Chapter 1

# Anesthetic Considerations for Deep Brain Stimulation

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**Abstract**

Deep brain stimulation (DBS) was used to treat refractory Parkinson's disease (PD) for the first time in 1987 by Professor Benabid's group by placing stimulating electrodes into targeted brain structures. DBS is a widely accepted neurosurgical treatment for Parkinson's disease (PD), benign tremor, dystonia, epilepsy, and other neuropsychiatric disorders with no significant changes in anatomical brain structures. Prior to the introduction of DBS, traditional treatment for PD involved surgical removal of parts of the brain known as thalamotomy, pallidotomy, and cingulotomy. Intraoperative identification of the affected areas of brain is possible through a couple of mechanisms involving electrical stimulation and monitoring of the brain function, known as "functional neurosurgery". Implantation of electrodes in the targeted area and the insertion of a programmable pulse generator under the clavicle or in the abdomen are the main steps in DBS surgery. Anesthetic management for DBS remains controversial and might vary between institutions and physicians. Although no guidelines have been developed, there are some common anesthetic considerations for DBS surgery, including difficult airway management, facilitation of neuromonitoring, and anesthetic drugs interference with microelectrode recordings (MERs). Local anesthesia, general anesthesia, and monitored anesthesia care (MAC) have been used worldwide in patients undergoing DBS.

**Keywords:** deep brain stimulation, functional neurosurgery, neurodegenerative disorders, general anesthesia, monitored care anesthesia

# 1. Introduction

## 1.1. Technique and physiological considerations

Imaging techniques play an essential role in neurological diseases, offering precise information of anatomical location of the lesion, facilitating the identification, description, and prognostic evaluation of the disease in the vast majority of cases.

Affected areas of brain, contributing to patient signs and symptoms, may vary according to the type of disorder and treatment. Therapeutic protocols have been elaborated based on signs and symptoms, and different patient response. Modern medicine offers intraoperative identification of affected areas through a couple of mechanisms involving electrical stimulation and intraoperative brain function monitoring, known as "functional neurosurgery" [1].

Deep brain stimulation (DBS) is known as a neurosurgical treatment for several functional disorders through neuromodulation. Its use has been described in Parkinson's disease (PD), benign tremor, dystonia, epilepsy, and psychiatric disorders with no significant changes in anatomical brain structures [2].

Molecular and physiological responses to DBS are deeply studied. Several mechanisms have been described, including inhibition and stimulation processes that induce different reactions, not only in the targeted area but also in its vicinity [3]. Velasco et al. showed some variations in metabolism of five patients with PD after DBS of prelemniscal radiations (RAPRL), using F-FDG PET (2-deoxy-2-fluoro-D-glucose positron emission tomography). In order to corroborate definitive electrodes' position, microelectrode recordings (MERs) and macrostimulation were performed during the insertion process. They concluded that DBS produces a significant clinical improvement in these patients as a result of the reduction in metabolic rate in the Raprl, which led to decreased electrical responses of these cells in spite of high stimulation rates [4].

Characteristics of the stimulus are dependent on some modifiable factors such as type (monopolar or bipolar), frequency (usually high-frequency ranges), amplitude, and pulse width [5]. With respect to the physiological basis of neurons' connections, monosynaptic and polysynaptic functioning should be taken into consideration. Therefore, identification of dysfunctional areas and their networks in terms of derived extensive signaling would categorize eligibility of patients for DBS treatment [5] as well as the most suitable anesthesia technique for each case.

Implantation of electrodes in the targeted area and the insertion of a programmable pulse generator under the clavicle or in the abdomen are the main steps in DBS surgery [1, 6]. Generators might work during a few years, depending on the stimulation rates, although some of them are rechargeable [5]. The process of electrodes' placement is guided by MERs and concomitant macrostimulation, which consists of intraoperative physical stimulus or mental tasks to assess the responses of patients to DBS [7]. Anesthetic drugs have an important impact at this stage of the surgery [7, 8].

Surgery-related complications include perioperative and hardware-related issues. Beric et al. published in 2001 their experience with 86 patients and 149 DBS surgeries. They described perioperative complications in eight patients (hemorrhages, confusion, and seizures) and long-term postoperative complications in eight patients (delayed hematoma, behavioral changes, confusion, apraxia of eyelid opening, and peripheral nerve injury). Hardware-related issues were studied in nine patients (DBS electrode failure, extension wire failure, pulse generator malfunction, and pain over pulse generator) and stimulation-induced side effects were diagnosed in four patients (dysarthria, facial contraction, and confusion) [9].

