L-dopa). 4- Pallidal electrodes can be implanted under the effect of local or general anesthesia. 5- Lead positioning can be assessed using MER (intra-operative micro-electrode-recording) (Figure 4) and macrostimulation, and their position can be verified immediately by means of a post-operative stereotactic image [15].



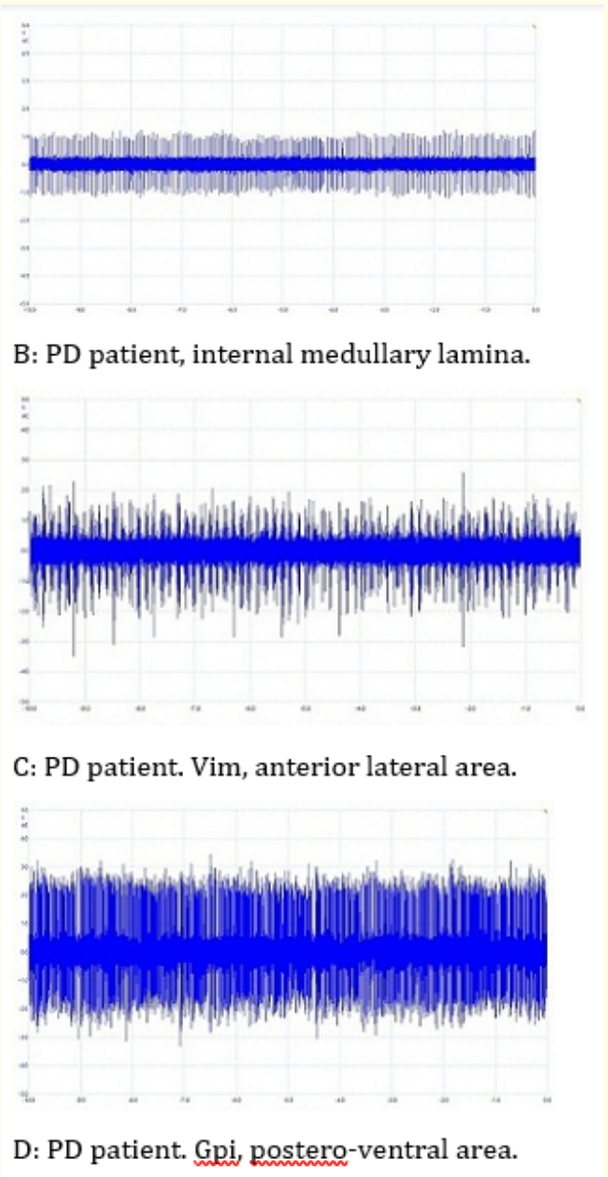


Figure 4: *AIntra-operative micro electrode recording (MER) images.*

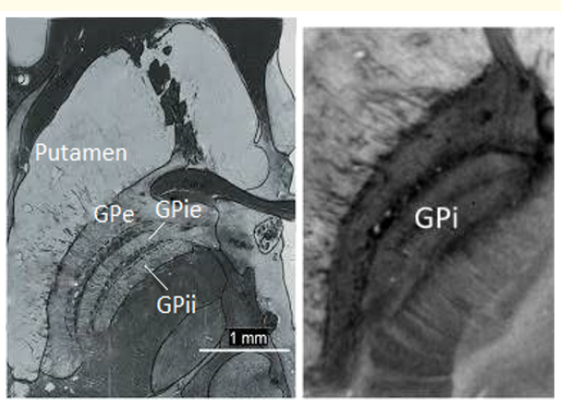


Figure 5: *RM.T2. Visualization of the globus pallidus internus. 1: Gpii. 2: GPie. 3: GPe. 4: Putamen.*

Relevant characteristics of VIM as a target in PD

1- The anterior lateral part of the Vim and the posterior lateral part of the Vop in the thalamus, constitute the targets of choice for DBS in patients with tremors refractory to pharmacological treatment. 2- The different subnuclei of the thalamus cannot be visualized by magnetic resonance imaging (MRI), even with high power, and the final electrode position is determined by macroelectrode test stimulation. 3- Thalamic DBS is performed under local anaesthesia. This allows visualizing the response to macrostimulation and has predictive value of an adequate post-operative clinical response [16].

