Cell Tissue Res (2004) 318: 275–288
DOI 10.1007/s00441-004-0936-0

REVIEW

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Deep brain stimulation

Received: 30 January 2004 / Accepted: 1 June 2004 / Published online: 19 August 2004

Abstract During the last decade deep brain stimulation (DBS) has become a routine method for the treatment of advanced Parkinson's disease (PD), leading to striking improvements in motor function and quality of life of PD patients. It is associated with minimal morbidity. The rationale of targeting specific structures within basal ganglia such as the subthalamic nucleus (STN) or the internal segment of the globus pallidus (GPi) is strongly supported by the current knowledge of the basal ganglia pathophysiology, which is derived from extensive experimental work and which provides the theoretical basis for surgical therapy in PD. In particular, the STN has advanced to the worldwide most used target for DBS in the treatment of PD, due to the marked improvement of all cardinal symptoms of the disease. Moreover on-period dyskinesias are reduced in parallel with a marked reduction of the equivalent daily levodopa dose following STN–DBS. The success of the therapy largely depends on the selection of the appropriate candidate patients and on the precise implantation of the stimulation electrode, which necessitates careful imaging-based pre-targeting and extensive electrophysiological exploration of the target area. Despite the clinical success of the therapy, the fundamental mechanisms of high-frequency stimulation are still not fully elucidated. There is a large amount of evidence from experimental and clinical data that stimulation frequency represents a key factor with respect to clinical effect of DBS. Interestingly, high-frequency stimulation mimics the functional effects of ablation in various brain structures. The main hypotheses for the mechanism of high-frequency stimulation are: (1) depolarization blocking of neuronal transmission through inactivation of voltage dependent ion-channels, (2) jamming of information by imposing an efferent stimulation-driven high-frequency pattern, (3) synaptic inhibition by stimulation of inhibitory afferents to the target nucleus, (4) synaptic failure by stimulation-induced neurotransmitter depletion. As the hyperactivity of the STN is considered a functional hallmark of PD and as there is experimental evidence for STN-mediated glutamatergic excitotoxicity on neurons of the substantia nigra pars compacta (SNc), STN–DBS might reduce glutamatergic drive, leading to neuroprotection. Further studies will be needed to elucidate if STN–DBS indeed provides a slow-down of disease progression.

Keywords Deep brain stimulation · Basal ganglia · Subthalamic nucleus · Globus pallidus · Parkinson's disease

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History of surgical treatment and deep brain stimulation for Parkinson's disease

Surgical treatment for Parkinson's disease (PD) and other movement disorders was first introduced approximately 50 years ago by lesioning different functional targets within the basal ganglia. As the post-operative complications and morbidity were relatively high and the levodopa therapy emerged by the beginning of the 7th decade of the last century, surgical treatment for PD was almost completely abandoned. In the late 1980s and early 1990s a resurgence of new surgical techniques directed to new functional basal ganglia targets was observed. For the first time, the Grenoble group introduced high-frequency stimulation of the ventralis intermedius nucleus of the thalamus (Vim) to

replace thalamotomy in the treatment of tremor (Benabid et al. 1987, 1989). Concomitantly, Laitinen reintroduced the posteroventral pallidotomy as a therapeutic option for the treatment of advanced PD (Laitinen et al. 1992a,b). Following new insights into the pathophysiology of basal ganglia achieved by experimental work on animal models of PD (Albin et al. 1989; Alexander and Crutcher 1990; Alexander et al. 1990; DeLong 1990), the bilateral high-frequency stimulation of the subthalamic nucleus (STN) was introduced for the first time in 1993 in the treatment of advanced PD (Benabid et al. 1994; Limousin et al. 1995). During the last decade, deep brain stimulation (DBS) of the STN emerged to the most frequently applied surgical therapy for movement disorders, representing a most promising breakthrough in the treatment of advanced PD. Siegfried and Lippitz introduced in 1994 the DBS of the globus pallidus internus (GPi) for the treatment of advanced PD (Siegfried and Lippitz 1994). Following these pioneering works showing striking improvements in PD patient's motor function and quality of life, an increasing number of groups started to use DBS worldwide as a routine method for treatment of advanced PD. DBS has almost completely replaced lesioning procedures for several reasons: (1) DBS does not require deliberate destruction of brain regions and due to its reversibility it does not preclude the use of future therapies, (2) stimulation parameters can be tuned post-operatively in order to improve efficacy and reduce adverse effects, (3) in contrast to ablative procedures it can be safely performed bilaterally.

Pathophysiological basis for surgery for Parkinson's disease

The knowledge of the functional changes of basal ganglia activity in the parkinsonian state as it emerged from extensive experimental studies on animal models has provided the theoretical basis for surgical therapy in PD. The 6-hydroxydopamine (6-OHDA) rat model and the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) primate model of PD provided powerful research tools for uncovering the pathophysiology of changes in functional basal ganglia activity in PD. By the end of the 1980s, a pathophysiological model of basal ganglia was established (Fig. 1A), which was able to explain in part some of the cardinal motor manifestations of PD (Albin et al. 1989; Alexander and Crutcher 1990; Alexander et al. 1990; DeLong 1990). Among the segregated circuits that form the cortico-basal ganglia-thalamo-cortical loops (Alexander et al. 1990), research has focused on the motor circuit, which is the most relevant for understanding the cardinal features of PD. The motor circuit connects the motor cortical areas and the primary somatosensory cortical areas with the dorsolateral putamen. At the cellular level, cortical glutamatergic neurons project to both medium spiny striato-pallidal GABAergic projection neurons and to large aspiny cholinergic interneurons in the striatum. The nigrostriatal dopaminergic projection originating in the substantia nigra pars compacta (SNc), which degenerates in PD leading to a striatal dopaminergic deficit, mainly modulates the excitatory influence of the cortical afferents on the striatal projection neurons. The striatum influences the efferent activity of the basal ganglia output structures, which are the internal segment of the globus pallidus (GPi) and the substantia nigra pars reticulata (SNr), by means of the "direct" and of the "indirect" pathways. Neurons from the "direct pathway" establish a