## 2. Deep brain stimulation: history

### 2.1. DBS history

Electrical stimulation of an affected zone by placing an “electric fish” on its surface was surprisingly used from ancient eras up to eighteenth century. Headaches, epilepsy, and gout benefit of its clinical use [2, 10].

In the last century, DBS surgery was associated with three major events. In 1947, the use of a stereotactic device in humans was first described as “stereoencephalotomy” [11]. In 1952, local low-frequency stimulation was implemented in psychiatric interventions, leading to a successful use of high-frequency stimulation in patients with intractable tremor in 1987 [11, 12]. In 1997, Food and Drug Administration (FDA) approved the use of DBS in patients with essential tremor (ET) [2].

Prior to the introduction of DBS, the stereotactic frame was commonly used in surgical removal of parts of the brain, such as thalamotomy, pallidotomy, and cingulotomy in patients with functional pathologies. From this point on, the use of ablation techniques led to several clinical responses obtained from stimulation at low frequency and high frequency, with relevant findings in patients with Parkinson’s disease [13]. Nevertheless, the introduction of levodopa during the 1960s offset existing interest in stereotactic surgery [14].

In 1991, Benabid et al. published data from 32 patients diagnosed with levodopa-resistant tremor, 18 of them with past surgical history of bilateral thalamic surgery. Electrodes and semi-microelectrodes were used to stimulate ventral intermediate nucleus (VIM) with high frequency (100 Hz or more), being stimulation-adjusted depending on the level of tremor suppression. After definitive placement of electrodes, general anesthesia (GA) was administered to insert a programmable stimulator in the chest wall. They concluded that the capability to modify the intensity of the stimulus and other characteristics of this kind of stimulation, such as reversibility of the effects, might have a huge advantage, when compared with thalamotomy [12].

During the last decades, advances in electrophysiology and imaging have allowed more accurate localization of particular altered areas, as well as their different reactions under stimulation, either activation or inhibition, with the consequent widespread of signals [3, 15].

Outcomes in DBS surgery rely on accuracy during the electrodes’ insertion and placement. “Indirect” and “direct” techniques describe neuroimaging use during different stages of the procedure [16]. Indirect techniques, involving the use of MERs and a stereotactic frame to identify the targeted area, have been replaced in the vast majority by magnetic resonance imaging (MRI) for direct evaluation of anatomical structures during surgery [16, 17]. Nevertheless, safety MRI use in DBS surgeries follows the current FDA recommendations requiring system integrity [17].

### 2.2. DBS ethical nuances

As a consequence of satisfactory results obtained from the use of DBS in PD and other movement disorders, interest in showing efficacy of DBS in other disorders such as obesity and obsessive–compulsive disorder among other psychiatric pathologies has been growing in the last decade [18]. Despite the published data from several clinical trials, it is vital to understand that patients' and caregivers' high expectances may be deleterious, mostly in psychiatric patients, as DBS outcomes vary between patients and pathologies. Therefore, ethical issues, such as identifying suitable subjects and their allocation, either in control or in interventional arms, should be considered when designing protocols, to assure patients' safety [18, 19].

Ethical and regulatory committees worldwide should be actively involved in protocols' design regarding DBS surgery in neuropsychiatric patients, emphasizing in all the stages of subjects' participation such as informed consent and misunderstanding of expectations during research [20].

## 3. Deep brain stimulation: principles and practices

In order to understand the impact of anesthetic drugs either during surgery or in patients' outcomes, it is important to summarize some clinical evidence and to identify the most common targeted structures.

### 3.1. DBS in movement disorders

Benabid et al. described for the first time in 1987 the use of high-frequency stimulation (100 Hz) in patients with PD. The targeted thalamic nucleus was the ventralis intermedius (VIM), providing an important reduction in bilateral tremor under constant stimulation [21]. Definitely, these outcomes would generate several studies using DBS in patients with movement disorders. The same author published in 1991 a series of 32 patients with intractable tremor who underwent DBS surgery with similar findings. At this time, the authors stated that satisfactory outcomes obtained from continuous VIM stimulation were comparable with those achieved after thalamotomy, suggesting the need for developing new devices that might increase the frequency of stimulation above 100 Hz [12]. Subthalamic nucleus (STN) and globus pallidus interna (GPi) have been described as additional targets for patients with PD, with comparable long-term effects [22].

The ability of DBS to improve quality of life in patients with PD led to its use in different clinical entities, such as hyperkinetic disorders. Montgomery published in 2004 an overview describ-

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ing patient selection issues generated by these types of disorders, offering a brief description of the pathophysiological aspects and encouraging results of DBS use in this patient population [23].