Relevant characteristics of PPN as a target in PD

1- Axial motor symptoms, usually resistant to L-dopa, turn out to be the most disabling in advanced stages of PD. 2- The peduncle-pontine nuclei (PPN) have demonstrated in animal experimental models, a fundamental role in the control of posture and gait. 3- The currently available human data demonstrate how low-frequency stimulation of the PPN improves L-dopa resistant axial symptoms in PD. 4- The PPN can be accurately and safely targeted using an MRI-guided technique for placement of a DBS electrode [17].

Deep brain stimulation in PD. Relevant clinical trials

Various clinical trials have been developed to establish the efficacy of STN or GPi as targets of choice in the treatment of motor and non-motor symptoms of PD compared to the best pharmacological treatment strategies.

The German Parkinson Study Group compares the results obtained in patients under pharmacological treatment, with respect to those patients with pharmacological treatment and bilateral STN DBS. A total of 156 patients with advanced PD, younger than 75 years, were enrolled and randomized in both groups. Changes in quality of life were assessed through the Parkinson Disease Questionnaire (PDQ-39) and severity in motor symptoms using the Unificated Parkinson s Disease Rating Scale (UPDRS) part III to assess motor score. The group under pharmacological treatment was compared with the group with pharmacological treatment and bilateral STN DBS. PDQ-39 and UPDRS III showed a significant improvement in the pharmacological/DBS group compared to the exclusive pharmacological group [18].

The Veterans Administration CPS 468 Study Group evaluates the clinical response in those patients who received a bilateral STN DBS or bilateral GPi DBS, compared to a group of patients under exclusive pharmacological treatment regimen. It was subdivided into two groups, older or younger than 70 years. The trial shows a marked improvement in motor symptoms and quality of life in both groups who received bilateral STN or GPi DBS [19]. The same group (CPS 468 Study Group) reported sustained benefits in motor function, in those patients who had received STN or Gpi DBS after 36 months of follow-up between 2009-2012 [20].

The Dutch trial, a clinical trial carried out in the Netherlands, confirms the findings described by the CPS 468 SG, both for bilateral STN o Gpi DBS [21].

The PD SURG trial, evaluated in 366 patients, enrolled and randomized, the benefits of bilateral STN or GPi DBS, associated with pharmacological treatment compared to exclusive pharmacological treatment, in patients with advanced stage PD. This study confirms the findings of the CPS 468 SG 2009-2012 clinical trial. In this study, the group that received DBS demonstrated a significant improvement in quality of life (PDQ 39) after one year of follow-up [22].

The St. Jude Medical DBS Study Group investigated the impact of an implanted constant current device on both STNs evaluated in on state in the absence of dyskinesias. In the control group, DBS was kept off for three months after its implantation. The quality of life improved in both groups, being significantly better in the stimulated group [23].

The Early STIM trial evaluated 251 patients with PD, aged between 18 and 60, who had 4 or more years of PD with a severity equal or less than stage III of Hoen Yahr scale and presence of fluctuations or dyskinesias for at least 3 years. In said study, 124 patients received bilateral STN DBS and were compared to 127 who received only pharmacological treatment. An improvement in both the quality of life (PDQ 39) and in score motor (UPDRS III) was observed. Other variables considered in the study showed an improvement in the DBS group compared to the only pharmacological group [24]. Further studies are required to evaluate the effect of DBS in patients with early stage of PD, without motor complications.