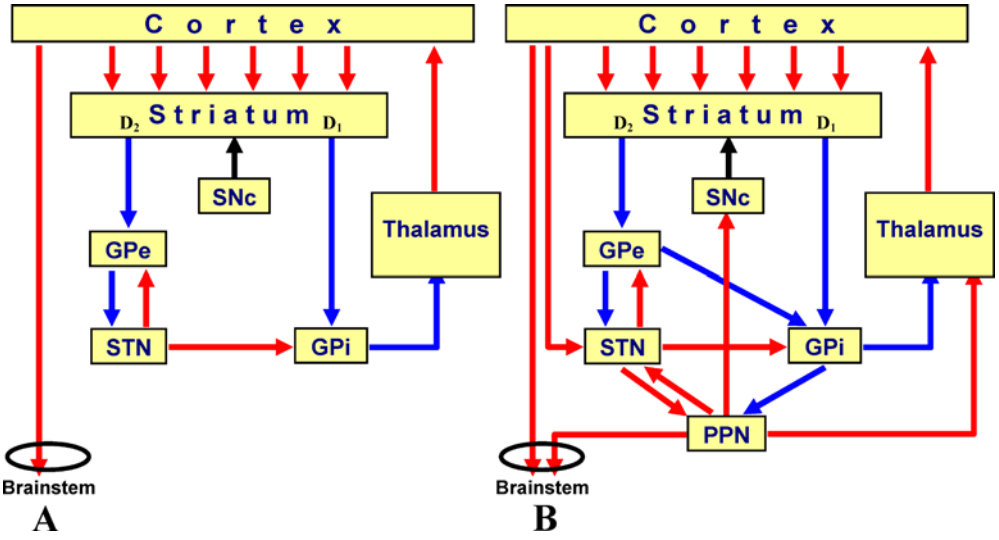

Fig. 1 Schematic diagram of the basal ganglia-thalamocortical circuitry under normal conditions: **A** classical basal ganglia model, **B** extended basal ganglia model. Inhibitory connections are shown as *blue arrows*, excitatory connections as *red arrows* and the dopaminergic nigrostriatal projections as a *black arrow*. The nigrostriatal projections modulate the activity of the striatal neurons of the direct pathway via D_1 receptors and of the striatal neurons of the indirect pathway via D_2 receptors. The following abbreviations were used: *SNc* substantia nigra pars compacta, *GPe* external part of the globus pallidus, *STN* subthalamic nucleus, *GPi* internal part of the globus pallidus, *PPN* pedunculopontine nucleus

monosynaptic GABAergic projection from the striatum to GPi/SNr. Striatal projection neurons in the "indirect pathway" send their GABAergic projections to the external segment of the globus pallidus (GPe), which in turn sends GABAergic projections to the STN, which projects through glutamatergic synapses to GPi/SNr (DeLong and Coyle 1979; Groenewegen and Berendse 1990; Feger and Robledo 1991; Parent and Hazrati 1995; Yelnik 2002). The dopaminergic nigrostriatal projection exerts a dual action on efferent striatal projection neurons. It inhibits D_2 receptors in the "indirect pathway" and activates D_1 receptors in the "direct pathway." The dopamine deficiency in the parkinsonian state leads over a cascade of activity changes to an increased neuronal activity of the STN and conversely of the GPi/SNr (Filion 1979; Bergman et al. 1994). In the classical basal ganglia model the STN hyperactivity in the parkinsonian state originates in the over-inhibition of the GPe neurons by the increased activity of the D_2 receptor expressing striatal projection neurons due to the dopamine depletion. As a result of the well-established excessive output activity of the GPi/SNr, which was extensively demonstrated by means of electrophysiological and metabolic studies, the thalamo-cortical projection and the brainstem nuclei were inhibited. Consequently movement initiation and execution as well as the performance of sequential tasks are inhibited, giving rise to bradykinesia, a cardinal symptom of PD. Lesions of the STN and GPi induced marked clinical improvement in MPTP-treated monkeys, which is accompanied by a marked reduction in neuronal activity of GPi/SNr neurons (DeLong and Coyle 1979; Bergman et al. 1990; Aziz et al. 1991; Mink and Thach 1991; Wichmann et al. 1994).

