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Deep brain stimulation for Parkinson's disease

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Deep brain stimulation at high frequency was first used in 1997 to replace thalamotomy in treating the characteristic tremor of Parkinson's disease, and has subsequently been applied to the pallidum and the subthalamic nucleus. The subthalamic nucleus is a key node in the functional control of motor activity in the basal ganglia. Its inhibition suppresses symptoms in animal models of Parkinson's disease, and high frequency chronic stimulation does the same in human patients. Acute and long-term results after deep brain stimulation show a dramatic and stable improvement of a patient's clinical condition, which mimics the effects of levodopa treatment. The mechanism of action may involve a functional disruption of the abnormal neural messages associated with the disease. Long-term changes, neural plasticity and neural protection might be induced in the network. Similar effects of stimulation and lesioning have led to the extension of this technique for other targets and diseases.

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Abbreviations

BDI	Beck depression inventory
BG	basal ganglia
CM-Pf	centrum medianum-parafascicularis complex
DA	dopamine
DBS	deep brain stimulation
GPi	globus pallidum pars interna
HFS	high frequency stimulation
MPTP 1	methyl-4-phenyl-1,2,3,6-tetrahydropyridine
MRI	magnetic resonance imaging
PD	Parkinson's disease
PDQL	quality of life in Parkinson's disease
SNc	substantia nigra pars compacta
SNr	substantia nigra pars reticulata
STN	subthalamic nucleus
UPDRS	unified Parkinson's disease rating scale
Vim	thalamic nucleus ventralis intermedius

Introduction

Deep brain stimulation (DBS) is a technique used in functional neurosurgery, which consists of delivering a neural brain structure continuous electrical stimulation through chronically implanted electrodes connected to an internalized neuropacemaker or stimulator, usually programmable in amplitude, pulse width and frequency. The electrodes are inserted using stereotactic methods (including radiological methods to localize the targets and electrophysiological exploration of the target area) and then connected to the chronically implanted stimulator. The tuning of this stimulator can be done at intervals depending on the patient's needs, and allows adaptation of the therapy to the evolution of the symptoms. The most common utilisation has been to treat pain, by stimulating, usually at classical physiological frequencies (30 to 60 pulses per second, or Hertz) considered as excitatory, various neural structures such as nuclei or fiber tracts. The discovery we made in 1987 that frequencies at 100 Hz and above were, on the contrary, inhibitory, has provided a new and powerful method to achieve similar effects to lesions at the same site, in a titratable and reversible, and therefore safer, manner than the former destructive (or ablative) stereotactic methods (mainly thalamotomies and pallidotomies). Besides the reversibility of its effects, high frequency stimulation has proven to be well tolerated in a large variety of deep brain structures, and its effects can be adapted to the specific patient's needs by adjusting the parameters of stimulation (current intensity, pulse width, frequency). During surgery, the reversibility of the effects provides a powerful tool for exploring the patient and their functional targets, and for optimizing the placement of the electrode. This provides a powerful method applicable to a large variety of pathological situations, which are far from being fully explored at the present time. Since 1987, high frequency stimulation (HFS) in the basal ganglia has been proven to produce the same effects as lesioning, which previously was used as a treatment for movement disorders. This has been quickly extended from the thalamus to the pallidum and finally to the subthalamic nucleus (STN) to treat Parkinson's disease (PD). The literature on the subject has quickly grown, providing additional confirmation of the efficiency of HFS as well as opening debates on the various topics related to this method, including the methodology and moreover the mechanisms, which are still yet not completely understood. This has triggered a vast amount of research, both clinical and basic, and more recently, new applications outside of the movement disorders field have been initiated, such as those for epilepsy (in the anterior nuclei of the thalamus, the subthalamus and the centrum medianum-parafascicularis complex [CM-Pf]), psychosurgery (in the anterior limb of the internal capsule, the nucleus accumbens, and the subthalamic nucleus), and cluster headaches (posterior hypothalamus), or they have been experimentally investigated, such as those for obesity (in the

anterior hypothalamus, ventromedial and lateral). The concept of manipulation of brain structures by HFS has been introduced, raising questions and hypotheses about the effects of chronic HFS on membranes, cells, axons, networks, biochemistry and gene expression. This also leads us to revisit the data and concepts of the organization of the basal ganglia (BG) that is involved in the control of movement. Here, I discuss mainly the application of HFS DBS to movement disorders, and in particular to Parkinson's Disease. I review the current indications and the average rates of improvement, highlighting the technical aspects that are specific to these applications. I then review current opinion on the mechanisms involved in the observed effect of HFS and highlight the various hypotheses that are currently being debated.

