Postoperative management of deep brain stimulation in Parkinson's disease

CASTRIOTO, Anna, VOLKMANN, Jens, KRACK, Paul


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INTRODUCTION

Since its introduction in the late 1980s and early 1990s (Benabid et al., 1987, 1991, 1993), deep brain stimulation (DBS) has become an established treatment for advanced Parkinson’s disease (PD) (Schuurman et al., 2000; Deuschl et al., 2006; Follett et al., 2010). Different nuclei are targeted in the treatment of PD, namely the subthalamic nucleus (STN), the ventral intermediate thalamic nucleus (VIM), and the globus pallidus pars interna (GPI). The first target, stemming from the observation that intraoperative high-frequency stimulation used in the targeting during thalamotomy allowed tremor control, was the VIM (Benabid et al., 1991). Because thalamic stimulation improved tremor, but not the other cardinal signs of PD (Benabid et al., 1991), interest moved to STN and GPI in the context of the revival of pallidotomy (Laitinen 1995) and better knowledge of basal ganglia pathophysiology (Alexander and Crutcher, 1990; Bergman et al., 1990). Although stimulation of both of these targets greatly alleviated cardinal signs of disease, motor fluctuations, and dyskinesias, only STN stimulation allowed the reduction of dopaminergic medication (Limousin et al., 1994, 1995, 1998, 1999; Krack et al., 1996, 1997; Kumar et al., 2000; Deep-Brain Stimulation for Parkinson’s Disease Study Group, 2001).

The immediate postoperative management of stimulation is a crucial phase for the optimization of motor and nonmotor outcomes. In addition to the practical—technical aspects of neurostimulation, this process requires a good knowledge of the functional neuroanatomy of target regions, as well as of the medical treatment of PD.

This chapter focuses on the postoperative management of DBS of the three nuclei used in PD in routine clinical practice: STN, GPI, VIM.

GENERAL PROGRAMMING STRATEGY

DBS mimics the clinical effects of lesioning in all three target structures, when “high-frequency” (>100 Hz) stimulation is applied. The exact cellular mechanism by which high-frequency DBS exerts a “lesioning-like” effect is still unknown, although several hypotheses have been proposed. In particular, there is strong debate as to whether DBS effects result from “inhibition” or “excitation” of neural elements. The clinical effects of stimulation critically depend on the exact electrode location, characteristics of current pulses (electrode polarity, amplitude, pulse width, and frequency), and properties of the excitable brain tissue around the electrode (e.g., thick myelinated fibers are activated before small axons or cell bodies; fibers oriented parallel to the cathode before those transversally oriented; fibers closer to the cathode before those closer to the anode) (Ranck, 1975; Nowak and Bullier, 1998; Volkmann et al., 2002). At first glance, the infinite number of theoretically possible parameter combinations seems to make programming of DBS a complex and time-consuming art. However, only a narrow range of parameters has proven to be useful in clinical practice, and this handful of combinations may often be tested during a single visit.

The entire programming process consists of an initial programming visit, followed by a stepwise adaptation.
of stimulation parameters. The goal of the initial programming visit is to screen for the optimal electrode contact, and to initiate stimulation with predefined parameters with a view to avoiding adverse effects of stimulation, optimizing benefits, and minimizing current consumption.

**STIMULATION PARAMETERS**

The relevant stimulation parameters, which can be controlled telemetrically by an external programmer after implantation of the internal pulse generator (IPG), are electrode polarity, amplitude, pulse width, and frequency.

**Electrode polarity**

The most widely used electrodes are quadripolar. Each electrode contact can be programmed as cathode (−) or anode (+). Monopolar stimulation (electrode as cathode, the case of the neurostimulator as anode) produces a spherical current field of activation. Bipolar stimulation (between different contacts of an electrode) provides a narrower and more focused current field, with the maximal effect of stimulation near the cathode (Ranck, 1975; Volkmann et al., 2002). Monopolar stimulation requires a lower intensity than bipolar stimulation to achieve the same clinical effect with subsequent lower consumption, and is therefore preferable. It may be useful in certain instances, when broader current diffusion and overlapping effects are desired, to activate two adjacent contacts.

More modern neurostimulators allow the stimulation of several cathodes with different current amplitudes. This helps further to shape the volume of tissue activated (VTA), for example in a “pear-like” manner, if necessary. Some DBS devices allow nonsimultaneous stimulation of different contacts in the so-called interleaving mode.

**Amplitude**

By increasing current amplitude, neural elements at a gradually increasing distance from the electrode are stimulated. Charge can be injected into the tissue in either constant voltage or constant current mode. The current/voltage relation follows Ohm’s law and depends on impedance at the electrode–tissue interface, which may change over time. Some IPGs keep the delivered voltage constant and the injected current may therefore vary depending on changes in tissue impedance, which are most prominent during the first weeks after electrode implantation. A postoperative increase in tissue impedance may, therefore, contribute to the necessity of gradual voltage increase with constant voltage DBS devices during the first postoperative weeks in order to maintain the stimulation-induced benefit. Other IPGs operate in constant-current mode, adapting the voltage required to the resistance at the electrode interface. Therapeutic amplitudes for DBS normally range between 1 and 4 V (or 1–4 mA at a typical impedance of around 1000 Ω).

**Pulse width**

Amplitude and pulse duration both influence stimulation efficacy, but amplitude can be adjusted on a much finer scale with most DBS devices. The excitability of neural elements follows an approximately inverse hyperbolic relation of current amplitude and pulse width. In a strength–duration curve, the rheobase current is the minimal amount of intensity needed to obtain an effect, whereas the chronaxie represents the pulse width needed to obtain a response using twice the rheobase current (Rizzone et al., 2001; Volkmann et al., 2002). Chronaxie studies have suggested that DBS in several targets is likely to activate thick myelinated axons (Holsheimer et al., 2000a, b; Rizzone et al., 2001). The measured chronaxies were in the range of 60–70 μs, suggesting a 60-μs pulse width as a good starting point for programming. Increasing pulse width does not significantly change clinical efficacy, but will increase current consumption and may lower the threshold for side-effects, consequently narrowing the therapeutic window, and thus reducing the possibility of “titrating” amplitude in order to achieve the highest possible benefit.

For this reason, screening for DBS effects should always be carried out at the lowest possible pulse width (60 μs for most DBS devices). An unsatisfactory clinical response following the increase of voltage or current to the maximum range could be a reason for increasing pulse width beyond the initial setting of 60 μs. In such cases, pulse width should be set at the next increment of 90 μs. In our own experience, the pulse width for stimulation of the subthalamic nucleus is 60 μs (rarely 90 μs), for VIM 60 μs (rarely 90–120 μs), and for the anatomically larger pallidal target usually higher (60–90 μs, rarely 120 μs, with reports in the literature of up to 450 μs).