Similar results were obtained by high-frequency stimulation of the STN or GPi in the MPTP animal model (Benazzouz et al. 1993, 1996; Boraud et al. 1996). Although the pathophysiological mechanisms of high-frequency stimulation were not known, the empirical findings that high-frequency stimulation of the STN and GPi lead to similar clinical effects as ablation of these structures lead to the hypothesis that high-frequency stimulation induces a functional inhibition preserving the advantage of reversibility. High-frequency stimulation of the STN or GPi in patients with PD was shown to improve all cardinal symptoms such as akinesia, rigidity, and tremor (Benabid et al. 1994; Limousin et al. 1995; Krack et al. 1998c; Kumar et al. 1998; Deep-Brain Stimulation for Parkinson's Disease Study Group 2001; Volkmann et al. 2001). Positron emission tomography (PET) studies (Brooks and Samuel 2000) showed increased regional cerebral metabolism in the ipsilateral supplementary motor cortex and dorsolateral prefrontal cortex associated with motor improvement in PD patients treated by pallidotomy (Ceballos-Baumann et al. 1994; Eidelberg et al. 1996; Samuel et al. 1997) or DBS of the STN (Ceballos-Baumann et al. 1999; Hilker et al. 2002) and GPi (Davis et al. 1997; Fukuda et al. 2001).

The classical model of basal ganglia fails to explain the therapeutic effect of Vim-DBS on various tremor forms including parkinsonian tremor. The most favored hypothesis is based on the strategic position of the Vim as a cerebellar relay nucleus and/or on the jamming of the oscillatory loop by DBS. PET studies performed on PD tremor treated by DBS of the Vim showed controversial results. One study showed a reduction of regional blood flow during Vim-DBS in the ipsilateral putamen, sensorimotor cortex, and supplementary motor area (Parker et al. 1992) suggesting a tremor generator within the basal ganglia-thalamo-cortical loop, whereas another study showed only a reduction in cerebellar activity during Vim-DBS (Deiber et al. 1993) favoring the tremor generation in the cerebello-thalamic loop. Tremor-synchronous neuronal activity was found in different human basal ganglia and thalamic nuclei, such as the ventral thalamus (Lenz et al. 1988, 1994), the globus pallidus (Hutchison et al. 1997a; Hurtado et al. 1999) and the STN (Levy et al. 2000; Magarinos-Ascone et al. 2000; Rodriguez-Oroz et al. 2001).

The major paradox of functional surgery for the treatment of PD is the dramatic effect of pallidotomy or GPi-stimulation on levodopa induced dyskinesias (for review, see Marsden and Obeso 1994). Following the classical basal ganglia model, the appearance of dyskinesias should correlate with a decreased firing rate in the GPi. Indeed, several studies showed a decreased firing rate associated with the appearance of dyskinesias. The administration of the dopamine agonist apomorphine decreases firing rate in the GPi both in the primate MPTP model (Filion et al. 1991) and in PD patients (Hutchison et al. 1997b). Intra-operative administration of apomorphine reduces the activity of both STN and GPi and increases the activity of GPe, the induction of dyskinesias resulting from a dramatic decrease in GPi firing (Lozano et al. 2000). Following the basal ganglia model the lesioning of the GPi should lead to a worsening of dyskinesias. In sharp contrast to the classical theory and to the experimental findings of reduced GPi activity in the dyskinetic state stays the consistent observation that ablation or DBS of the GPi leads to a dramatic improvement of dyskinesias (for review, see Marsden and Obeso 1994; Obeso et al. 1997, 2000). The debate about the paradox of surgery regarding the dyskinesias shows that the classical basal ganglia model, which is mainly a "firing rate"-based model, has significant limitations, despite its incontestable merits. The changes in firing pattern as well as the pathological synchronization within and between basal ganglia nuclei in the parkinsonian state represent new aspects that gained increasing importance in the attempt to understand basal ganglia functioning (Brown et al. 2001; Levy et al. 2001). Limitations of the model became evident also from other experimental findings on animal models, the main inconsistencies being the origin of STN hyperactivity in the parkinsonian state, which cannot be explained solely by the hypoactivity of the GPe as predicted by the classical model (Chesselet and Delfs 1996; Levy et al. 1997; Parent and Cicchetti 1998). Furthermore, descending projections from the basal ganglia to the brainstem nuclei and spinal

cord, mainly via the projections to the pedunculopontine nucleus (PPN) were often neglected and may play an important role mainly in axial symptoms of PD such as gait disorders and postural instability (Delwaide et al. 2000; Pahapill and Lozano 2000; Breit et al. 2001; Nandi et al. 2002a,b,c,d). Feedback projections such as from the parafascicular nucleus (PF) of the thalamus to the STN (Feger et al. 1994) and from the PPN to the SNc (Lavoie and Parent 1994; Forster and Blaha 2003) may also play an important role in basal ganglia pathophysiology. Consequently the classical basal ganglia model should be extended by at least following important projections: Cortex–STN, PF–STN, PPN–STN, GPe–GPi, PPN–SNc, STN–PPN, and GPi–PPN (Fig. 1B). Further progress in understanding basal ganglia pathophysiology may lead to the definition of even better targets for surgical therapy.

Patient selection

The selection of the appropriate candidates for DBS surgery is important. The main goal of the selection process is to identify those patients in whom the expected benefit would outlast the potential risk associated with the surgical intervention, i.e. to evaluate the individual risk/benefit profile. The main indication for DBS in PD is advanced idiopathic PD with motor complications such as fluctuations and dyskinesias with relevant disability or therapy-resistant parkinsonian tremor. Other parkinsonian syndromes than idiopathic PD such as multiple system atrophy, progressive supranuclear palsy, corticobasal degeneration or Lewy body dementia do not benefit from DBS. The ideal candidate with advanced idiopathic PD should have a preserved good levodopa response but long-term treatment side effects such as motor fluctuations and dyskinesias (Welter et al. 2002). A good levodopa response of parkinsonian tremor is not necessary in order to predict the success of DBS, although medical treatment attempts with high doses of levodopa (up to 1500 mg per day), dopamine agonists and clozapine are mandatory before deciding on surgery. The main exclusion criteria are severe brain atrophy, severe vascular encephalopathy, dementia, major depression or acute psychosis. General health conditions are important prerequisites in order to minimize general intra-operative and peri-operative complications and to ensure good cooperation during prolonged awake surgery. The patient's own expectations from surgery need to be carefully addressed before deciding on the intervention. The treating physician should inform the patient about the realistic perspectives and should correct unrealistic expectations. In some situations, it might be even beneficial to have psychotherapeutic counseling of the patient before the final decision is taken.