### 3.2. DBS in neuropathic pain

Based on previous clinical evidence, Boccard et al. prospectively studied within 12 years, 197 patients diagnosed with neuropathic pain. After excluding patients for several reasons (e.g., contraindications or refusal of surgery), 85 patients were scheduled to undergo DBS surgery. The study was focused on periventricular gray (PVG) area, ventral posterior lateral (VPL), and ventral posterior medial (VPM) thalamic nuclei. Intraoperative macrostimulation was performed instead of MERs to define electrodes' location, and low-frequency (≤50 Hz) stimulations were used with satisfactory results. The procedure was completed with the insertion of the generator in just 74 patients, of which 15 patients did not offer complete data. The authors concluded that despite different degrees of neuropathic pain, the study offers long-term positive responses to DBS [24].

### 3.3. DBS in neurodegenerative disorders

Recent clinical trials investigated the outcomes of patients diagnosed with moderate dementia of Alzheimer's type scheduled to undergo DBS surgery. The fornix/hypothalamus has been pointed out as the target area of intervention. Laxton et al. published in 2010 a phase I trial, where six patients with Alzheimer's disease (AD) were scheduled for DBS surgery, targeting the fornix/hypothalamus region. Findings were encouraging, with consistent clinical improvement and lesser cognitive decline during 12 months of stimulation [25]. Changes in volumetric measurements of the hippocampus after fornix DBS have also been associated with clinical improvement, suggesting a potential ability of DBS to interfere with the natural progression of the brain atrophy in patients with AD [26]. DBS at variable frequencies and amplitudes has been used with promising results in cognitive impaired animal models [27].

### 3.4. DBS in psychiatry

Psychiatric disorders are well known as one of the major causes of disability worldwide, depression being the most common among them in both genders, with an annual incidence of 10% of the general population. Between 60 and 70% of patients will experience an improvement, using current antidepressant therapies. Nevertheless, there are an important number of patients where current pharmacology therapies will not lead to satisfactory results [28]. DBS has been shown to be an alternative in these treatment-resistant patients. **Table 1** summarizes most common psychiatric disorders and their areas of interest for DBS [29].

Different areas have been targeted under DBS with satisfactory results in patients with treatment-resistant depression. Lozano et al. studied the outcomes of 20 patients classified within major depressive disorder who underwent subcallosal cingulate gyrus (SCG) DBS. Patients with a decrease in 50% or more in the 17-item Hamilton Rating Scale for Depression (HRSD-17) were considered as "response". They found satisfactory results after 1 week, with

40% of subjects reaching significant reductions in the HRSD-17. Additionally, 60% of subjects reflected significant improvement within the first semester after surgery, whereas 35% reached remission [14].

| Target/disease | Depression | Anorexia | OCD | Addiction | Tourette syndrome |
|---|---|---|---|---|---|
| Lateral habenula | X | | | | |
| Subcallosal cingulated | X | X | | | |
| Ventral capsule/ventral striatum | X | | X | X | |
| Nucleus accumbens | | | | X | |
| Inferior thalamic peduncle | X | | X | | |
| CM–PF of thalamus | | | | | X |
| GPi/GPe | | | | | X |
| Subthalamic nucleus | | | X | | |
| Medial forebrain bundle | X | | | | |

CM–PF, centromedian–parafascicular nuclear complex; GPi/GPe, globus pallidus (internal/external). Adapted from Cleary et al. [29].

**Table 1.** DBS and psychiatric disorders: common nuclei for stimulation according to diagnosis.

Despite satisfactory outcomes obtained from clinical trials regarding DBS use in neuropsychiatric patients, it is noticed by the consensus published in 2014 that DBS surgery for any kind of psychiatric disorder has been established as an investigational procedure [20]. With this respect, Hamani et al. carried out an extensive review regarding the uses of DBS in patients with obsessive–compulsive disorder (OCD), concluding that more clinical trials are needed to collect quality evidence before making any recommendations for the therapeutic uses of DBS in this clinical setting, encouraging researchers to develop new protocols in the near future [30].

### 3.5. DBS in metabolic disorders

Obesity is well known as a public health problem. Recently, Fryar et al. published results from the National Health and Nutrition Examination Survey, concluding that more than two-thirds of the U.S. population is overweight, obese, or extremely obese [31]. Based on the neurohormonal components involving obesity and other metabolic disorders, the questioning of the potential effects of DBS in these patients has emerged.

Hypothalamic stimulation in patients with PD showed potential benefits for obesity as a secondary outcome [32]. Cortico-striato-pallido-thalamo-cortical (CSPTC) circuit activity is associated with obesity. Therefore, stimulation at different sites such as ventromedial hypothalamus and nucleus accumbens might be necessary to obtain satisfactory outcomes [33].