Dystonia

Dystonia is a heterogeneous disorder with different ethologies, age of onset, distribution and phenomenology that results from co-contraction of agonist and antagonist muscles. Patients who suffer from it, are characterized by presenting involuntary repetitive movements, that result in abnormal torsion postures, commonly associated with tremor. It can be focal, segmentary, generalized or it can affect one hemibody (hemi-dystonia, frequently associated with structural damage). Pharmacological treatment and/or rehabilitation in the long term results insufficient. Lesion surgery (pallidotomy or thalamotomy) was initially used in primary or secondary dystonias, although it was posteriorly replaced for DBS, because bilateral lesions may result in speech (dysarthria) or cognitive issues [25]. The globus pallidus internus (GPi) results the target of choice in DBS surgery and has shown to be effective in reducing symptoms in patients with primary generalized dystonia (PGD), segmentary or focal dystonia. Primary dystonia responds better to DBS compared to secondary dystonia, with exception of late onset syndromes (late-onset dystonia) in the context of chronic treatment with neuroleptic drugs which block D2 post synaptic dopamine receptors [26]. In 2003, DBS received a humanitarian exemption by the Food an Drugs Administration (FDA) in the United States for use in dystonia. Posteriorly, this concept changed and currently DBS of GPi constitutes a choice of first line in the surgical treatment of dystonia. Diverse clinical studies have been developed until now to evaluate clinical response to DBS in patients with PGD (DYT1 type). Consecutive experience has shown significative and persistent clinical improvement [27]. Currently, other targets (STN) are being studied and the spectrum of dystonias feasible of DBS is being amplified: 1- resistant cervical dystonia, 2- myoclonus/dystonia, 3- X-linked dystonia-parkinsonism (Lubag disease) 4- dystonias in the context of a cerebral palsy. The combination of preoperatory MRI/CT images and intra-operative microelectrode recording (MER) allows a correct location of electrodes in both Gpi (Figure 6). Intra or post-operative complications are very infrequent to observe in mainly young patients. Clinical response posterior to bilateral Gpi DBS is not immediately observed as in PD. In many cases the effects of DBS seem to be delayed and appear gradually, progressive (weeks to months) and involves the necessity of modifying programming variables in different sessions. Neuroplasticity phenomenons have been postulated as responsible for progressive clinical response but its true mechanism remains unknown. Patients' stimulators are programmed approximately 2 o 3 weeks after the final stage of surgery. The parameters of stimulation in bilateral GPi DBS in dystonias are different to those of PD. Low frequencies (60 to 80 Hz) are used in children and high frequencies (130/180 Hz) are used in adults, greater pulse width of stimulation (60 to 210 us), being voltage variable [28]. It is unusual to observe dysarthria, cognition or mood changes.

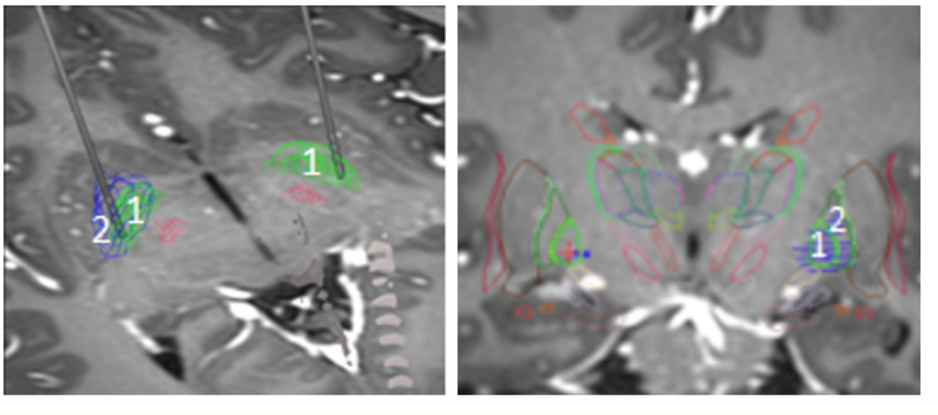


Figure 6: *3D reconstruction. DBS electrodes on both Gpi. 1: Gpi. 2: Gpe.*

Relevant characteristics of GPi as a target in dystonias

1- Bilateral GPi DBS improves motor function and reduces disability in patients with PGD (DYT1) and in smaller measures those with secondary generalized dystonia (SGD). 2- There is a remarkable variability in clinical response during long term monitoring. 3- Phasic involuntary movements and postures respond better and more quickly to Gpi DBS unlike tonic movements (fixed postures). 4- Clinical improvement is objectified over weeks or months after surgery. 5- In patients with PGD, the therapeutic effect of GPi bilateral DBS is maintained in the long term (over 5 years). 6- Implantation procedure is usually well tolerated and can overcome commonly reversible adverse effects [29,30].