Technical approach and optimal site of stimulation

The ultimate goal of the DBS surgical procedure is the precise implantation of the stimulation electrode in the targeted brain area and its connection of the electrode to an internal programmable pulse generator usually located in the chest area. The stimulation is accomplished via one or more of the four contacts on its distal end. The pulse generator settings can be adjusted post-operatively by telemetry with respect to electrode configuration, voltage amplitude, pulse width, and frequency. The implantation of the electrode is done by a stereotactic procedure in the awake patient in the medication-off state after 12-h drug withdrawal. Prior to the operation, the target is predetermined by means of stereotactic imaging procedures such as MRI, CT or ventriculography. The imaging-based pre-targeting relies on direct visualization of the region of interest and/or on geometric construction after determination of stereotactic landmarks such as the anterior or posterior commissure. Image fusion may help improving the accuracy of pre-targeting. All imaging procedures have their own advantages but also their own limitations with respect to the accuracy of target determination. In addition the trajectory planning has to be performed carefully in order to minimize damage induced by the insertion of electrodes. To date, there is no consensus on the imaging procedure that should be used for pre-targeting. Prior to the implantation of the electrode for chronic stimulation, an electrophysiological exploration of the targeted region via test electrodes has to be performed in order to increase confidence in the accuracy of the localization. Electrophysiological exploration can be performed either using parallel simultaneous exploration trajectories or sequential exploration trajectories and generally involves two major steps: microrecording and test-stimulation. The microrecording helps to identify specific firing patterns along the traversed brain regions. The firing characteristics of the regions of interest have been described in several published studies on DBS of the Vim (Ohye et al. 1976, 1977; Lee et al. 2003), the STN (Hutchison et al. 1998; Benazzouz et al. 2002; Sterio et al. 2002) and the GPi (Vitek et al. 1998; Lozano and Hutchison 2002). Both spontaneous activity and evoked activity induced by passive or active joint movement were recorded and evaluated. The identification of receptive fields is of major importance, as it helps identify the sensorimotor region of the targeted areas. About half of the STN neurons show a response to passive joint movements (Magarinos-Ascone et al. 2000; Abosch et al. 2002; Benazzouz et al. 2002). A somatotopic organization in PD patients was shown for the GPi (Taha et al. 1996; Kishore et al. 2000), whereas the studies questioning human STN somatotopy yielded controversial results, one study showing a somatotopic organization (Rodriguez-Oroz et al. 2001) similar to the findings in primate STN (Nambu et al. 1996), while another study failed to detect consistent somatotopy (Abosch et al. 2002). There is no consensus regarding the need of microrecordings in targeting for DBS. The most cited arguments against the use of microrecordings

for refinement of the targeting procedure are the potential increased risk of hitting a blood vessel, the increased operation time and the limited information gain achieved by microrecordings. The major arguments in favor to the use of microrecordings are the increased confidence in correct target localization due to refined target region characterization and the absence of evidence-based support of an increased bleeding risk. Most of the groups that favor the exploration of the STN by microrecording are using it for identification of the STN borders (Sterio et al. 2002). Others are using the response of the neuronal activity to passive movement as the main criterion for implantation (Saint-Cyr et al. 2002). The second intra-operative exploration tool is the test stimulation. The intra-operative stimulation at various sites along the trajectory can be used both for assessing the stimulation induced symptomatic improvement, such as suppression of rigidity or tremor, and for detecting the threshold for inducing adverse effects by current spreading into adjacent brain structures. Intra-operative stimulation is usually performed using a monopolar, monophasic, cathodic configuration, with a fixed stimulation frequency of 130 Hz and at a fixed pulse width of 60 μs, while progressively increasing the amplitude of the current pulse and observing the clinical improvement of the symptoms until the appearance of adverse effects. There is overall agreement regarding the need of intra-operative stimulation especially to ensure a sufficiently high current threshold for inducing adverse effects. Nevertheless, there is disagreement over the degree of refinement of the exploration by intra-operative stimulation. While some groups are only briefly testing for adverse effects by stimulating via the implanted electrode, others are performing stimulation for detecting the threshold for adverse effects only for the trajectory that yielded the best results on microrecording exploration. We favor extensive exploration by microstimulation, while testing for both symptomatic improvement and for the threshold for inducing adverse effects. Together with the information obtained by microrecordings of spontaneous and evoked neuronal activity, the acute effects of the stimulation were used for an optimal placement of the chronic stimulation electrode.