**Frequency**

Pulse frequency can be set technically in a wide range of 2–250 Hz in different neurostimulators. Improvement of cardinal signs usually starts at 50 Hz and gradually augments with frequency increase, reaching a ceiling effect at between 130 and 185 Hz (Pollak et al., 1994). In order to reach maximal benefit with minimal battery drain, a frequency of around 130 Hz is typically chosen for initial programming. In the case of incomplete symptom control, it can sometimes prove useful to increase frequency up to 200 Hz (essentially for tremor control).
The increase in frequency does not increase the volume of tissue activated and might therefore optimize stimulation efficacy without greater risk of current diffusion into neighboring structures.

**BATTERY REPLACEMENT**

Current drain and battery life depend on the hardware of the IPG and the setting of stimulation parameters. Stimulation parameters are usually higher in the GPI, which is a larger target than the STN and the VIM (Krack et al., 2002). The average battery life with standard settings is more than 5 years for STN DBS for first- or second-generation neurostimulators (Anheim et al., 2007). In patients with severe PD, dual-channel IPGs should be monitored and replaced before the battery runs out, as complete and sudden arrest of DBS could prove dangerous and cause a life-threatening parkinsonism–hyperpyrexia syndrome, especially after a large decrease in dopaminergic medication (Hariz and Johansson, 2001; Kadowaki et al., 2011).

**INITIAL PROGRAMMING SESSION**

The initial programming session is typically scheduled after the microlesioning effect of electrode insertion has subsided. This may take several days or up to a few weeks after surgery. In order to evaluate stimulation effects without any drug-induced fluctuations of the motor state, the first programming is carried out in the drug off-state. Each contact of the lead is tested in monopolar mode at a predefined pulse width (typically 60 μs) and frequency (typically 130 Hz), and the amplitude is increased carefully until the first stimulation-induced adverse effects appear. The adverse-effect threshold defines the upper limit of the therapeutic window for the contact in question. The clinical efficacy of each contact is then determined either by testing the threshold of a beneficial response in the same way as described previously, or in a more time-efficient way by comparing the stimulation-induced benefit of each contact at a predefined intermediate amplitude (e.g. 1.5–2 V or mA). After carefully testing each lead separately in bilateral implants, stimulation is initiated in a monopolar mode with the contact as the cathode, which provided the most benefit and had the largest therapeutic window during the screening session. Because in the case of STN DBS the therapeutic effect may increase within the first hours, the starting amplitude does not normally exceed 1 V or mA. It may be uptitrated after a waiting period of a few hours. In VIM and GPI DBS, therapeutic amplitudes may be chosen from the outset, because delayed adverse effects or a progressive increase in stimulation efficacy are uncommon.

**STABILIZATION PERIOD AND BEYOND**

The stabilization period is dedicated to the gradual adjustment of stimulation parameters and medication. It is normally completed within the 3–6 months after surgery, but complicated cases may take up to a year. When response to DBS is clinically satisfactory, medication can be downtitrated carefully. Compensatory increases in stimulation amplitude are often required. Other stimulation parameters are changed only if the clinical benefit remains unsatisfactory or the amplitude increases exceed the adverse effect threshold. During the stabilization period “troubleshooting” visits are common, and the patient should be encouraged to return for reprogramming or medication adjustments when necessary. This applies particularly to STN DBS, which results in the most extensive changes in medication. Target-specific recommendations for programming and troubleshooting are provided in subsequent sections. It is important that the patient with PD begins first follow-up visits with the referring neurologist immediately after surgery, during the stabilization period. The referring neurologist will gradually take over follow-up of the chronic neurodegenerative disease, while the long-term management of stimulation parameters may be handled either in the surgical center or under the responsibility of a specifically trained neurologist outside the center. Such shared long-term follow-up requires provision of patient information about the roles of each healthcare professional in a given setting, as well as communication and collaboration between the neurologist in charge of DBS, the neurosurgical center, and the referring neurologist.

**SUBTHALAMIC NUCLEUS STIMULATION**

Target symptoms of programming

As mentioned above, rigidity is the most reliable symptom for assessing in the programming setting. Its improvement appears rapidly within 1 minute. Rigidity is stable and less variable than bradykinesia (which fluctuates with motivation and fatigue) and tremor (which fluctuates spontaneously depending on motor activity and psychic state). When not very pronounced, stable rigidity can be obtained using a Froment maneuver (Krack et al., 2002; Pollak et al., 2002; Broussolle et al., 2007). Improvement in rigidity is usually associated with an improvement in the other cardinal signs in the long term, although it is not specific to the STN, and can be achieved by stimulating surrounding pallidothalamic projections. Conversely, improvement in bradykinesia and induction of dyskinesias are highly specific to the sensorimotor area of the STN. The delay in obtaining improvement in bradykinesia (and in inducing dyskinesia) is longer and more variable. The maximal...
antiakinetic effect usually builds up over one to several minutes, and tends to reach a plateau after several hours or even days. Tremor is a very unstable sign over time and therefore difficult to assess. Its improvement is time-locked, appearing within a few seconds after stimulation is switched on. The maximal benefit is usually seen within 1 minute, but, if incomplete, some additional benefit may be observed over several days or weeks. As for rigidity, tremor control can be achieved with electrodes located outside the target. Therefore, although tremor assessment is useful, selection of the optimal contact based on tremor alone can be difficult and misleading. Off-dystonia is directly and rapidly improved by stimulation of the STN (Krack et al., 1999; Fraix et al., 2000).

Assessment of side-effects

The type and threshold of side-effects enable better localization and therefore facilitate selection of the optimal contact to be used for chronic stimulation. A change in the kind or the threshold of side-effects over time might signal electrode dislocation. When assessing side-effects, it is important to distinguish between those that may disappear progressively and those that will remain unchanged (Table 11.1).

The assessment of effects and side-effects enables selection of the contact with the widest therapeutic window, i.e., with the lowest voltage warranting the antiparkinsonian effect and the highest threshold for side-effects. Although they can be disabling at the outset, dyskinesias are associated with a good outcome and are a sign of good localization of the electrode. In such cases, the voltage needs to be decreased transiently, with acceptance of suboptimal antiparkinsonian effects. Decreasing dopaminergic treatment will progressively increase the threshold of STN-induced dyskinesia, allowing for a progressive increase in voltage up to optimal antiparkinsonian effect (Krack et al., 2002). This desensitization depends mainly on drug management and typically takes from several weeks up to several months, or sometimes even years. If the therapeutic window is too narrow, it might be useful (transiently) to choose bipolar stimulation or an adjacent contact that has less effect on akinesia.