Surgical consensus for deep brain stimulation

Financial, social, regulatory, technical and profit oriented considerations are different around the globe, making it difficult to reach an international surgical consensus. The goal is to agree upon a general surgical concept meant to achieve the best clinical results with minimal complications. The worldwide interest in the method has opened discussions about all kinds of features that could optimize the surgical process. Everyone agrees that clinical improvement depends on the accuracy of implantation of the electrode within the spatial limits of the target. However, the technical components are still debated.

General or local anesthesia?

Evaluation of symptoms and clinical effects during surgery requires the participation of the patient, and therefore limits the use of anesthesia.

Targeting modalities

The goal of functional stereotaxy is to reach with optimal accuracy the structure (therefore called target), which has been chosen for its role in the patient's disease. Statistical data from brain atlases provide us with average coordinates of the neural target chosen on the basis of its effect on the patient's symptoms. Aiming the instrument's exploring electrodes at this theoretical-statistical point in space is the 'pretargeting' phase. However, individual variability is responsible for spatial inter-individual fluctuations of the real patient's target, which might significantly differ from the theoretical statistical target. Aiming more precisely at the real patient's neural structure (or target) requires additional steps during the stereotactic neurosurgical procedure to achieve the precise final targeting of the neural structure aimed for and then permanent implantation of the chronic electrode in the most efficient position in the neural structure. The efficacy of DBS depends on accurate targeting. Optimal pretargeting reduces the number of passes, the risk of bleeding and the duration of surgery, including the neurophysiological session. One can either choose the best method or combine several or all modalities to optimize the localization of the target.

Magnetic resonance imaging

Magnetic resonance imaging (MRI) is the best method to visualize brain structures [1]. STN is visible on T2 weighted MRI sequences, the globus pallidus pars interna (GPi) is visible on T2 and inversion recovery sequences, and only the external limit of Vim (thalamic ventral intermedius nucleus) can be visualized using MRI. However, MRI distortion is not yet perfectly corrected and only electrophysiology, at least during intraoperative stimulation, detects the sites that will be of use for clinical improvement and those that will cause side effects.

Ventriculography

Ventriculography, which is the visualization of the shape and size of the cerebral ventricles using injection of a contrast medium (air or iodine compound opaque to X-rays), is the most controversial issue with regards to DBS. Some consider it as the gold standard for surgery, as it avoids distortions other than magnification, which is caused by the conic projection of the X-ray image on the photographic film [2], others blame it for increased risk of complications [3] on the basis of previous reports [4,5]. One of the major drawbacks is the need for X-ray setup in the operating theatre.

Microrecording

Microrecording (MER) with a 1–2 micron tip electrode is another controversial issue, it is considered either as the ultimate tool which reveals the signature of the nucleus through typical firing patterns [6••,7,8] or as an increasing risk of causing bleeding and extending the duration of the procedure [9].

Intraoperative stimulation

Intraoperative stimulation is more widely accepted as a tool for use during surgery, the debate is between microstimulation (accused of burning tissue) and macrostimulation (easier, close to chronic parameters) [8]. Interest in intraoperative stimulation stems from the observation during its use of clinical improvement of symptoms (such as, improvement of rigidity of the wrist rather than akinesia, or improvement of speech, which is even more difficult to test), which indicates the location of the best target, or of those that will cause side effects (motor, sensory, oculomotor, and signs and symptoms of a vegetative state), by stimulating structures surrounding the target. Moreover, the therapeutic window (the difference between the intensity of the electrical current thresholds of best clinical effects and side effects) predicts clinical long-term efficacy, and shows which track to implant the macroelectrode for best results [10]. Performing surgery either in one step or in several staged steps, which depends on local circumstances and hospital policies, does not seem to interfere with the outcome.