Another issue under debate represents the optimal site of stimulation within the target structure, especially for DBS of the STN. Inactivation studies using injections of the GABA agonist muscimol in the STN and GPi of MPTP treated monkeys showed optimal reversal of parkinsonian signs when the injection was performed within the centromedial extent of the sensorimotor territory of the GPi or within the lateral extent of the sensorimotor region of the STN (Baron et al. 2002). Behavioural and metabolic studies performed on 6-OHDA treated rats revealed hyperactivity of the zona incerta and the involvement of this structure in inducing abnormal movements (Perier et al. 2000, 2002). As the zona incerta is located in the immediate dorsal vicinity to the STN, the authors suggest the possibility that the clinical effect of DBS of the STN might be partly mediated by current spreading into this region. Correlation studies between post-operative localization of the most effective contacts for STN-DBS showed slightly discrepant results. Voges et al. (2002) concluded that the DBS effect is mainly induced by stimulation of surrounding fibers in close vicinity of the STN like the pallidothalamic bundle, the pallidosubthalamic tract or the zona incerta than by stimulation of the cell bodies inside the STN. Hamel and colleagues (2003) found that the dorsal border area of the STN is the most effective target area, suggesting that beside the dorsolateral sensorimotor portion of the STN other structures like the zona incerta or the pallidofugal projections in the fields of Forel might be involved in the DBS effect, although a definite proof of this assumption cannot be provided for the moment. The Toronto group (Saint-Cyr et al. 2002) found the clinically effective stimulation most commonly directed at the anterodorsal STN, with the current spreading into the dorsally adjacent zona incerta and fields of Forel. Our own unpublished results indicated that the most effective stimulation site is located within the anterodorsal part of the STN. Correlation studies between localization of the lesion site in pallidotomy and clinical outcome also showed discrepant results. Two studies failed to detect any correlation between lesion location and clinical outcome (Burns et al. 1997; Krauss et al. 1997). The Toronto group showed in one study that pallidotomy of the posteroventral GPi improves rigidity and dyskinesia when lesion location was located more anteromedial, whereas a more central lesion location most likely improves akinesia and gait disturbances (Gross et al. 1999), whereas in another study cognitive functions were improved with more posterolateral lesion and worsened with more anteromedial lesion location while motor functions improved after an intermediate lesion location within posteroventral GPi (Lombardi et al. 2000). The Grenoble group showed that opposite motor effects could be obtained by stimulating within different territories of the globus pallidus (Krack et al. 1998b). Stimulation on the most ventral contacts lying at the ventral margin of the GPi improved dyskinesias and rigidity and blocks the anti-akinetic effect of levodopa, whereas stimulation of the most dorsal contacts lying at the dorsal border of the GPi or in the GPe moderately improves akinesia and could also induce dyskinesias. A major drawback of all the cited correlation studies is the inherent error induced by the 3D reconstruction of the localization based on data resulting from indirect criteria such as electrophysiology, imaging or atlas projection.

Clinical results and target selection

Optimal clinical results were obtained on an empirical basis with monopolar cathodic stimulation, 120–180 Hz stimulus frequency, 60–200 μs pulse width and 1–5 V stimulation amplitude. Thalamic stimulation is especially beneficial to PD patients with upper limb rest tremor. Vim stimulation alleviates contralateral tremor in 80–90% of patients with parkinsonian tremor (Benabid et al. 1991; Benabid et al. 1996; Limousin et al. 1999; Schuurman et

al. 2000). The effect on the other cardinal symptoms and on dyskinesias is less pronounced and inferior to DBS of STN or GPi. Even in patients treated by Vim DBS for tremor-dominant PD some disability due to akinesia or rigidity or levodopa-induced dyskinesias might appear throughout the development of the disease, necessitating a new surgical intervention in another target. As the stimulation of the STN has excellent effect on both tremor and akinesia/rigidity, STN stimulation has fully replaced Vim stimulation for tremor-dominant PD. To date there is almost no indication for performing Vim stimulation on PD patients.

Clinical results of GPi-DBS consistently show a dramatic reduction of levodopa-induced dyskinesias (Gross et al. 1997; Krack et al. 1998b; Kumar et al. 1998; Deep-Brain Stimulation for Parkinson's Disease Study Group 2001; Volkmann et al. 2001). Improvement of the unified Parkinson's disease rating scale (UPDRS) motor score in the off period was more variable but significant in most studies in the range of 30–50% for bilateral stimulation. Significant improvements of the UPDRS subscores were found for bradykinesia, posture, gait and tremor and to a lesser extent for rigidity. The average post-operative levodopa dose did not change.

Bilateral DBS of the STN was shown to consistently improve the UPDRS motor score in the off period by 50–70% (Krack et al. 1998a; Limousin et al. 1998; Fraix et al. 2000; Houeto et al. 2000b; Deep-Brain Stimulation for Parkinson's Disease Study Group 2001; Tavella et al. 2002; Vesper et al. 2002; Herzog et al. 2003; Pahwa et al. 2003). DBS of the STN markedly improves all the cardinal symptoms of PD such as akinesia, rigidity and tremor (Krack et al. 1998a,c). Moreover, most axial features such as gait disturbances, postural instability and balance were improved if they responded to levodopa before surgery (Bejjani et al. 2000b). The average post-operative levodopa dosage was reduced by 50–65%, with complete discontinuation of dopaminergic medication in 10–50% of patients (Moro et al. 1999; Volkmann et al. 2001; Herzog et al. 2003). Parallel to the levodopa reduction, the levodopa-induced dyskinesias decrease (Krack et al. 1999). The sensitisation phenomenon induced by long-term pulsatile levodopa administration, which is believed to be responsible for the induction of dyskinesias, was shown to be partially reversible after STN–DBS (Bejjani et al. 2000a). In the long-term, the anti-dyskinetic effect of the STN–DBS may be equivalent or superior to that of GPi DBS if the levodopa dose remains reduced. Overall, the motor fluctuations tended to disappear and activities of daily living together with the quality of life were markedly improved. Sleep architecture was also improved, probably as a consequence of reduced night-time akinesia (Arnulf et al. 2000). The most important predictive factor for a favorable outcome of STN–DBS was shown to be the levodopa responsiveness (Charles et al. 2002; Welter et al. 2002).