Adjustment of stimulation parameters

Parameters are initially set at monopolar stimulation, 130 Hz and 60 μs. Amplitude starts typically at 1.0 V and is increased progressively in steps of 0.2–0.5 V to avoid delayed-onset dyskinesias or impulsive behaviors. Dopaminergic treatment can be reduced progressively, in parallel with improvements in parkinsonism. Parkinsonian signs can reappear after the initial weeks, owing to ending of the lesion-like effect and to the progressive decrease in the long-term response to L-dopa, and will require readaptation of stimulation amplitude or medication. Amplitude is increased to control parkinsonian signs in the off-medication condition, to an extent similar to that of L-dopa. Further increases do not bring any additional benefit, but they do increase battery consumption and carry a risk of potential side-effects related to current diffusion. Amplitude is set at least 10% below the threshold for side-effects. If the antiparkinsonian effect is suboptimal using a single monopolar contact, it may be useful to add the second best contact for double monopolar stimulation. If current diffusion is the issue, an alternative strategy is to use bipolar stimulation, with the contact with the best clinical effect serving as cathode. Increasing frequency may be useful to optimize tremor control. Increase in pulse width may add some further benefit if all these strategies are still not satisfactory.

It is also important to evaluate the patient in the on-medication condition. This allows detection of the worsening of dyskinesias, behavioral changes such as hypomania, which is typically associated to dyskinesias, or, in contrast, the reappearance of parkinsonian signs, due to either an excessive reduction in dopaminergic treatment or to current diffusion to neighboring pallidothalamic projections. If this is the case, rigidity and tremor remain improved, but stimulation partially blocks the benefit of L-dopa on akinesia and mood, inducing an acute improvement of dyskinesias at the cost of an acute worsening of bradykinesia and mood (Krack et al., 2002), as in stimulation of pallidothalamic fibers in patients with pallidal stimulation (Bejjani et al., 1997; Krack et al., 1998a, b).

Table 11.1

Habituation to side effects induced by subthalamic nucleus stimulation

<table>
<thead>
<tr>
<th>Adverse effects</th>
<th>Tolerance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pyramidal contractions</td>
<td>No</td>
</tr>
<tr>
<td>Ipsilateral monocular deviation</td>
<td>No</td>
</tr>
<tr>
<td>Dysarthria</td>
<td>No</td>
</tr>
<tr>
<td>Inhibition of levodopa effect (including akinesia and gait worsening)</td>
<td>No</td>
</tr>
<tr>
<td>Eyelid opening apraxia</td>
<td>No</td>
</tr>
<tr>
<td>Dysautonomic symptoms (mydriasis, flushing, sweating)</td>
<td>Yes (seconds to minutes)</td>
</tr>
<tr>
<td>Paresthesia</td>
<td>Yes (seconds to days)</td>
</tr>
<tr>
<td>Conjugate ocular deviation</td>
<td>Yes (minutes to days)</td>
</tr>
<tr>
<td>Dyskinesia</td>
<td>Yes (days to months)</td>
</tr>
</tbody>
</table>
In some cases, especially when symptoms are very asymmetrical, unilateral surgery may be performed. Management of unilateral subthalamic surgery does not differ substantially from that of bilateral procedures. The only difference is that in the phase involving decrease of dopaminergic drugs motor signs might reappear on the side contralateral to the nonstimulated STN. In this case, medication needs to be adapted to the unoperated side and stimulation should be reduced to avoid dyskinesia. Considering both that unilateral stimulation is performed in asymmetrical disease and that unilateral stimulation can have an ipsilateral effect (Bastian et al., 2003; Slowinski et al., 2007; Agostino et al., 2008; Alberts et al., 2008; Arai et al., 2008; Tabbal et al., 2008; Castrioto et al., 2011b), a good compromise is generally achieved.

After the first months, once stimulation parameters have been optimized, only minor changes in stimulation parameters are usually needed and medical management comes close to that of earlier-stage PD, typically allowing the referring neurologist to become the main actor again.

**Adjustment of medication**

Parallel to the setting of stimulation parameters, it is also necessary to adjust dopaminergic medication. Stimulation improves parkinsonian signs, and consequently dopaminergic drugs can be slowly reduced (Limousin et al., 1998; Moro et al., 1999; Krack et al., 2003; Kleiner-Fisman et al., 2006). This medication decrease is also required for better control of dyskinesias, which can be increased in the short term by subthalamic stimulation (Limousin et al., 1996; Krack et al., 1997, 1999). A too abrupt and total interruption of dopaminergic therapy should be avoided, as this might trigger delayed motor and/or nonmotor withdrawal syndromes (Krack et al., 2002; Thobois et al., 2010). After the initial months, once the lesion-like effect has vanished and desensitization has taken place, there is typically a progressive and generally mild worsening of parkinsonian motor and nonmotor signs, requiring adaptation of anti-parkinsonian treatment and/or parameters of stimulation. Patients must therefore be taught that in the early months they might experience a worsening of parkinsonian signs or of mood, motivation, and anxiety (Thobois et al., 2010). On the other hand, STN stimulation itself might induce euphoria and hypomania with an additive effect on the psychotropic effects of l-dopa (Krack et al., 2001; Funkiewiez et al., 2003), requiring a reduction of dopaminergic treatment, and, in the case of full-blown mania, psychosis, or impulse control disorders, reduction of stimulation parameters also.

Considering the potential appearance of a delayed dopamine withdrawal syndrome following dopamine agonist interruption (Thobois et al., 2010), it may be preferable to maintain a small dose of a dopamine agonist for most patients after surgery to ensure continuous dopamine receptor stimulation. Dopaminergic medication is adapted in order to optimize both motor and behavioral states, typically by titrating nonpulsatile treatment with l-dopa to avoid akinesia or dyskinesia, and long-acting dopamine agonists to avoid apathy or impulse control disorders (Lhomme et al., 2012).

**Management of side-effects**

The possibility of acute presentation of adverse events in patients with subthalamic stimulation suggests a close relationship with stimulation. In such cases, it is essential to understand the origin of the adverse event (related to the target versus related to current spread to neighboring structures), because this will alter the therapeutic approach. However, some issues may develop insidiously, be of multifactorial origin, and therefore require a therapeutic strategy on several fronts.

**Acute issues**

**Intrinsic side-effects**

Intrinsic side-effects might require an initial reduction of voltage, bipolar stimulation, or the selection of another electrode at the cost of losing some benefit.