Tremor

Tremor is defined as an involuntary and rhythmic oscillation of a body part and has been classified according to its etiology and/or by it characteristics (phenomenology and physiology). Some kinds of tremor recognize an alteration in cerebello-thalamic or pallidus-thalamic networks. Thalamic VIM nucleus has proved to be an effective target for control some tremors refractory to pharmacological treatment, with the most common being essential tremor (ET) [31]. The effectiveness of DBS in Vim results similar to thalamotomy [32]. Unilateral thalamic VIM DBS has been used in the control of refractory tremor, being more effective in tremor of a contralateral limb. Ataxia and dysarthria can be observed as adverse effects of DBS, being more frequent in bilateral VIM DBS. Axial tremor (cephalic and/or of vocal chords), doesn't respond to DBS in similar ways to limbs tremor [33]. In ambulatory control long term benefits of VIM DBS are observed. Essential tremor, being a degenerative disease, has a progressive nature. For that reason, recurrence or aggravation of the tremor is observed in the long term in patients who have received VIM DBS [34]. In Patients with ET or in some selected patients with predominantly tremorous PD refractory to pharmacological treatment, bilateral VIM DBS results the target of choice. Patients with other kinds of refractory tremor: cerebellar, mesencephalic, post traumatic or linked to multiple sclerosis don't respond in a significative way to VIM DBS, being able to use other targets: Thalamic ventralis oralis posterior (Vop) or Zona incerta [35].

Relevant characteristics of the VIM as a target in tremors

1- Thalamotomy and VIM DBS of the thalamus have similar efficacy to alleviate the symptoms of ET. 2- DBS however, has a higher safety profile, it is programmable, reversible and, consequently, the greater the impact on the quality of life of the patient. 3- The tremor in the extremities observed in multiple sclerosis is usually associated with other neurological signs such as weakness or ataxia that do not subside after the suppression of the tremor. 4- Thalamic DBS (VIM or Vop) reverses other tremors (Holmes tremor, primary scribe tremor, neuropathic tremor associated with IgM paraproteinemia, post-traumatic, dystonic and cerebellar). 5- The kinetic tremor reverts with bilateral VIM DBS of the thalamus [36].

Neuropsychiatric disorders

Giles de la Tourette syndrome

Tourette syndrome (TS) is a complex neuro-psychiatric disorder that manifests itself in childhood, although it can usually do so in adolescence before the age of 18. It is characterized by motor and vocal (phonatory) tics, which must be present at least one year prior to the consultation and are changing in nature with respect to number, frequency and complexity [37]. TS patients frequently show psychiatric co-morbidities, namely: 1- attention deficit hyperactivity disorder (ADHD), 2- obsessive-compulsive disorder (OCD), 3- self-injurious behavior, 4- anxiety, 5- depression and/or 6- impulse control disorder (ICD) that affect the patient's personal, social and work life. Throughout life, motor and/or vocal tics decrease or even disappear, while neuro-psychiatric manifestations persist [38]. Some patients with TS progress to a severe, refractory, or even malignant clinical form. These clinical forms are refractory to behavioral and/or pharmacological