Global consensus on the management of Parkinson's disease

Which target?

Although comparative studies have not been performed for all targets, the general trend that appears is that treating the STN improves all symptoms, directly (akinesia and rigidity) or indirectly (dyskinesias), making it the best target for DBS. Treating Vim solely improves tremor [11,12], but only as efficiently as treating the STN. Stimulation of the CM-Pf might be involved in the suppression of tremor as well as suppression of levodopa induced dyskinesias [13], treatment of GPi [14] specifically improves dyskinesias, but also moderately akinesia and rigidity, and enables the patient to decrease slightly their levodopa doses [15–17].

Surgical contraindications include impaired general status, cardiac failure, a patient taking anticoagulants, pacemakers in sentinel mode or dementia, and are probably exclusion criteria.

Criteria of inclusion and ideal indications for subthalamic nuclei deep brain stimulation

Current consensus on the best candidates for this treatment is that they are idiopathic PD patients, with motor fluctuations and levodopa induced dyskinesias. The patient's response to levodopa is the best outcome predictor [18,19]. The best time to operate would be before medical treatment fails to provide the patient with adequate control of symptoms that is compatible with maintained quality of their life, professional and family activities [20••].

There is currently no systematic study about DBS in atypical Parkinsonian syndromes (multiple systemic atrophy [MSA], progressive supranuclear palsy [PSP]). The results so far have reported that motor improvement provides short-term benefit, but evolution of non-dopamine sensitive symptoms (gait, balance, vegetative symptoms) and dementia alter the quality of the outcome.

Bilateral or unilateral surgery?

Thalamotomies, surgical procedures during which the thalamus was destroyed, were mostly performed unilaterally because of the complications associated with bilateral lesioning procedures. Vim DBS allows bilateral simultaneous procedures for bilateral tremor in about 50% of patients [11,12] without significant complications [21]. GPi DBS may be uni or bilateral according to the needs of the patient. Conversely, the strictly contralateral effects of STN DBS require bilateral surgery, as when patients have been operated on unilaterally, the levodopa doses needed to control symptoms on the non operated side have created dyskinesias.

Postoperative management

Monopolar stimulation provides better localization of the target, that is, of the place where beneficial effects of stimulation are observed, whereas neurosurgeons believe that bipolar stimulation has a better spatial restriction of effects (which is true in neurosurgical electrocoagulation with high current intensity, but not in DBS where intensities are close to threshold values). The combined regimen of drugs and stimulation intensity is the most important and awkward task of the neurological team. Simultaneous decrease in drug dosages and increase in stimulation parameters must be progressive, to avoid dyskinesias and side effects, which tend to decrease with time [19,22,23].

Clinical results of deep brain stimulation

Clinical benefits

Motor symptoms

STN deep brain stimulation improves the motor symptoms of the disease in the 'off' drug condition (when the patient is not under the effect of their medication, as opposed to the 'on' situation, when the patient has taken and experiences the effects of the drugs) as well as activities of daily living as assessed by either part II of the Unified Parkinson's Disease Rating Scale (UPDRS) or the Schwab and England scale. Moreover, levodopa induced dyskinesias are improved in the 'on' drug condition. At the 12-month follow-up, bilateral STN stimulation greatly improved motor symptoms (UPDRS III −55%), activities of daily living (UPDRS II −45%, Schwab and England Scale +142%) in the 'off' drug condition, and dyskinesias in the 'on' drug condition (−40%). It was also possible to decrease dopaminergic treatment by 50%. This improvement is stable over time, even during periods longer than five years [20••,24–26]. Speech is improved but to a lesser degree than other symptoms, and is less sensitive to DBS than it is to levodopa treatment, which cannot be totally suppressed in patients with severe preoperative hypophonia (when the air flow during speech is reduced to a level where the patient is almost inaudible) [27•,28]. When the stimulation is turned off, 90% of the UPDRS motor score worsening occurs within 2 hours. Switching STN DBS on again improves all motor UPDRS subscores at a faster rate than they worsened [29••].