**Dyskinesias.** Subthalamic nucleus stimulation can specifically induce dyskinesias (Limousin et al., 1996; Krack et al., 1999). Patients with preoperative l-dopa-induced dyskinesias are more likely to show stimulation-induced dyskinesias (Krack et al., 1999). Dyskinesias usually develop after a variable delay, ranging from a few minutes up to several hours after the setting of stimulation parameters (Krack et al., 1999). The threshold for stimulation-induced dyskinesias increases progressively over time. Therefore the voltage should be set below the threshold and increased progressively. Stimulation-induced dyskinesias can be an issue limiting voltage increase and control of parkinsonian signs. If dyskinesias appear, the first step is reduction of l-dopa dosage (Krack et al., 2002). In the rare case of difficulty in controlling dyskinesias despite l-dopa reduction, bipolar stimulation or monopolar stimulation using a less effective adjacent contact might be tried. In the long term, peak-dose dyskinesias are improved as a result of the reduction in l-dopa dosage and subsequent chronic desensitization (Bejani et al., 2000; Krack et al., 2002). Diphasic dyskinesias are also improved and the mechanism of this improvement is probably mixed, related indirectly to the reduction of medication and directly to the stimulation of the STN (Krack et al., 1999). A third mechanism of improvement in dyskinesias might be related to current
diffusion to pallidothalamic fibers in the zona incerta region (Obeso et al., 2000; Brodsky et al., 2006).

**Hypotonia.** This adverse effect is linked to an excessive reduction of rigidity. In some cases, hypotonia might become pronounced, causing balance and gait impairment. Both dopaminergic treatment and stimulation may contribute to hypotonia, which may be suspected in patients complaining of new-onset balance or gait impairment, which appears in the on-periods. In such cases, either stimulation or medication should be reduced.

**Conjugated ocular deviation.** In the operating theatre, it is not rare to observe contraversive conjugated ocular deviation induced by intraoperative microstimulation with microelectrodes correctly placed inside the STN (Pollak et al., 2002). However, during postoperative and long-term management, this side-effect rarely recurs as a clinically relevant problem (Sauleau et al., 2007). Conjugated ocular deviation (contralateral to the stimulated STN) is preceded by limiting gaze toward the stimulated STN, and it can be associated with contralateral head deviation and intense bilateral blinking, which prevents accurate ocular examination. Interestingly, bilateral STN stimulation is able to rapidly reverse the contralateral conjugated eye deviation induced by unilateral stimulation (Sauleau et al., 2007). The underlying mechanisms of contraversive ocular deviation remain unknown. Current diffusion to adjacent frontocollicular or frontomesencephalic projections cannot be excluded (Shields et al., 2007), but habituation to this side-effect and its induction with wellplaced electrodes are arguments in favor of stimulation of the subthalamic oculomotor area, which is part of the oculomotor loop (Krack et al., 2002; Sauleau et al., 2007; Nambu, 2011). Management of this side-effect is rarely a problem, because tolerance develops rapidly, and it is immediately reversed by either voltage reduction or bilateral stimulation.

**Mood and behavior.** Within the subthalamic nucleus, three different functional territories, namely the limbic, associative, and sensorimotor regions, can be distinguished along a medioventral–laterodorsal gradient (Parent and Hazrati, 1995; Yelnik, 2002; Mallet et al., 2007). The theoretical target of the electrode for PD is the sensorimotor region – the dorsolateral part of the nucleus. In a small nucleus such as the STN (Yelnik 2002), it is conceivable that one contact is located in the sensorimotor region, whereas a more medioventral one is located within the associative and limbic regions.

There have been several reports on acute behavioral and mood changes following parameter setting. In the postoperative phase, a state of mild euphoria and hyperactivity can frequently be observed, but this is generally transient if medication is reduced in tandem (Krack et al., 2002). However, an excessively rapid increase in stimulation parameters can also induce hilarity, hypomania, mania, or impulse-control disorders (Krack et al., 2001; Kulisevsky et al., 2002; Romito et al., 2002; Herzog et al., 2003; Mandat et al., 2006; Ulla et al., 2006, 2011; Mallet et al., 2007; Raucher-Chene et al., 2008; Coenen et al., 2009; Chopra et al., 2011) requiring adaptation of medical treatment and/or stimulation settings. These behavioral changes are usually induced by stimulation with the more ventral and medial contacts (i.e., stimulation of the ventral limbic STN) (Krack et al., 2001; Mallet et al., 2007). Nevertheless the exact postoperative localization of active stimulating contact is difficult to achieve and there is still uncertainty concerning the exact mechanism underlying mania in patients with PD and STN stimulation, with some authors claiming it is related to current diffusion to the medial forebrain bundle and lateral hypothalamus (Coenen et al., 2009), and others to ventrally located regions such as the substantia nigra (Kulisevsky et al., 2002; Ulla et al., 2011). When mania occurs, it may be necessary to change the active contact to a more dorsal one, to reduce dopaminergic medication (especially dopamine agonists), and, in the most severe cases, to use atypical antipsychotic (Krack et al., 2002; Kulisevsky et al., 2002; Mallet et al., 2007; Raucher-Chene et al., 2008). Transient acute depression induced by stimulation of the subthalamic region has also been described (Bejjani et al., 1999; Blomstedt et al., 2008; Tommasi et al., 2008b) and is suggested to be related to stimulation of the substantia nigra (Bejjani et al., 1999; Blomstedt et al., 2008) or of the zona incerta (Tommasi et al., 2008b). More rarely, stimulation can induce aggressive behavior, and this has been attributed to stimulation of fibers outside the STN in the nearby triangle of Sano (Bejjani et al., 2002b; Sensi et al., 2004), or to diffusion to the lateral part of the posteromedial hypothalamus. Alternatively, these behaviors (acute mania, depression, or aggressiveness), even though quite diverse, might all be specific to the limbic STN and represent disinhibition of normally controlled behavior (Frank et al., 2007; Krack et al., 2010). Studies assessing the acute effects of neurostimulation have shown that STN DBS has psychostimulating effects that mimic those of L-dopa (Funkiewiez et al., 2003; Schneider et al., 2003; Berney et al., 2007).

When an acute mood change time-locked to stimulation is induced, whether it involves mania, depressive mood, or aggressive behavior, the strategy is to reduce voltage or use a more dorsal contact. Mania or impulse control disorders may additionally require reduction of dopaminergic medication, especially dopamine agonists, and, in the most severe cases, the use of an atypical
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antipsychotic (Krack et al., 2002; Kulisevsky et al., 2002; Mallet et al., 2007; Raucher-Chene et al., 2008). Taking into consideration interactions between dopaminergic medication and stimulation, STN-DBS allows stabilization of medication-induced behavioral side-effects (Lhomée et al., 2012).

Cognition. The specific effects of subthalamic stimulation on cognition are best evaluated in studies comparing performances on and off stimulation (Volkmann et al., 2010). The most consistent finding in these studies (Jahanshahi et al., 2000; Pillon et al., 2000; Witt et al., 2004) is an impairment in the Stroop test with stimulation, especially in response inhibition in the conflict situation.