treatment, which can also produce severe adverse effects [39]. Lesional surgeries (cingulotomy, limbic leukotomy, medial thalamotomy, infra-thalamotomy) not without sequelae have been tried and due to this, are currently in disuse. TS patients who are candidates for DBS must meet selection criteria, which depend on the heterogeneity of the clinical motor and/or behavioral symptoms. The Tourette Syndrome Association and European Society for the Study of Tourette Syndrome have published guidelines for selection of DBS candidates and for the preferred standardized outcome measures that should be employed if attempting these surgeries. It is recommended not to do it in TS patients under 18 years of age and only when the instances of behavioral and pharmacological treatment are considered exhausted. Pharmacological treatment should include: 1- typical alpha 2 adrenergic agonists, 2- typical and atypical antipsychotics (at least 4 drugs) and 3- presynaptic dopamine depleting agents. The clinical response to each drug must be thoroughly controlled in the motor sphere and in the context of psychiatric comorbidities, as well as the adverse effects caused in chronic treatment [40]. Numerous treatment strategies regarding patient behaviour have been tried: 1- habit-reversal therapy, 2- massed negative practice, 3- self-monitoring, 4- contingency management, 5- exposure and response prevention, 6- cognitive behavioral treatment. Although the mechanisms which cause TS are unknown, abnormalities within the limbic and motor loops of the cortical-basal ganglia-thalamocortical circuitry that involve both dopaminergic and serotonergic neurotransmission are likely contributory to the motor and behavioral manifestations. DBS constitutes a programmable and reversible modality of neuromodulation over associative or limbic areas at the level of the basal nuclei. Various targets are considered in the TS with variable impact on the clinical manifestations, namely: 1- centro-median-parafascicular complex (CM-Pf) of the thalamus [41], 2- GPi motor-sensory area (anterior and medial region) and non-motor area (posterior and lateral region) [42], 3- anterior limb of internal capsule [43], 4- nucleus accumbens, 5- external pallidus globe, 6- posterior limb of internal capsule, 7- antero-medial region of the GPi associated with the external pallidus globe (Gpe) (Figure 7) [44]. DBS results at the striatum and/or thalamus level in patients with TS, demonstrated a 60-80% decrease in the severity of the tics. Bilateral DBS in the motor-sensory region of GPi can significantly improve tics when they severely compromise the patient's quality of life. DBS in the vicinity of GPi is successful in a wide range of hyperkinetic disorders. DBS at the level of the CM-Pf of the thalamus has shown a frank remission of OCD. Future studies may establish the impact of DBS in the area of associated neuro-psychiatric co-morbidities [45].

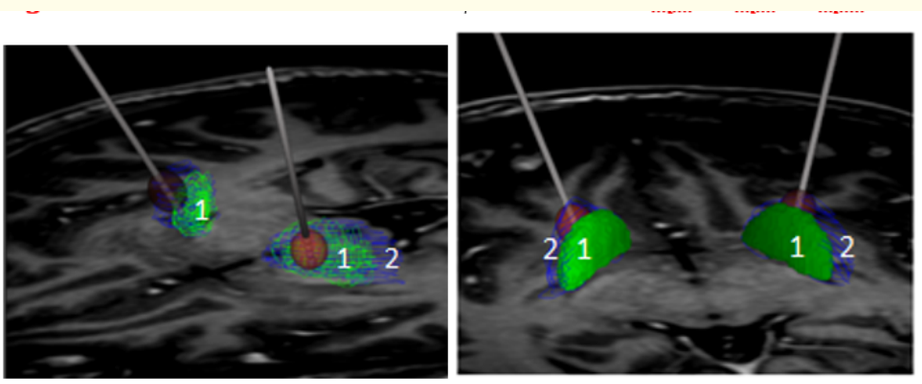


Figure 7: *3D images of an electrical ECP simulation. 1: GPi. 2: GPe [44].*

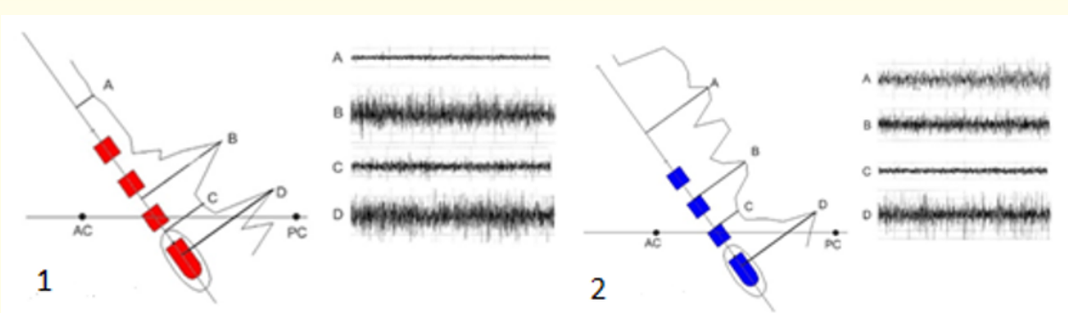


Figure 8: *1. Right electrode. 2. Left electrode. Micro-electrode-recording and final position of the electrode. AC: anterior commissure, PC: posterior commissure, A: striatum, B: GPe (maximum activity), C: internal medullary lamina, D: GPi (maximum activity).*