Quality of life, mood and depression

The motor improvement may not reflect the therapeutic impact of the procedure, as the scales used to assess motor function hardly take into consideration the social and emotional dimensions of the disease. Social isolation, depression, and cognitive impairment may have a greater impact on quality of life in PD (PDQL) than the motor symptoms. Moreover, the side effects related to surgery, STN stimulation, or changes in medication could mitigate the positive effects on motor symptoms. PDQL is assessed using a health-specific scale [30], which takes into account physical aspects and the patient's own perception and self-evaluation. STN DBS improves all aspects of PDQL by +43%, including motor (−48%),

systemic (−34%), emotional (−29%), and social (−63%) dimensions. Patients that are mildly depressed before surgery are slightly (18%) but significantly improved on mood Beck Depression Inventory (BDI) scores. The improvement in the motor UPDRS III correlates with the improvement in the total PDQL, but not with the improvement in the BDI [20••,31,32].

Is there any neuroprotection?

There are, so far, no reported clinical data substantiating changes in the rate of evolution of the disease. Obviously, evaluation is difficult because of the advanced stages of the disease in patients operated on with a sufficient follow-up, and the difficulty in obtaining a sufficient period of time in the off medication-off stimulation condition. However, in a yet unpublished follow up of 89 patients monitored for five to eight years, we have observed that the UPDRS III scores in the off-off situation continued to decline (more than 10% of the baseline) in 25% of the patients, remained stable (within ±10% of the baseline) in 36%, and improved (more than 10% of the baseline) in 38% after one year. Half of the patients (19%) showed a continuous significant improvement of the levodopa sensitive symptoms over five years after treatment. Axial and non-levodopa sensitive symptoms continued to worsen. The short duration of the off-off period before evaluation of these patients is not sufficient to rule out a semi-long-lasting effect of both levodopa treatment and/or STN-HFS, which therefore weakens the conclusions that can be made about the putative neuroprotective effect.

A demonstration of neuroprotection by STN DBS will require prospective clinical trials including functional and metabolic assessments using positron emission tomography (PET) studies in addition to observation of clinical scores.

In the meantime, the concept has to be substantiated by experimental data. Lesioning of the STN in rats, which is considered to be an equivalent of STN DBS, decreases the dopamine cell loss in the substantia nigra pars compacta (SNc) induced by intrastriatal injection of 6OHDA (6 hydroxydopamine), which suggests that STN inactivation could provide neuroprotection by shutting down the STN glutamate output [33]. However, Nakao *et al.* [34] found that STN inactivation protects the nigral dopaminergic cells against 3-nitro-propionic acid and not against 6OHDA. Moreover, as it has not yet been demonstrated that STN lesioning is equivalent to DBS, chronic STN DBS has to be evaluated in non-human primates. Demonstration of such a neuroprotective effect would have important consequences for the use of DBS in Parkinson's disease.

Stimulation induced side effects

Sensory motor

The sensory motor side effects of stimulation are always mild and controllable by decreasing the voltage or by bipolar stimulation, but this is a limiting factor for efficiency of the technique.

Neuropsychological effects

STN DBS is reported to induce variable neuropsychological changes in patients, from laughter [35•] to depression, to suicidal ideas [36,37], and other mood changes [38–41]. This might reflect the involvement of neighboring structures, caused by mislocation of the electrode or the use of excessive voltages. Therefore, it might not be related to STN function, as the majority of patients, while significantly improved, do not experience them at a low threshold stimulation. However, the real impact of DBS on behavior, and the involvement of limbic structures [42], has still to be thoroughly investigated [43].

There is no current evidence that depression or suicide occur at a significantly higher rate in STN stimulated patients than in the average Parkinsonian population. The cause of depression is probably multifactorial, due to the drastic social and individual changes in lifestyle after surgery, the strong decrease in dopaminergic drugs and the subsequent loss of psychotropic effects, as well as the disappointment of the patient at the lack of return to a totally normal life despite the important clinical improvement. This stresses the need for extensive discussions with the patients and their families before surgery.

Surgical complications

Although complications vary with surgical teams, their rate is usually low and their severity mild and reversible. Infections are mostly superficial and manageable, and are caused by skin erosion over the hardware; intracranial infection is rarely reported; although rare, hemorrhages are the worse complications and may induce permanent deficits; and finally, the observation of blood traces on postoperative MRI is frequent and usually harmless. Hardware failure is mainly due to breakage of wires or to movement of the electrodes because of insufficient fixation to the skull, but the device as a whole is safe and reliable.