In the immediate postoperative phase, patients may present cognitive deterioration and disinhibition. These are more frequently found in the elderly (Saint-Cyr et al., 2000) and in people with preoperative cognitive impairment (Hariz et al., 2000). These cognitive side-effects tend to disappear partially in the following weeks to months, and seem to be more a consequence of brain surgery than of stimulation per se.

Confusion and psychosis can be observed after STN stimulation. The origin of these adverse events is typically multifactorial. Perioperative drug withdrawal, stress, surgery, anesthesia, and stimulation might play a role. Hallucinations and delusions may require a decrease in stimulation and dopamine agonists, and in some cases the introduction of antipsychotics. The most common cognitive side-effect of chronic subthalamic stimulation is a decrease in verbal fluency (Pillon et al., 2000; Troster, 2008; Volkmann et al., 2010). This side-effect, although systematically found across studies and highly significant in statistical terms, is usually minor in terms of effect and is not usually accompanied by a corresponding complaint from the patient. As the mechanism is not known, no specific therapeutic recommendation can be given.

Extrinsic adverse effects

Side-effects related to current diffusion to neighboring structures can be partially managed by changing stimulation parameters, for example by using another contact or switching from monopolar to bipolar stimulation. In the rare cases when, despite these strategies, side-effects outweigh antiparkinsonian benefit, it might be reasonable to envisage reimplantation. Knowledge of anatomical regions surrounding the STN is a prerequisite to the management of these side-effects (Fig. 11.1).

Diffusion of current to the corticobulbar and corticospinal tract may elicit muscle contraction. Pyramidal side-effects are usually time-locked to stimulation (appearing as soon as stimulation is turned on, and disappearing as soon as it is switched off). They are very reproducible, and involve mainly the upper face, where they can be bilateral or contralateral, or the lower face, where they are contralateral (Tommasi et al., 2008a). In the upper face, pyramidal contractions may present as “eyelid-opening apraxia,” caused by bilateral contractions of pretarsal orbicularis oculi muscles (Weiss et al., 2010; Tommasi et al., 2012). Corticobulbar fibers, directed to upper facial muscles, project bilaterally, whereas fibers directed to lower facial muscles project contralaterally. In patients with subthalamic stimulation, eyelid-opening apraxia might be the result of either lateral spreading of current to the pyramidal tract, and therefore be worsened by stimulation, or be a form of dystonia linked to the disease process, and therefore be improved by stimulation. Differentiation of these two forms is important during postoperative management as their therapeutic approaches are different, the former involving stimulation reduction, and the latter involving stimulation increase or L-dopa administration (if L-dopa-responsive). Pretarsal botulinum toxin injections can be helpful in both conditions. Activation of corticobulbar fibers might induce dysarthria, which is induced more frequently by left STN stimulation (Tommasi et al., 2008a). Speech in these cases presents as hypophonic, slurred, rapidly fatigue, hesitant, due to frequent and long pauses (Krack et al., 2002; Tommasi et al., 2008a), and may be difficult to differentiate from parkinsonian speech.

In some cases current spreads preferentially to corticospinal fibers, causing contralateral upper-limb contractions, which generally involve first the eminence thenar and then progressively recruit other muscles, inducing hand spasms such as carpopedal spasm. Further increase in stimulation intensity will lead to contraction of the face and upper limb or hemibody. Isolated contraction of leg muscles is rare.

Pyramidal side-effects are not subject to habituation; the threshold of pyramidal contractions must be sought carefully in order to set stimulation at least 10% below it. Chronic stimulation exceeding that threshold may induce brisk reflexes and typical dystonic hand-posturing. If such posturing is chronic it will not be immediately reversible on stimulation arrest.

Stimulation of the STN proper can induce dystonia, which is usually less time-locked and more mobile. It can sometimes be difficult to distinguish pyramidal contractions from dystonia induced by STN DBS. In such cases, low-frequency stimulation (2–3 Hz at a larger pulse width of about 210 μs) can be used. In the case of pyramidal contraction, rhythmic myoclonus synchronous to stimulation frequency will appear in the same territory as motor contractions (Krack et al., 2002; Tommasi et al., 2008a).
Stimulation can induce monocular deviation, which is neither target-specific nor subject to habituation. It generally consists of ipsilateral eye adduction or downward movement, or a combination of these (Bejjani et al., 2002a). Before ocular deviation is observed, the patient might complain of blurred or double vision or drowsiness. This effect is probably the result of current diffusion to oculomotor fibers of the third nerve (Krack et al., 2002). It is more commonly induced by the ventral contacts, and indicates a medial position. Therefore, when ocular deviation occurs, a more dorsal contact should be used, and in some cases a bipolar setting to focus the stimulation field (Krack et al., 2002).

The medial and posterior spread of current might activate the sympathetic fibers located in the zona incerta, inducing ipsilateral sweating of the face and chest and ipsilateral mydriasis (Krack et al., 2002). The threshold for these symptoms tends to increase over time and so these side-effects rarely represent an issue in postoperative management.

Dysarthria, and impairment of balance and walking might result from current diffusion to cerebellothalamic fibers (Plaha et al., 2006; Gallay et al., 2008; Tripoliti et al., 2008). Reducing amplitude, using bipolar stimulation or a more dorsal contact, located more laterally, are useful measures that allow reduction or avoidance of these side-effects. In some cases, if improvement in parkinsonian signs cannot be achieved despite these changes, electrode reimplantation might be considered.

Diffusion of current to the medial lemniscus can induce contralateral paresthesia, which is generally transient and not bothersome. If paresthesia persists and is very uncomfortable at low voltages, the position of the electrode may be too posterior. Using the more dorsal contact usually allows an increase in their threshold and overcomes this problem.

Stimulation of the nigra improves rigidity, but not bradykinesia (Krack et al., 2002). Both acute depressive state and hypomania have been described with acute stimulation by electrodes located in the substantia nigra (Bejani et al., 1999; Kulisevsky et al., 2002; Ulla et al., 2006, 2011) (see previous paragraph on mood and behavior). These behavioral changes are generally time-locked, appearing in the hours immediately following stimulation setting, and disappearing when it is switched off. Therefore, if a state of depression, aggressiveness, or (hypo) mania occurs soon after modification of stimulation parameters, a more dorsal contact should be chosen.
When the electrode contact position is either too dorsal (field H2 of Forel in the zona incerta) in a well localized quadripolar electrode, or too medial and anterior in a misplaced electrode, stimulation can induce acute block of L-dopa’s effect with abrupt interruption of dyskinesia and worsening of bradykinesia, and at the same time improve rigidity. This could suggest current diffusion to the pallidothalamic tract located in the zona incerta region dorsally, and medially in relation to the STN (Obeso et al., 2000; Parent and Parent, 2004; Brodsky et al., 2006; Tommasi et al., 2007; Gallay et al., 2008). This effect is also found with pallidal stimulation when the electrode is located in the ansa lenticularis (Bejjani et al., 1997; Krack et al., 1998b). In such cases one strategy might be to use a more ventral contact to avoid current diffusion to the dorsal zona incerta. Otherwise, when electrode implantation is too anterior or too medial, reimplantation should be considered.