Obsessive compulsive disorder

Obsessive compulsive disorder (OCD), is characterized by recurrent intrusive thoughts or obsessions which produce extreme anxiety that is relieved by compulsive behaviors, commonly associated with depression and anxiety. It compromises 2 - 3% of general population. Functional neuroimaging studies have shown hyperactivity in ventral striatum, medial thalamic region and the orbitofrontal cortex. Ten percent of patients with OCD suffer a chronic and progressive course, refractory to pharmacological treatment and/or behavioural therapy. They could be candidates for DBS therapy. OCD produces severe disability in patients, especially in the familiar, social and laboral sphere. Patients can manifest eating disorders, depression and, in consequence, they have elevated suicide rates. Pharmacological treatment is based in drugs that inhibit serotonin reuptake, with positive or negative outcomes being observed in the long term. Recently, the FDA in the United States approved DBS as compassionate treatment for patients with OCD resistant to different treatment options [46]. Initially, lesional surgery was performed in different targets, observing severe adverse effects (apathy, irreversible behavioural alterations), therefore lesional surgery was abandoned in favour of DBS [47]. DBS aims to create an electric field that disconnects the frontal lobe from basal ganglia networks. Bilateral DBS in the anterior limb of the internal capsule has reported benefits, with remission of symptoms in 50% of patients [48]. Other targets have been used, as follows: 1- STN. 2- inferior thalamic peduncle, 3- accumbens nuclei [49] and 4- The medial forebrain bundle [50]. Selection criteria for OCD patient liable to DBS imply: 1- refractoriness to all reasonable medication and behavioral therapies, 2- possible benefits of DBS exceed risks, including those associated with comorbidities like depression or suicide, 3- feasible access to post-operatory DBS programming. The selection must be carefully evaluated by a multidisciplinary committee This committee consists of psychiatrists, neurosurgeons, medical ethicists, scientists and lay people, chaired by a psychiatrist and must include an informative consent [51]. The mechanism of how electrical stimulation induces the obtained effects is largely unknown. The effects obtained in electrical brain stimulation are probably a consequence of direct grey matter stimulation. However, effects may also be obtained by electrical stimulation of white matter. Response to DBS in OCD patients is not immediate as in PD. There is a latency that extends for a few months until obtaining satisfactory clinical improvement. Initially, improvements in anxiety and mood are observed. Clinical profile improves according to modifications of stimulation parameters. At the moment, bilateral DBS in the anterior limb of the internal capsule and recently, the medial forebrain bundle result safe and effective for OCD treatment.

Depression

Major depression is the most common psychiatric disease in the general population and is a frequent cause of severe disability among patients younger than 50 years of age. Initial treatment with antidepressant drugs and psychotherapy, allows a favorable clinical response. However, not all patients respond, even using various pharmacological schemes, associated with cognitive/behavioral treatment and even electroconvulsive therapy (ECT) and remain resistant to the standard modalities of therapy. Depression severe and refractory to medical treatment is an indication for DBS. The pathophysiology of depression is unknown, although experts have hypothesized that there is an abnormality in the cortico-striatal-thalamic-cortical (CSTC) network in severely depressed humans and that by lesioning or neuromodulating at specific nodes clinical symptoms may be reduced. The interruption of said circuit can be achieved through lesional surgery, namely: 1- anterior cingulotomy, 2- anterior capsulotomy, 3- undercaudate tractotomy and/or 4- limbic leukotomy or neuromodulation (DBS) of said circuit, improving the symptomatology [53]. Brodman's area 25 (BA25) is located on the medial surface of the frontal lobe, at the level of the subgenual cingulate girus, below the corpus callosum knee. It receives input from the frontal and temporal cortex, hippocampus, amygdala, thalamus, and hypothalamus, and projects mainly to medial frontal cortical regions, the nucleus accumbens, amydgala, thalamus, hypothalamus and brainstem structures, including peri-aqueductal gray matter (Figure 9).