Although STN–DBS is to date considered being superior to GPi–DBS and has advanced to the worldwide most used target for surgical therapy of PD, few studies have compared the effect of DBS in these two targets (for review, see Vitek 2002). Most of the retrospective (Krack et al. 1998a; Volkmann et al. 2001) or prospective (Deep-Brain Stimulation for Parkinson's Disease Study Group 2001; Krause et al. 2001) studies are parallel group comparisons. The only randomized, but underpowered clinical trial with only five patients in each group showed no difference in relief of akinesia, rigidity or dyskinesias between STN and GPi–DBS (Burchiel et al. 1999). The largest comparative study, a non-randomized multicenter study found better results for all outcome variables in the STN–DBS group, except for dyskinesias, which showed similar improvement (Deep-Brain Stimulation for Parkinson's Disease Study Group 2001). Anecdotal case reports showed clinical failure of GPi–DBS with subsequent improvement after STN–DBS (Houeto et al. 2000a). A study assessing effects of STN–DBS and GPi–DBS on executive functions showed better results for the STN group (Jahanshahi et al. 2000). Another PET study comparing effective and ineffective stimulation of the STN showed significantly higher movement-related increases in regional cerebral blood flow (rCBF) during effective stimulation in supplementary motor area, cingulate cortex and dorsolateral prefrontal cortex compared to ineffective stimulation, whereas in the GPi group no significant change was observed in any of these areas during stimulation (Limousin et al. 1997)

Morbidity, hardware failure, and adverse effects

Adverse effects of DBS have several causes, such as (1) adverse effects related to surgery, (2) hardware failure, (3) adverse effects related to stimulation, and (4) adverse effects related to medication changes necessitated by DBS. In addition disappointed expectations but also problems with social adaptation after dramatic motor improvement following DBS are influencing the outcome of the therapy (Perozzo et al. 2001b).

The major surgery related risk is the intra-cranial hemorrhage resulting in permanent neurological deficit. Careful trajectory planning is thus mandatory. Although the risk of intra-cranial hemorrhage should correlate with the number of penetrating tracks, the data from the Grenoble group, which always uses five parallel exploration electrodes during DBS surgery, has similarly low incidence of hemorrhage compared to other groups using on average less penetrating tracks. Other causes of severe morbidity are pulmonary embolism, chronic subdural hematoma, venous infarction, and seizure. A literature review of complications of DBS in larger series showed an overall risk for severe morbidity in the range of 1–3% (Limousin et al. 1999; Beric et al. 2001; Deep-Brain Stimulation for Parkinson's Disease Study Group 2001; Oh et al. 2002; Pollak et al. 2002; Starr et al. 2002; Umemura et al. 2003). The rate of hardware related failure such as lead extension fracture, lead migration, short or open circuit, malfunction of the pulse generator, skin erosion, or infection varies greatly between different

centers in the range from 5% to 25% in the larger series (Hariz et al. 1999; Oh et al. 2002; Pollak et al. 2002). Most of the problems occured in the first patients of a series and were less frequent as the expertise increases.

Current spreading into adjacent structures during DBS of the STN can induce acute but reversible adverse effects such as tonic muscles contraction, dysarthria, paraesthesia, ocular deviation, ipsilateral mydriasis, eyelid opening apraxia, flushing, perspiration, worsening of akinesia, and reversal of levodopa effect. These side effects are very useful during intra-operative target exploration. Acute stimulation induced dyskinesias indicate correct placement of the stimulation electrode. The most frequent acute adverse effects induced by DBS of the GPi are tonic muscle contraction and phosphenes. A special category of post-operative adverse effects of STN–DBS is related to problems with speech, gait and postural stability. Often these problems are not induced by stimulation, but are pre-existing symptoms of the disease that are unmasked by a reduction of levodopa therapy. The verbal fluency is commonly affected by STN–DBS probably due to stimulation-induced interference with a frontotemporal network as demonstrated in a recent PET study (Schroeder et al. 2003).