**CHRONIC ISSUES**

**Gait and balance.** Subthalamic stimulation can improve gait and balance impairment to an extent similar to that observed with L-dopa. However, after surgery an increase in freezing of gait can be observed. This can be the result either of an overly drastic reduction of dopaminergic treatment, or of current diffusion to efferent fibers of the internal pallidum (Tommasi et al., 2007). Lowering the frequency of stimulation to 60 or 80 Hz has been proposed as a strategy for the improvement of postoperative freezing of gait (Moreau et al., 2008; Tagliati, 2008; Ricchi et al., 2012). If worsening of freezing of gait is an effect of stimulation per se via activation of pallidothalamic fibers, lowering the frequency of stimulation then induces reduction of freezing as a side-effect related to L-dopa inhibition, but at the same time this will also weaken antiparkinsonian efficacy. Therefore a different strategy, which is more cost-effective in terms of current drain, consists of lowering stimulation amplitude and reincreasing L-dopa.

Decreasing asymmetry of lower-limb akinesia (by reducing stimulation contralateral to the less affected side) can also improve freezing of gait (Fasano et al., 2011). In the management of balance, factors other than postural stability should be considered, such as dyskinesia or orthostatic hypotension.

**Posture.** The role of STN DBS in postural deviation in PD is unknown, with reports of both improvement and worsening after surgery (Sako et al., 2009; Umemura et al., 2010). In the case of lateral trunk or head deviation, efforts should be made to adapt stimulation parameters in order to decrease asymmetry of parkinsonism between the two sides of the body.

**Dysarthria.** Speech impairment is a relevant issue after STN DBS, as a result of lack of sustained and global improvement in, and worsening of, persisting dysarthria (Krack et al., 2003; Pinto et al., 2005; Tripoliti et al., 2011). An association between speech deterioration and higher stimulation parameters (voltage and frequency) has been found (Tornqvist et al., 2005; Tripoliti et al., 2008, 2011; Moreau et al., 2011). Diffusion to the corticospinal tract has been suggested as one explanation for speech deterioration (Krack et al., 2002). However, medially located electrodes and left-side stimulation have also been found to be associated with speech deterioration, suggesting that spreading to the cerebellothalamic pathways and a possible lateralization of speech within the basal ganglia may also be possible culprits (Tripoliti et al., 2011). Inhibition of L-dopa effects by current spread to pallidothalamic fibers may be yet another potential mechanism. When speech deterioration occurs after STN DBS, assessment of different conditions of stimulation (unilateral and bilateral stimulation, assessment on and off drugs) allows the detection of any association with stimulation in order to determine whether decreasing parameters of stimulation might be useful.

**Weight gain.** One of the most common chronic side-effects of DBS is weight gain (Moro et al., 1999; Barichella et al., 2003; Krack et al., 2003; Macia et al., 2004; Perlemoine et al., 2005; Kleiner-Fisman et al., 2006; Montaurier et al., 2007; Bannier et al., 2009; Sauleau et al., 2009; Walker et al., 2009; Strowd et al., 2010; Locke et al., 2011; Rieu et al., 2011). Typically, weight gain is maximal in the first year after surgery (Barichella et al., 2003; Macia et al., 2004). Different mechanisms may contribute to weight gain. The reduction in energy expenditure related to reduced rigidity, and dyskinesia (Montaurier et al., 2007; Bannier et al., 2009) seem to play a key role. The latter can be even enhanced by reduced activity when apathy occurs (Thobois et al., 2010). More rarely, behavioral screening may also detect binge-eating, in which case dopamine agonists should be reduced. Patients need to be warned of this potential side-effect before surgery, and monitoring of weight should be part of routine postoperative follow-up. Patients who have a significant increase in weight during the early postoperative months should receive dietary counseling.

**Apathy.** Apathy, defined as lack of interest and motivation, is one of the most frequent psychiatric side-effects of STN DBS (Funkiewiez et al., 2004; Volkman et al., 2010). Postoperative apathy is related to excessive withdrawal of dopaminergic treatment (Thobois et al., 2010) and responds well to dopamine agonist drugs (Czernecki et al., 2008). Because of its frequency, delayed appearance, association with other
hypodopaminergic symptoms, impact on quality of life, and potential reversibility, apathy needs to be screened for systematically, especially during the first year of postoperative follow-up (Thobois et al., 2010; Lhommeé et al., 2012). Although apathy has been reported frequently after STN DBS, it is not an issue if patients have best medical treatment. This highlights the importance of optimal postoperative management in the prevention of complications (Schuepbach et al., in press).

**Depression.** Depression has been described as a common side-effect following STN DBS (Houeto et al., 2002). However, the pictures depicted by large randomized controlled trials (Deuschl et al., 2006; Witt et al., 2008; Weaver et al., 2009) and from long-term outcome studies (Krack et al., 2003; Castrioto et al., 2011a) differ as, in the former, measures of depression were found to be slightly improved in the surgery group whereas in the latter depression was not described as a frequent side-effect. The main risk factors for the occurrence of postoperative depression include preoperative history of depression, rapid or excessive dopaminergic medication withdrawal, and difficulties adjusting to life-changing surgery (Agid et al., 2006; Volkmann et al., 2010). The withdrawal of dopaminergic medication might unmask depression, covered up by dopaminergic treatment in the preoperative phase (Thobois et al., 2010; Volkmann et al., 2010). L-Dopa and STN DBS share stimulating psychotropic effects (Funkiewiez et al., 2003), but only L-dopa seems able to restore hedonic tone (Witt et al., 2006). Therefore, when a patient treated with stimulation develops postoperative depression, it is important to consider readjustment and possible increase of dopaminergic treatment. Antidepressive treatment and psychological support should also be considered. Furthermore, in rare cases, stimulation can induce an acute depressive state (Bejjani et al., 1999). Thus, when depression occurs soon after setting of stimulation parameters, this possibility and reprogramming should be considered.