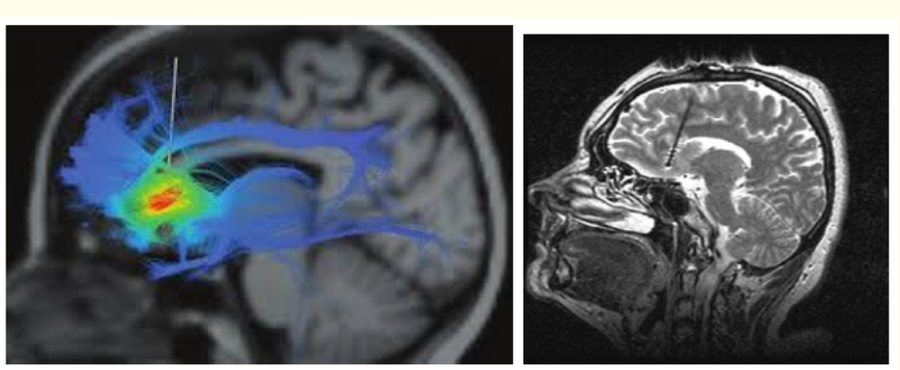
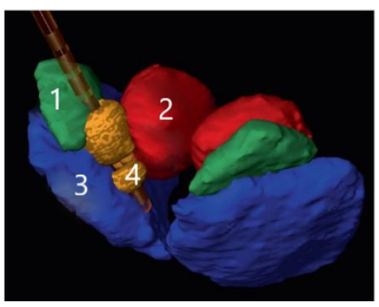
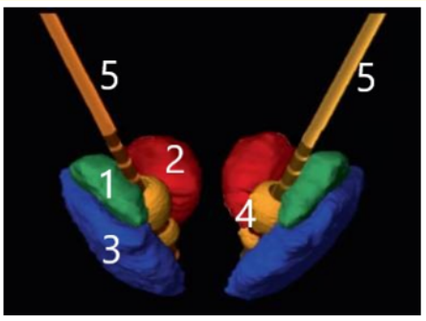


Figure 9: *A. MRI tractography area BA 25. B. T2 sagittal image, implanted electrode.*

Bilateral DBS surgery has been tried at this level. A selected group of 25 patients with refractory depression (failure to respond to various antidepressant treatment strategies, including pharmacological treatment, psychotherapy, and ECT), with major depression (last episode of major depression lasting no less than one year), were operated (bilateral DBS) in the BA25 area. Drug abuse, mania, or suicidal ideation was ruled out prior to surgery. Patients were evaluated in the pre and postoperative period using the Hamilton Depression Rating Scale -17 (HDRS-17), showing an improvement of 60% with respect to the pre-surgical baseline score [54]. To locate the target, multi-planar MRI images are used in T1 and T2/Flair sequences with intravenous contrast. During surgery, the intra-operative microelectrode recording (MER) is used to locate the transition between the gray matter (bioelectric activity is detected) and the white matter (absence of bioelectric activity). At approximately 3 - 4 weeks after the surgery, the IPG is switched on and programmed. Not all patients have reliable immediate response to DBS but some patients improve within hours. The commonly used parameters are: 130 Hz (frequency), 60 mcsec (pulse width) and 3 - 4V (amplitude). Patients are seen on a weekly basis. The contacts leading to the best clinical response are chosen for chronic stimulation. Sleep disturbances remit quickly and is the first sign of improvement seen after DBS. Patients continue on regular antidepressant medication. Other targets for DBS in depression were tested: 1- anterior limb of internal capsule, 2- nucleus accumbens, 3- inferior thalamic peduncle, that showed no better clinical response with respect to BA25 area [55]. A recent DBS study of the anterior limb of internal capsule target, demonstrated negative results in refractory depression [56]. PET studies showed hyperperfusion in the BA25 area in patients with severe and refractory depression prior to DBS surgery. The patients who underwent surgery demonstrated a normalization of blood flow. No relevant adverse effects were observed. New DBS studies in area BA25 are awaiting, to confirm results in long-term follow-up. Currently, DBS of the superior and lateral branch of the medial forebrain bundle (slMFB) has become relevant for the treatment of major depression. The clinical validation of stimulation in this target is supported by the findings of the early onset antidepressant action and a response rate of 85% after 3 months of treatment. Antidepressant efficacy is maintained for more than 4 years. Those patients who responded to this target maintained the response criteria in the long term. The clinical trial consisted of implanting bilateral DBS electrodes, with the patient under local anesthesia. DBS diffusion tensor imaging-assisted neural circuit techniques were applied. After the fibro-tractographic reconstruction of the slMFB, the microelectrode recording (MER) was used to identify the localized target, medial to the STN and the SN and thus be able to exclude the nuclear environment from stimulation. Intraoperative stimulation allows to determine: 1- the autonomic response (increase in heart rate), 2- the psychotropic effects (euphoria, joyous laughter, confusion) and 3- threshold of oculomotor compromise. The definitive location of slMFB is determined with post-operative helical CT (Figure 10) [57].