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## 4. Anesthetic considerations in patients undergoing DBS

Currently, limited data has been published with regards to the anesthetic management of DBS with no strict guidelines to follow by healthcare providers [8]. Nevertheless, there are some common concerns for DBS surgery, including patient comfort, Airway and blood pressure management , neuromonitoring, and anesthetic drugs interference with MERs. Particularities of anesthetic management for DBS surgeries with respect to different techniques, their outcomes, and anesthetic-related complications will be discussed.

Local anesthesia (LA), general anesthesia (GA), and monitored anesthesia care (MAC) have been used worldwide in patients undergoing DBS. Advantages and disadvantages have been described for each technique.

Abosch et al. published in 2012 the results of an international survey carried out in 185 DBS centers [34]. All of them were classified based on the number of DBS surgeries per year (1–12 per year, 13–24 per year, 25–52 per year, and >52 per year). Additionally, other variables were studied, such as surgical technique and time of surgery. The primary aim was to identify global factors surrounding DBS surgery, allowing all centers to compare their own experience and to recognize possible difficulties among their counterparts. Local anesthesia was used in 100% of the cases in centers with the lowest number of DBS surgeries per year (1–12 per year), whereas in centers with more than 52 cases per year, only 74% of the patients received local anesthesia, and 26% received general anesthesia. Regarding the type of disorder in patients, 93% of PD patients, 100% of ET patients, and 44% patients with dystonia underwent DBS surgery under local anesthesia [34].

Two main tendencies are noticed regarding the use of LA or GA during DBS surgery. The first one agrees with no use of any systemic anesthetic drug to obtain ideal MERs. Clinical evidence promotes the capabilities of imaging (MRI or MR/CT) to target STN without performing MERs, regardless of the type of anesthesia [35].

Chakrabarti et al. summarized anesthesia management during DBS surgery in three groups, based on patient considerations, surgical techniques, and disease-related [6].

A multidisciplinary preoperative approach is necessary to evaluate the risks of DBS surgery. As neurosurgeons carefully select patients who might benefit from DBS treatment based on certain medical criteria, anesthesiologists are expected to decide the type of anesthesia in a similar manner [36].

### 4.1. Local Anesthesia

LA as a subcutaneous infiltration or scalp block with long-lasting local anesthetics such as bupivacaine (0.5%), levobupivacaine (0.5%), and ropivacaine (0.75%), potentially offers certain benefits [7]. The absence of interference with MERs, decreased incidence of sedation-related complications such as nausea and vomiting, and reduced effects on hemodynamics or cognitive status are some of the benefits associated with LA.

Different techniques have been described by using LA in patients undergoing neurosurgical procedures, and have been named according to patients' level of consciousness during the stages of the intervention. The awake technique consists of performing scalp block with long–lasting local anesthetics, allowing simultaneous communication between the care team and the patient. This "therapeutic communication" is crucial and may be supplemented with music and other hypnotic techniques during neurosurgery [37].

Combined techniques limiting local anesthetic infiltration to the location of the pins with concomitant conscious sedation, have been described as "asleep-awake-asleep technique". Lange et al reviewed 38 subjects with PD who underwent DBS surgery using two different kind of anesthesia management. Local infiltration with conscious sedation was used in the first group (16 patients), whereas the second group (22 patients) received scalp nerve blockade with any or very little systemic anesthetic use. Any of the AE collected were considered as serious, although a significant difference in the onset of intraoperative delirium was found among groups (3 patients in group I vs 0 patients in group II. p=0.034). In general, scalp nerve blockade without supplemental systemic anesthetics could decrease the incidence of intraoperative neuropsychiatric adverse events and the length of the surgery [38].

Although scalp block is usually associated with decreased postoperative opioid consumption [39] and decreased opioid-related adverse events (post-operative nausea and vomiting - PONV- among others), some studies have shown no clinical significant advantage associated with its use. Gazoni et al studied 30 patients schedule to undergo craniotomy under standard general anesthesia. Based on the scalp block administration after the induction of GA, patients were randomized into two groups (receivers/ nonreceivers). Authors did not report any significant differences between groups with respect to postoperative opioid consumption, PONV, and hemodynamic variations [40].

Non-common adverse events have been reported while using local anesthesia including severe hypertension and coronary artery vasospasm [41, 42]. Additionally, airway management during an "awaked" anesthetic technique should be considered. Stereotactic frame might represent a challenge during the surgery, limiting patients' airway access [6]. Specific disease-related considerations, such as PD and obesity, should be evaluated with respect to airway management. Intraoperative larynx related neuromuscular dysfunction has been described in PD patients, increasing the potential risk of aspiration [43].