Postoperative mood should be assessed and monitored systematically, because a higher suicide rate has been reported among parkinsonian patients with STN DBS (Voon et al., 2008). Postoperative depression was found to be one of the risk factors for attempted suicide. Other factors include more premature PD onset, being single, younger in age, having a previous history of impulse control disorders, compulsive medication use, or previous suicide attempts (Voon et al., 2008). This increased suicide risk might also be caused by the development of impulsive behavior disorders after STN stimulation, and may be related to impaired decision-making (Frank et al., 2007; Volkmann et al., 2010). Another major contributing factor is the delayed withdrawal syndrome that occurs in up to half of all patients if dopaminergic treatment is reduced drastically (Thobois et al., 2010). The higher suicidal risk in parkinsonian patients with STN DBS seems, therefore, to be related to multiple factors. Patients should be informed of this increased risk prior to surgery. Patients with a positive history of psychiatric issues, especially of previous suicide attempts, impulse control disorder (ICD), or dopamine dysregulation syndrome (DDS), should be followed up and monitored strictly after surgery. Patients who develop apathy after surgery also need particularly careful follow-up and titration of dopaminergic treatment, as isolated apathy can worsen progressively and become part of a broader hypodopaminergic treatment, as isolated apathy can worsen progressively and become part of a broader hypodopaminergic syndrome that also includes depression and suicidal ideation (Thobois et al., 2010; Lhommeé et al., 2012). Postoperative monitoring to detect and treat depression have been proposed in order to prevent suicide (Thobois et al., 2010; Deuschl et al., 2013).

**Impulse control disorder and dopamine dysregulation syndrome.** Debate and controversy as to whether STN stimulation improves or exacerbates ICD and DDS in Parkinson’s disease are still ongoing, with reports having opposing findings (Witjas et al., 2005; Ardouin et al., 2006; Lim et al., 2009). Some studies have suggested that subthalamic stimulation could worsen impulsivity in high-conflict decisions, impairing response inhibition (Frank et al., 2007; Ballanger et al., 2009). Other studies have drawn attention to preoperative psychiatric comorbidity as a possible risk factor (Houeto et al., 2002, 2006). Persistence, aggravation, or new-onset ICD after STN DBS have all been reported (Smeding et al., 2007; Lim et al., 2009), but in these cases high doses of dopaminergic medication were typically maintained after surgery. A recent prospective study showed that ICD and DDS disappeared completely after STN stimulation with experimental drug management, involving complete arrest of dopamine agonists and marked reduction of L-dopa (Thobois et al., 2010; Lhommeé et al., 2012), suggesting the preponderant role of pharmacological treatment compared with STN DBS per se. This evidence supports the concept of similar mechanisms for dyskinesia, ICD, and DDS (Voon et al., 2009). Ventral striatum sensitization underlies ICD and DDS, as well as dorsal striatum sensitization dyskinesia. In this perspective, subthalamic stimulation, with subsequent reduction and replacement of pulsatile dopaminergic treatment, would allow reversal of ventral sensitization and behavioral disorders (Thobois et al., 2010; Volkmann et al., 2010). As a practical recommendation, in the case of ICD in patients with STN DBS, medical treatment should be revised and dopamine agonists discontinued, with careful monitoring of motivated behavior (Thobois et al., 2010; Lhommeé et al., 2012).
Cognition. Long-term studies (Funkiewicz et al., 2004; Contarino et al., 2007; Fasano et al., 2010) and large randomized controlled studies (Witt et al., 2008; Okun et al., 2009; Weaver et al., 2009; Williams et al., 2010) have found that STN DBS is relatively safe from a cognitive point of view, with overall cognitive performance remaining stable, except for a reduction in verbal fluency (Parsons et al., 2006). Therefore, when cognitive decline or frank dementia develops over the years, this is more likely related to disease progression, and its management should not differ from that of patients with PD without stimulation.

Sleep and restless leg syndrome. Sleep is reported to improve after subthalamic stimulation (Arnulf et al., 2000; Nishida et al., 2011). However, data on restless leg syndrome are conflicting (Hjort et al., 2004; Chahine et al., 2011). In some patients, restless leg syndrome has been described to worsen or to occur after surgery in the context of dopaminergic withdrawal (Kedia et al., 2004; Thobois et al., 2010). It might therefore be necessary to reintroduce dopamine agonists or to increase their dosage, or increase voltage in such patients.

DEEP BRAIN STIMULATION OF THE GLOBUS PALLIDUS INTERNA

Target symptoms of programming

Pallidal DBS can be programmed like STN DBS in the off-medication state. In this case, rigidity and bradykinesia are monitored during the monopolar review session, as is typically done for STN DBS. Alternatively, when suppression of dyskinesia is the primary goal of surgery, pallidal DBS can be programmed in the on-state. GPe DBS has an acute antidyskinetic effect, which is observed within seconds after initiating stimulation with effective parameters. However, maintaining a stable level of dyskinesia throughout an entire monopolar review session can be difficult to achieve. Choice of contact is often narrowed down during a monopolar review in the off-state, and the antidyskinetic effect of these contacts is then tested after a challenging medication dose.

Adjustment of stimulation

Unlike in STN DBS, the amplitude does not need to be uptitrated slowly in GPe DBS. Delayed adverse effects are rare with GPe DBS. As a precaution, stimulation can be initiated at 75% of the amplitude found to be most effective during the monopolar review. This allows evaluation of chronic benefit, leaving room for further amplitude adjustments, if necessary.

Several cases of late failure of pallidal stimulation have been described in the literature. In these patients, hypokinetic fluctuations and eventually even dyskinesia returned after several years of pallidal stimulation despite reprogramming attempts (Volkmann et al., 2004; Allert et al., 2010). The cause is unclear, but may be related to the larger volume of the GPe and to compensatory changes in areas not covered by the stimulation field. In several severely akinetic cases, DBS benefit could be rescued by reimplanting the leads into the STN (Houeto et al., 2000; Volkmann et al., 2004; Allert et al., 2010).

Adjustment of medication

Clinical trials of pallidal neurostimulation have reported little or no reduction in medication on average. Slow downtitration of medication may, however, be attempted in individual patients. When hypokinetic fluctuations return or worsen, medication needs to be increased to the previous level. In general, because of its antidyskinetic effect, pallidal neurostimulation improves tolerance to L-dopa. In patients with severe dyskinesia despite a low equivalent daily L-dopa dosage before surgery, an increase in postoperative L-dopa dosage may be justified, if off-period symptoms are not sufficiently controlled by DBS.