A. Electrode located between the SNr and the RN.



B. Anterior view of both electrodes.

Figure 10: *3D reconstruction of the position of the left slMFB ECP electrode. 1. STN: subthalamic nucleus. 2. RN: red nucleus. 3. SNr: substance nigra pars reticulada 4. VAT: tissue activation volume. 5. DBS: deep brain stimulation electrode.*

Ethical issues of deep brain stimulation

Since the introduction of L-dopa as a pharmacological treatment option in Parkinson's disease patients, the medical community, patients, and their environment have witnessed a miracle. A true pharmacological honeymoon that spans the first decade of treatment. Then, motor complications occur due to chronic levotherapy, many of them irreversible, which severely affect the quality of life of patients. The introduction of DBS as a treatment option has allowed patients to experience a second bioelectric honeymoon, that significantly improves the clinical picture. From now on, both treatments coexist and the neurologist must balance the effect of the pharmacological treatment and DBS, in order to obtain the maximum benefit in the quality of life of the patient. However, few patients access this last type of treatment. This situation raises important ethical questions if one feels compelled to guarantee access to all who could benefit. The high cost of the devices to be implanted greatly limits their routine use. Most doctors and health professionals observe certain ethical principles in their practice, in reference to who can and should receive this type of treatment [59].

Discussion

DBS surgery offers different treatment alternatives when the various pharmacological and/or rehabilitation options are insufficient in the context of serious neurological or neuropsychiatric complaints. To date, clinical trials evaluating the role of DBS in neurological or neuropsychiatric conditions have been developed and continue to be developed, which can be reviewed [58]. In the future, other conditions that compromise the CNS may be the subject of DBS surgery. Future research in the field of physiology and pathophysiology is required to understand them and how DBS can interact by modifying them, restoring normal functioning and consequently the health of patients

Conclusion

In the last 3 decades, DBS has become the treatment of choice in certain neurological diseases refractory to medical treatment, such as PD, dystonia and/or refractory tremors. Certain psychiatric disorders have benefited from DBS such as TS, OCD and depression. There are several other indications now under investigation for potential DBS therapies. It have been introduced novel lead designs and stimulation parameters to improve effectiveness and reduce adverse events. It is likely over the next years that DBS therapy will expand in indications and will become more personalized as the technology evolves and improves.

Acknowledgement

1-Authorities and staff of the "Anselmo Marini Rehabilitation Institute" and "Bernardo Houssay Hospital", 2- Engineer Daniel Cerquetti, who gave the images of intra-operative microelectrode recording.

Disclosure

The authors declare that they have no conflict of interest with the pharmaceutical industry. The present work was entirely solved by the authors, not having received financial aid from public or private institutions.

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