In a series of 60 patients, five neurosurgical complications occurred (two hematomas and three focal cerebral contusions), but only one patient had a residual permanent deficit, which consisted of mild aphasia. In addition, there were five transient psychiatric complications (one mania, one delusion, and three depressions, including two with suicide attempts) [20••].

Mechanism of action of deep brain stimulation

Knowing the mechanism of action of DBS might help to improve the type, parameters and tools for stimulation, to provide an even better clinical effect.

Moreover, basic neuroscience issues are involved: is HFS doing anything different to low frequency stimulation, which is namely exciting neural structures? The observed effect then relates to the specific wiring of the network, the excitation of one of its components leading to the final interruption of the network and the 'functional end product'. Or is HFS having a new and unknown effect on neural structures, leading to a profound change in the function of the stimulated neurons and the network that they belong to?

Practical observation has established that HFS induces effects similar to those created by surgical lesioning (using electrocoagulation, or chemical, radioactive or cryogenic agents) in all used targets (Vim, GPi, STN). The determinant in this paradox is the frequency, which is the key factor, as the effect is only observed above 100Hz [23]. The effect may be achieved at the level of the network, the synapses, the cell and axon membranes, or more subtly in the structure of the neuronal message and its modifications by HFS.

Concepts of the functional organization of the basal ganglia

The BG [44,45], thalamus and cortex are interconnected through five parallel circuits on the basis of several different characteristics. First, their anatomical/functional segregation into motor, oculomotor, prefrontal dorsolateral, orbitofrontal lateral, and anterior cingulate areas. Second, they are part of semi-closed loops: several cortical areas project on the input structure (striatum), where cortical projections form parallel longitudinal bands. Each single cortical area is innervated by the output structures (GPi and the substantia nigra pars reticulata [SNr]) through the thalamus. Third, they have similar synaptic organization at each level, which might suggest similar mechanisms. Fourth, their somatotopic organization is the same at every level. For the motor circuit, leg, arm, and face are represented from top to bottom. The loop is closed through the thalamus (ventrolateral, medialis and oralis) to the supplementary motor area (SMA) of cortex. Fifth, the subdivision of each circuit is related to cortical afferents (without overlap), movement parameters (in the putamen and pallidum, such as direction, amplitude, and speed), and movement status (in the putamen, for execution or planning).

These five parallel circuits are associated in three functional systems [46], associative (prefrontal dorsolateral and orbitofrontal lateral), sensorimotor (motor and oculomotor), and limbic (anterior cingulum).

The coherence of movement is probably the result of integration created by convergence at several levels, either within a functional territory (compartmentation of striatum) or between functional territories (a possible role of cholinergic tonically active neurons [TANs]).

Anatomical connectivity of the basal ganglia

These anatomo-functional concepts are formed on the basis of the anatomical description of the connectivity of the BG (Figure 1). This description has shown that the SNc, which contains tyrosine hydroxylase immunoreactive (TH-IR) dopaminergic (DA) neurons, projects on to the GABAergic medium spiny neurons of the striatum, which is made up of the caudate nucleus and the putamen (Cd-Put). These spiny neurons bear either D1 or D2 DA-receptors, on which DA has excitatory and inhibitory post-synaptic effects, respectively. D1 neurons, that co-express substance P and dynorphin, project directly onto GPi and SNr neurons, whereas D2 neurons, that co-express met-enkephalin, project onto the globus pallidus pars externa (GPe), which in turn projects onto the STN whose glutamatergic neurons project onto the neurons of the GPi and SNr. GPi and SNr, which are both γ-amino butyric acid (GABA)ergic, are the ouput structures of the BG and project onto the neurons of the motor thalamus, which in turn project onto the motor and premotor cortices. SNr and GPi therefore receive a dual input from direct and indirect striatal pathways. The STN plays a major role in the modulation of this network as it also receives strong excitatory glutamatergic afferents from the motor cortex, from the CM-Pf of the intralaminar nuclei of the thalamus, and from the pedunculo-pontine nucleus (PPN) of the brainstem.