At the beginning of the era of DBS of the STN or GPi one of the major concerns was the possibility that stimulation could disturb the cognitive and limbic basal ganglia loops. Most of the studies found no evidence for cognitive decline or impairment in neuropsychological functions (Ardouin et al. 1999; Jahanshahi et al. 2000; Pillon et al. 2000; Trepanier et al. 2000; Alegret et al. 2001; Perozzo et al. 2001a). However, there are few studies showing that STN–DBS may induce frontal executive impairment, particularly in older patients and in patients with minimal cognitive dysfunctions prior to surgery (Saint-Cyr et al. 2000; Trepanier et al. 2000; Dujardin et al. 2001). A recent PET study demonstrated a partial restoration of physiologic glucose consumption in limbic and associative territories of the basal ganglia after STN–DBS, suggesting a positive effect of the stimulation on mood and cognition (Hilker et al. 2004). When encountered post-operatively, psychiatric disturbances of STN–DBS are often mild and transient. Nevertheless, mood disorders were among the most frequently observed post-operative adverse effects of STN–DBS (Limousin et al. 1998; Volkmann et al. 2001). Despite the fact that DBS may directly affect the limbic basal ganglia loops as could be inferred from the finding that the acute emotional effect of STN–DBS is mood enhancing (Funkiewiez et al. 2003; Schneider et al. 2003), most of the psychiatric side effects of STN–DBS were not a direct consequence of the stimulation. First, mood disturbances after surgery often reflect a reactivation of pre-existing psychiatric condition (Houeto et al. 2002). Secondly, the reduction of levodopa after surgery could cause withdrawal phenomena of the known psychotropic effects of levodopa and could lead to depression, especially in the first post-operative months with an incidence of up to 25% (Volkmann et al. 2001; Berney et al. 2002). Manic disorders were less frequently encountered after STN–DBS (Kulisevsky et al. 2002; Romito et al. 2002; Daniele et al. 2003) and GPi–DBS (Miyawaki et al. 2000).

Mechanisms of stimulation

DBS advanced during the last decade to the most promising treatment option for advanced PD and other therapy-refractory movement disorders. Nevertheless, the mechanism of high-frequency (>100 Hz) stimulation is still not known. For decades, on the basis of fundamental physiological principles, the stimulation of neuronal structures was believed to be able only to excite axons or cell bodies. Surprisingly, starting with the era of DBS, it was realized that high-frequency stimulation mimics the functional effects of ablation in various brain structures. This effect was initially observed in the Vim and in the CM–PF complex of the thalamus and later in the STN or in the GPi, as well as in the ventromedial hypothalamus and more recently in the posterior hypothalamus, the later as an efficient treatment of cluster headaches (Franzini et al. 2003). There is a large amount of evidence from experimental and clinical data that stimulation frequency represents a key factor with respect to clinical effect of DBS. The main hypotheses for the mechanism of high-frequency stimulation were derived from physiological experiments in animals and from intra-operative findings in human: (1) depolarization blocking of neuronal transmission through inactivation of voltage dependent ion-channels (Benazzouz et al. 1995, 1996; Beurrier et al. 2001; Bikson et al. 2001), (2) jamming of information by imposing an efferent stimulation-driven high-frequency pattern (Garcia et al. 2003; Hashimoto et al. 2003), (3) synaptic inhibition by stimulation of inhibitory afferents to the target nucleus (Dostrovsky et al. 2000), and (4) synaptic depression by stimulation-induced neurotransmitter depletion (Urbano et al. 2002; Xia et al. 2004).

It has been known for decades that electrical stimulation of tissue is more likely to activate large myelinated fibers before small axons or cell bodies, axons near the cathode before axons near the anode, and axons oriented parallel to the current field before axons oriented transversely (Ranck 1975). Stimulation through an electrode placed within a nuclear region of the central nervous system will affect several neuronal components: cell bodies, afferent inputs and fibers of passage. On the single cell level each neuronal component in the proximity of the stimulation electrode will be subject to both depolarizing and hyperpolarizing effects (McIntyre and Grill 1999), having as a result that a neuron can be either activated and inhibited in different ways and in different compartments of the neuron, depending on its positioning relative to the electrode and current field and on the stimulation parameter used (McIntyre and Grill 2002). Experimental recordings after and during high-frequency stimulation revealed different aspects of the stimulation. In vivo recordings performed within the stimulated nucleus showed decreased activity (Benazzouz et al. 1995; Boraud

et al. 1996; Dostrovsky et al. 2000; Wu et al. 2001; Tai et al. 2003), as appears logical from phenomenological similarity between the effects of DBS and ablation. Consistently, in vitro experiments on brain slices demonstrated a frequency-dependent suppression of neuronal activity within the same frequency range as the therapeutic effects (Beurrier et al. 2001; Kiss et al. 2002; Magarinos-Ascone et al. 2002; Garcia et al. 2003). Probably more important than the effect on the cell bodies of the stimulated structure itself are the effects on the efferent projections. Therefore, several studies addressed the stimulation effects in efferent nuclei. The Grenoble group studied in vivo the after-effects of STN–HFS following the pulse train in the efferent nuclei of the STN, finding a decreased firing rate in neurons of SNr, EP and GP in the rat (Benazzouz et al. 1995, 2000). The suppressing effect of STN–HFS on SNr neurons was confirmed in a study addressing the stimulation effects during the stimulation (Tai et al. 2003). In contrast, other studies performing in vivo recordings in efferent nuclei during stimulation indicate that the output of the stimulated nuclei is increased by HFS. Thalamic activity increased during GPi–HFS in monkeys (Anderson et al. 2003), GPi and GPe activity increased during STN–HFS in MPTP monkeys (Hashimoto et al. 2003) and SNr activity increased during STN stimulation in rats (Maurice et al. 2003). Supporting the later electrophysiological results, microdialysis studies showed an increased glutamatergic STN outflow by detecting elevated levels of glutamate in both SNr and GP after STN–HFS in the rat (Windels et al. 2000, 2003). Surprisingly, GABA levels also increased after STN–HFS and both glutamate and GABA levels increased in a frequency dependent manner (Windels et al. 2003). These findings suggest network-wide modulatory effects of STN–HFS, but should be carefully considered as the observed increase in extracellular glutamate levels outlast by several tens of minutes the duration of the stimulation, questioning the significance of these data.