Intrinsic adverse effects

Because the GPe is much larger than the STN, current spread to nonmotor regions of the nucleus is less likely. This may explain why there are few reports of acute neuropsychiatric adverse effects of GPe DBS (Ghika et al., 1999). A ventrocaudal difference in stimulation effects has been described within the motor territory. Stimulation through ventral contacts has a better antidyskinetic effect, but can aggravate bradykinesia and even completely block the L-dopa response of akinesia, while antirrigidity, antitremor, and antidyskinetic effects persist, leading to pure isolated akinesia (Bejjani et al., 1997; Krack et al., 1998a, b). In contrast, stimulation through a more dorsal contact located in the globus pallidus pars externa (GPe) improves off-period symptoms but may at the same time induce dyskinesia (Krack et al., 1998b). The acute effects of stimulation in this location resemble the effects of STN DBS, but long-term stimulation in this location is different, as positive and negative effects are only transient (unpublished observations). Stuttering has been described as an adverse effect of pallidal neurostimulation in dystonia (Nebel et al., 2009), but not, as yet, in PD. Weight gain can occur after stimulation of the GPe, although less frequently than after STB DBS (Sauleau et al., 2009; Locke et al., 2011; Rieu et al., 2011).
Extrinsic adverse effects

The internal capsule forms the medial and posterior border of the GPi (Fig. 11.2). Current spread into the corticobulbar fibers (discussed in more detail in the STN DBS section in this chapter, paragraph on extrinsic adverse events p.135) can lead to tetanic contractions, but a subthreshold stimulation of the pyramidal tract is less obvious. It can result in slow and clumsy finger movements, micrographia, or other impaired fine motor skills. Costimulation of corticobulbar fibers causes dysarthria with a slurred and often spastic type of speech impairment. The optic tract runs ventral to the GPi. An electrode contact on the ventral border of the GPi often causes phosphene sensations, on initiation of stimulation. Persistent disturbances of vision are rare and indicate a misplaced (too ventral) contact. Acute stimulation of electrodes localized on the ventral border or below the GPi can induce subjective feelings of dizziness or nausea (Krack et al., 1998b).

Depression and suicide have also been reported following GPi DBS (Weintraub et al., 2012). Depression is multifactorial and therefore difficult to classify into intrinsic or extrinsic categories. It has been dealt with in detail in the STN DBS section in this chapter (paragraph on depression p. 138). Systematic screening for depression is even more important in operated patients than in the general PD population, especially in the postoperative period, paying particular attention to unmet expectations in the population of patients with PD, who invest a great deal of hope in the life-changing properties of surgery.

DEEP BRAIN STIMULATION OF THE VENTRAL INTERMEDIATE THALAMIC NUCLEUS

Target symptoms of programming

Thalamic DBS is a monosymptomatic treatment of tremor only. The effects are immediate. During the monopolar review session, a constant level of tremor should be maintained by contralateral physical activity or mental tasks. A cessation of resting tremor indicates effective stimulation. The contact with the lowest threshold for tremor suppression and the largest therapeutic window is chosen for chronic stimulation.

Fig. 11.2. (A) Sagittal (20 mm lateral to midline) and (B) frontal (2 mm anterior to the midcommissural plane (MCP)) sections of the pallidal area depicting the behavioral responses to high-frequency stimulation within the ventroposterolateral target region of the internal globus pallidus (GPi) and surrounding structures. AC, anterior commissure; Amg, amygdala; GPe, external globus pallidus; IC, internal capsule; OT, optic tract; PTT, pallidothalamic tract. (Modified from Morel, 2007.)
Adjustment of stimulation

The amplitude of stimulation can be adjusted if the microlesioning effect subsides or tremor aggravates in the long term. Normally, stimulation parameters remain remarkably stable over time, with no need for adjustment. Tolerance, which may be an issue in severe cerebellar-type tremor including essential tremor, is rarely an issue in PD. Tolerance can be partially prevented by overnight arrest of stimulation, but this is usually not acceptable for patients with PD, as rest tremor can be disabling at night. Strategies include maintenance of dopaminergic or even anticholinergic antitremor medication, or in rare cases adjunctive use of night-time clozapine, which is sedative and improves the quality of sleep and even daytime tremor.

Adjustment of medication

If high dosages of dopaminergic medication were taken before surgery for partial relief of tremor, with VIM DBS medication may be downtitrated to the level required to control any additional akinetic–rigid symptoms.

Intrinsic adverse effects

The VIM is the receiving area for dentate–thalamic fibers (Fig. 11.3). Stimulation within this nucleus or the afferent fiber tracts (prelemniscal radiation in the subthalamic area) is most effective in alleviating parkinsonian tremor. Cerebellar symptoms, such as hypotonia, dysarthria, or dysmetria, may occur at higher voltages, but do not typically limit the efficacy of thalamic DBS in PD. They are more problematic in the treatment of cerebellar-type tremors, such as essential tremor or tremor in multiple sclerosis.

Extrinsic adverse effects

The ventrocaudal thalamic nucleus and the afferent medial lemniscus form the posterior border of the target area. Current spread in a posterior direction activates sensory neurons and causes tingling sensations or pain. Tolerance to paresthesias develops quickly, and mild tingling in the contralateral face and hand when initiating stimulation is common, with an optimally placed lead. If the electrode is located too posteriorly, paresthesias become painful and may prevent tremor control. The site of paresthesias may help to predict the mediolateral

Fig. 11.3. (A) Sagittal (14 mm lateral to midline) and (B) frontal (8 mm anterior to posterior commissure (PC)) sections of the thalamic and subthalamic area depicting the behavioral responses to high-frequency stimulation within the target region for tremor control (ventral intermediate thalamic nucleus, VIM) and surrounding structures. AC, anterior commissure; CTT, cerebellothalamic tract; IC, internal capsule; MCP, midcommissural plane; RN, red nucleus; SN, substantia nigra; STN, subthalamic nucleus; VLa, ventrolateral anterior thalamic nucleus; VLP, ventrolateral posterior thalamic nucleus; ZI, zona incerta. (Modified from Morel, 2007.)
location of the electrode, because the somatotopy within the ventrocaudal and ventrointermediate nucleus is parallel. The leg area is lateral and closest to the internal capsule, the arm area occupies an intermediate position, whereas hand and face are represented within the medial part of the nuclei.

The internal capsule forms the lateral border of the target area and current spread in this direction can provoke the typical side-effects caused by stimulation of corticospinal or corticobulbar fibers discussed in detail in the STN DBS section in this chapter (paragraph on extrinsic adverse events p.135), mainly dysarthria and contralateral tetanic contraction of the contralateral face, hand, and, more rarely, lower limb. Nonlocalizing adverse effects, which are observed occasionally with thalamic stimulation, include a mild hemineglect, dizziness, and postural instability.

CONCLUDING REMARKS

The adjustability of stimulation parameters is the greatest advantage of DBS compared with lesional stereotaxy. Even the best of programming, however, cannot compensate for a poorly placed lead. The three different targets discussed here have different effects on clinical symptoms (see Chapter 10). At present, the STN is the most common target in PD surgery worldwide, although this is only part of the reason why it is overrepresented in this chapter. The other explanation relates to the fact that it is also the most complex target in terms of potential side-effects and adjustment of medication and stimulation. Postoperative management of DBS is a key factor in outcome, together with patient selection and surgical precision. Whatever the target, a surgical center requires high surgical and neurological expertise, good teamwork within the center, and a defined strategy and collaboration with referring neurologists for long-term follow-up.

REFERENCES