Network structure and parallel processing

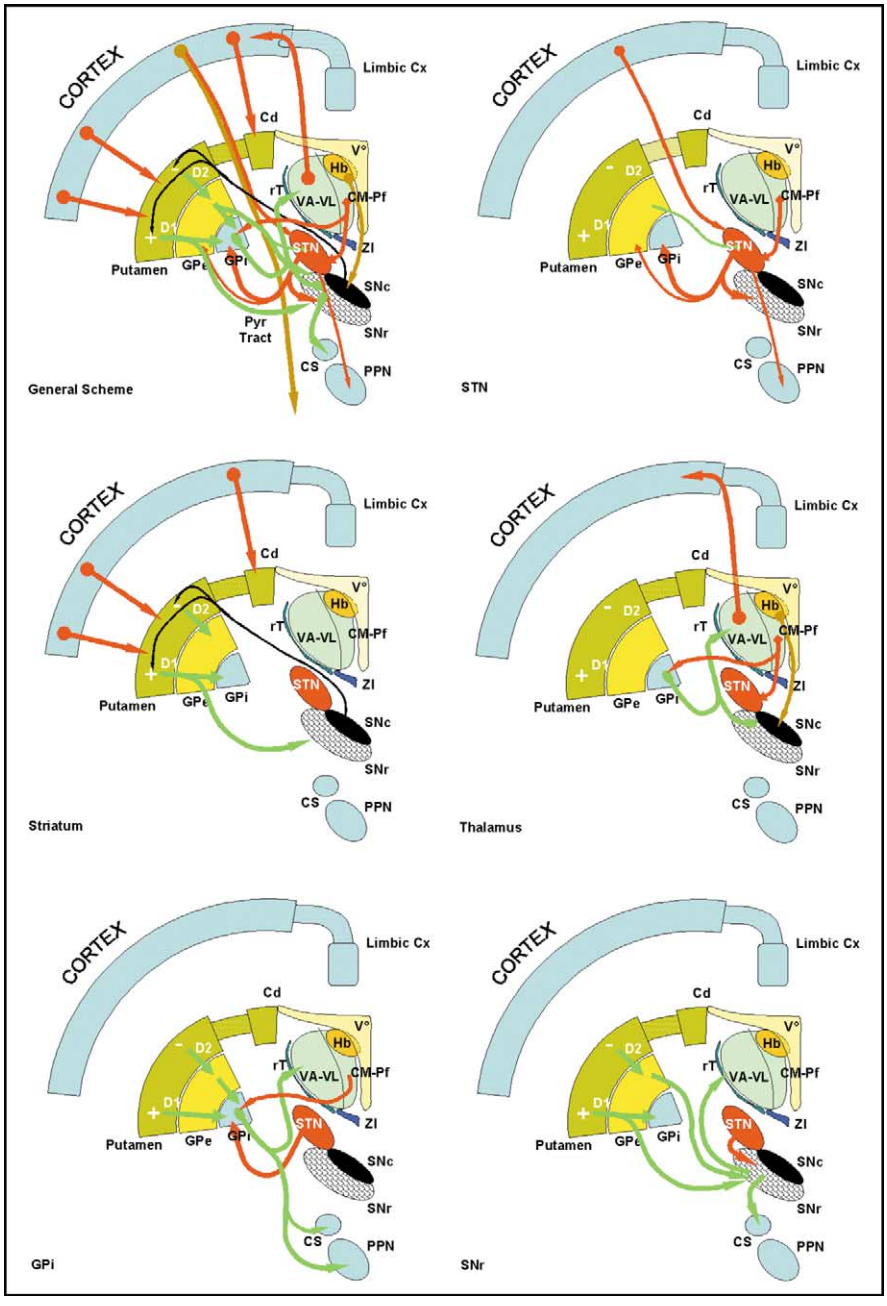
There is evidence that this BG system processes information pertaining to motor, oculomotor, sensory and limbic functional organization along parallel networks. The opposite effects (excitatory and inhibitory) of the two main neurotransmitters (glutamate and GABA) involved in this circuitry have led to the algebraic model of functioning of the BG, in which positive and negative actions compete and combine to achieve the functions of the network. This concept has received global support from microrecording studies in normal and Parkinsonian animal models. However, this model does not explain everything, and the role of neuron firing patterns is probably of major importance. The classical concepts of hyperactivity, excitation and inhibition being combined by parallel processing are being replaced by more holistic approaches that pertain to fuzzy systems. Ultimately, all these network changes in properties are reflected to the cortex, from which motor function is elaborated [47–49].