Although several simplified assumptions were made, theoretical models can help understanding the mechanism of DBS. Theoretical models used to date combined a finite element model of the electrical field generated by a DBS electrode, a homogenous isotropic extracellular environment and a simplified multicompartment cable model of a neuron (McIntyre et al. 2004a). Preliminary results show that DBS induces a complex pattern of activation and inhibition of the local cells in the vicinity of the electrode. Perhaps the most striking result inferred from the theoretical model is the finding that the firing of the cell body of directly stimulated neurons is not necessarily representative for the efferent output of the neuron (McIntyre et al. 2004b). Consequently a stimulation-induced functional decoupling between cell body and efferent projections is possible according to theoretical models and may help understand controversial experimental findings. First, the two hypotheses which come closest to explaining the similarity between the effects of DBS and ablation, i.e. depolarization blockade and synaptic inhibition of afferent projections, do not take into account the possibility of decoupling of the activity of efferent axons from the activity of cell bodies. Secondly, the hypothesis of stimulation-forced driving of the efferent axons ignores the possibility that the high-frequency synaptic action on efferent targets cannot be sustained due to neurotransmitter depletion (Wang and Kaczmarek 1998; Urbano et al. 2002; Zucker and Regehr 2002). Therefore, the hypothesis of synaptic failure due to transmitter depletion refocuses the attention back to the therapeutic similarities between DBS and lesioning. Supporting this hypothesis is the recent finding (Xia et al. 2004) that high-frequency stimulation inhibits the secretion of prolactin from the prolactinoma cell line GH3 in vitro in a similar manner to dopamine.

Another important issue is the prediction of the volume of tissue influenced by DBS, as the DBS targets are relatively small and are surrounded by structures that can induce adverse effects when co-stimulated. Major drawbacks in theoretically solving this problem are the highly anisotropic medium and the disturbances of the distribution of the electric field by the electrode and the penetrating track itself. In a recent study that tries at least to diminish these sources of error by using diffusion tensor imaging to estimate the electrical conductivity of the STN and surrounding tissue, estimates of the spatial extent of activation were made using finite element modeling (McIntyre et al. 2004b). When using therapeutic stimulation parameters, stimulation in the medial part of the STN the largest overall volume of activation and limited activation of the internal capsule could be achieved. In contrast, electrodes located close to the anterior or dorsal borders of the STN exhibited strong activation of the internal capsule. The strong dorsal–ventral anisotropy of the internal capsule limited stimulation anterior and lateral to the electrode and the moderate anterior–posterior anisotropy of the zona incerta region extended stimulation posterior to the electrode. On summary, modeling findings suggest that minor variations in the range of 1 mm in the electrode location within the dorsal STN can have substantial changes of the activation profile, confirming in our opinion the necessity of extensive electrophysiological target exploration prior to electrode implantation.

Neuroprotection issues

The hyperactivity of the STN is a well-recognized hallmark in the parkinsonian state, thoroughly demonstrated in both animal models of PD and in intra-operative recordings of PD patients. From the theoretical point of view, the excessive excitatory drive of the glutamatergic STN output, may induce excitotoxicity of the SNc, thus further aggravating the course of the disease (for review, see Rodriguez et al. 1998). This potential excitotoxic effect could be mediated either directly via the monosynaptic projection to the substantia nigra or indirectly via the projection to the PPN, which in turn sends strong

excitatory glutamatergic and cholinergic projections to the SNc. The PPN was shown to be hyperactive in the 6-OHDA rat model, probably as a consequence of the strong excitatory drive from the STN (Breit et al. 2001). Experiments on animal models support the excitotoxicity hypothesis. It was clearly demonstrated that both STN-lesion and STN–DBS exert a neuroprotective effect on SNc neurons when performed prior to 6-OHDA lesioning of the SNc (Piallat et al. 1996, 1999; Chen et al. 2000; Maesawa et al. 2004). Moreover, GAD gene therapy in the rat STN induces strong neuroprotection of nigral dopamine neurons (Luo et al. 2002). Similarly to the neuroprotective effects of STN manipulations, a lesion of the PPN was shown to be neuroprotective when performed prior to MPTP treatment in monkeys (Takada et al. 2000). Long-term follow-up results of PD patients treated by STN–DBS showed a remarkably stable therapeutic effect over several years (Krack et al. 2003). This observation does not represent a proof of disease progression slow-down, but might indicate the need of future studies to address this question.

Conclusion

DBS has emerged within the last decade as an important treatment option for advanced PD, with marked benefits and minimal morbidity. Although the method may represent the most significant single advance in decades in the treatment of neurological disorders and gains increasingly acceptance world-wide, the key for a successful intervention relies in careful patient selection and optimal interdisciplinary surgical technique in order to ensure precise implantation of the stimulation electrode. The rationale of targeting specific structures within basal ganglia such as the STN is strongly supported by the current knowledge of the basal ganglia pathophysiology. Despite the dramatic clinical improvement by DBS, there remain a number of aspects of the disease, predominantly the so-called non-motor and non-dopaminergic components, which are not improved. Consequently, the search for a better understanding of the disease pathophysiology and possibly for a better target will continue.

Little is known about the principles of high-frequency stimulation, the stimulation parameter used for DBS being to date empirically determined. Extensive research needs further to be done in order to thoroughly understand the mechanisms of DBS. This goal achieved may open the window of opportunity for the application of DBS beyond the treatment of movement disorders.

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