### 4.2. General Anesthesia

General anesthesia (GA) remains the preferred technique in certain patient population such as children, patients with non-controlled anxiety disorders, chronic pain, coughing, and severe movement disorders. Secured airway is the major advantage of GA, one of the major disadvantages being the interference with MERs and macrostimulation; with this respect, LA would be preferred to GA. However, some patients simply are not comfortable under LA due to several reasons (e.g. prolonged off-phase or without medication before surgery). Fluchere et al reported the outcomes of 213 PD patients that underwent DBS surgery between 2000 and 2009 with a variation of GA, with levels of sedation carefully titrated throughout surgical

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stages. All patients received a controlled general anesthesia using propofol and mechanical ventilation. MRI was used to identify the location of the leads, whereas stereotactic marks and trajectories were determined by the same neurosurgeon. At this time, propofol infusion was discontinued and sevoflurane was used for maintenance of anesthesia, allowing ideal sedation levels for MERs. Follow-up assessments were performed by the same neurologist one year post-surgery (in 188 patients), with a five years follow-up accomplished in only 65 patients. Authors concluded that this particular anesthesia technique did not affect short-term and long-term motor outcomes [44].

Essential neuromonitoring during DBS surgery will rely on the capability of some anesthetic drugs, such as propofol, to decrease tissue responses to stimulation or to allow intraoperative mental tasks. However, a case report published in 2006 by Deogaonkar et al described a PD patient developing midazolam and propofol-induced dyskinesia highlighting one of the undesirable effects of propofol [45].

Raz et al compared STN spiking activity in 16 PD patients alternating the exposure to propofol infusion. Once the electrodes were in place, traces of the STN were taken before and after the propofol infusion (50μg/kg/min). Low levels of sedation were accomplished within 11.9 ± 3.0 minutes, recorded either by Entropy (response and state entropy) or bispectral index (BIS), as well as capability of patients to respond to their names. STN activity is decreased in the presence of propofol infusion when comparing with baseline. Nevertheless, spiking activity returned to the baseline levels after 17 minutes from the time of propofol discontinuation [46].

Avoiding drugs that potentiate GABAergic transmission, such as propofol, may offer potential benefits during MERs [46, 47]. However, GA with propofol-remifentanil combination and successful identification of the subthalamic nucleus (STN) involving MERs and MRI techniques have been reported. This kind of anesthesia management requires an exceptional communication among anesthesiologists and the surgical team in order to achieve the expected goals through a close titration of anesthetic drugs [48].

### 4.3. Monitored anesthesia care

MAC is defined as a technique where local anesthesia is combined either with sedation (occasionally named as "conscious sedation") or with analgesia to obtain minimal changes in patients' consciousness, with response to verbal stimuli and spontaneous ventilation [49].

Electrophysiological evaluations during DBS surgery such as MERs and macrostimulation require an awake patient or the use of low levels of sedation. Dexmedetomidine is a well-known medication that has been used in anesthesia for more than 20 years with a distinctive effect at subcortical areas, producing ideal levels of sedation without respiratory impairments [1]. The ability to significantly decrease other anesthetic requirements, such as propofol and remifentanil, makes this $\alpha$-2-adrenergic agonist the drug of choice for DBS surgery as a part of the MAC technique. Pharmacodynamic and pharmacokinetic properties of these drugs allow big changes in the level of sedation in a short period of time [50]. Usually, high level of sedation or even general anesthesia is required for fixation of pins and for the insertion of the generator (last step), lower levels being used during intraoperative assessment of stimulation [1].

Respiratory complications (e.g., desaturation and airway obstruction) are the most feared during MAC, due to their association with devastating irreversible consequences [1, 6].

## 5. Future of deep brain stimulation: anesthesia guidelines

New technologies developed during the past 70 years impacted DBS surgery and patient outcomes. Researchers and physicians are encouraged to design prospective studies on DBS in different clinical settings. New stem cells investigational therapies in neurocognitive dysfunction evaluate the quality of outcomes using DBS as a baseline tool [51].

Anesthesia protocol is centered on patient comorbidities such as neuromuscular impairment for PD or morbid obesity cases where hypoventilation and difficult airway are the main concerns. Guidelines for DBS anesthesia should be elaborated based on the feedback provided by experienced anesthesiologists. Anesthesia in functional neurosurgery should be correlated with surgical goals, providing adequate combinations of anesthetic drugs with minimal impact on neurological monitoring, and contributing to patient comfort and safety.

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