How does deep brain stimulation interact with this network to improve clinical symptoms?

In this area of research, results are currently being produced at a rather high speed that will change our concept of DBS action within the next few years.

STN HFS does not replace the missing dopamine. Although in normal rats it increases the firing rate in

Figure 1



Schematic anatomo-functional organization of the basal ganglia: general scheme and subsets according to the major components (STN, GPi, SNr, thalamus, striatum) inspired by the work of Groenewegen and Berendse [87]. This figure, although simplified, schematizes the complex relationships among the components of the basal ganglia, and the inter-relationships are dissected in the individual schemes. This system appears a strongly interactive network, built in parallel to the main functional pathways, such as the cortico-spinal tract, and might play a sophisticated, although not mandatory, role in improving motor function and integrating various influences provided by the subcomponents of the system. Whatever the benefit provided by this network to the motor function is, it is clear that its complexity provides a template for easy functional disturbances, leading to abnormal symptoms. The interruption of this system, by lesioning or by jamming, is able to interrupt abnormal behaviors of the system, suppressing the abnormal symptoms, without altering too much the primary function, which can still be correctly performed. This suggests the possible futility of these networks, providing harmonization of primary functions such as motricity without being mandatory, but being able to generate strong disturbances of the function they are supposed to improve when something is awry in the system. This might also explain why interfering in several places of this network may have comparable effects in inducing pathological symptoms as well as relieving them.

the SNc [50], there is evidence that STN-HFS does not increase the DA production in Parkinsonian patients [51•,52,53].

Pattern organization and neuronal processing in pathological conditions

The temporal organization of the normal discharges from the BG conveys coded messages. These messages are distorted by pathologies, then become meaningless and cannot convey the necessary information through the network. Lesioning and HFS abolish and totally disrupt the incorrect message. 'No message is better than wrong message'.

Different mechanisms can be involved separately or combined, to achieve the inhibitory-like effect of high frequency DBS: jamming (alteration of the firing pattern to a meaningless and therefore inefficient code), suppression of firing (due to membrane interactions, loss of electrogenic properties or synaptic inhibition, e.g. GABAergic neurons), and excitation of a sequence of synaptic steps ending in an inhibitory result.

Excitation of a sequence of synaptic steps is difficult to reconcile with the production of similar effects by lesioning: this could happen by chance in one structure, but not in several different targets.

Suppression of firing is difficult to reconcile with the classical neurophysiological concepts of electrical excitation of the neural elements. However, this hypothesis was suggested from the observation of the equivalent effects of stimulation and lesions in animals [54–56], and clinical situations [15,16]. Microrecordings in rats [57,58] and STN slices [59] have shown that after cessation of the STN HFS related artifact, neural firing is temporarily arrested, which supports the hypothesis of neural silencing. Similar effects are observed in the CM-Pf following VPL (venteroposterolateral nucleus of the thalamus) stimulation [60] and in the hippocampus [61].

However, these data concern the post-stimulation period, and do not relate to the clinical improvement contemporary to stimulation.

Artifact suppression methods allow us to record neurons during stimulation. These data show a total suppression of STN neuronal activity in humans during surgery (B Pidoux, personal communication), whereas in slices [62] the pattern of firing is composed of silent periods interspersed among bursts of firing in synchrony with stimulation (at 130 Hz). This is related to specific inactivation of Ca^{2+} and Na^{+} voltage dependent channels, which normally modulate STN neuron activity [63]. This pattern is very similar to what is observed in the GPi of monkeys [64]. In the two situations in which the neural firing is not suppressed but profoundly altered, one may start to understand how lesioning and high frequency could provide the same effect. During stimulation, the altered pattern bears no functional significance to the rest of the network including the stimulated target, which fails to achieve its normal role, leading us to revisit the concept of functional inhibition. Globally, this fits with our initial interpretation of how Vim HFS and thalamotomy provide similar effects. We considered that Vim HFS was 'jamming' [2,11,12] the Vim bursting activities related to the tremor, and reflecting the agonist and antagonist muscular contractions. HFS induced spikes would fill the gaps between the bursts, making the outgoing neuronal message devoid of oscillatory activity, and therefore unable to generate and sustain tremor. If proven, this would constitute a totally new approach to stimulation of neural elements, which could be applied on a much larger scale to targets and clinical pathological situations as well.

Discussion

Positive aspects

The reversibility of DBS is a unique surgical feature, and it matches one of the major advantages of pharmacological approaches: it allows us to explore putative targets, and to cease all activity in case of unacceptable side effects. It leaves our options open in case a better treatment is found in the future. The adaptability through adjustable parameters is another similarity with pharmacological treatment. However, the strict spatial localization of DBS effects is an advantage over pharmacological treatment, whose side effects are most often due to the action of drugs far from the target site. This also accounts for reduced invasiveness, allowing bilateral operations in one session without the complications of bilateral lesions. Multiple electrodes in one target for optimal coverage of a symptom or multiple electrodes in several targets could be envisioned for these reasons.

Drawbacks

Cost is one of the major problems of DBS, but recent studies [65] demonstrate that over periods of time equal to the duration of batteries of the implanted stimulators (which determine the timing of replacement, and therefore the cost of the method), DBS is a better option financially when compared to drug therapy.

Tuning of the parameters of the stimulator at intervals creates a higher burden on neurologists than the follow-up of thalamotomies or pallidotomies. However, this is in fact an advantage, as it suppresses the need for repeated operations, and insures the optimal control of symptoms.

Comparison to other methods (lesions, neural grafts, molecular therapies)

For several reasons, lesioning methods, particularly thalamotomy, had almost disappeared from neurosurgical practice. Complications were not rare, and often irreversible, and the effect tended to fade with time, sometimes

requiring repeated operations [66]. Bilateral lesions were seldom performed because of post-operative speech and neuropsychological deficits. Pallidotomies, abandoned in the 1950s were reintroduced in 1992 by Laitinen and co-workers [67] essentially because of their strong effect on levodopa induced dyskinesias, which were absent of the time of Leksell as they are iatrogenic complications following the introduction of dopamine treatments. The success of DBS has been responsible for a rebirth of functional neurosurgery for movement disorders, despite the drawbacks of the thalamotomy period and the associated reasons as to why this procedure almost disappeared. The study by Speelman and co-workers compared unilateral Vim lesioning and DBS in tremoric PD patients, and DBS demonstrated similar effects with decreased morbidity [21]. Tronnier and co-workers questioned the advantages of GPi stimulation versus pallidotomy [68], whereas five years later the benefits are considered quite clear [69], as is the advantage of STN DBS versus GPi DBS [17,64].

Gill and co-workers have tried subthalamotomy, with good immediate results that do not last, and require repeated operation for the enlargement of the lesion, which therefore leads to complications [70•]. It is still advocated in some countries, mainly because of non-medical (embargo in Cuba [71•]) or financial reasons (such as in India [72]) despite the frequent hemiballic complications [73,74].

Neural grafts have been an intense field of research during the past few decades. Although progress has been made, this attractive and potentially restorative approach remains experimental, and will continue to benefit from studies conducted on stem cells, the development of competent transformed cell lines [75••] and studies on encapsulated cells [76•].

Striatal infusion of growth factors [77••] and gene therapy have [78••] opened new avenues of research, and might be the replacement methods for STN DBS, but they remain to be evaluated.

Where is the real target?

Localization of the electrode tip by MRI is acceptable but difficult because of MRI artifacts and distortion, and the importance of the mismatch is still difficult to evaluate precisely. There is still a debate about the most efficient target for DBS. Most authors agree that it lays in the antero-latero-upper part of STN [79], the location of the somatomotor area in non-human primates, which rules out the possibility of SNr being the active target. We define here directions to the target area [80], which are close to the values from other teams (mean 1.62 mm posterior to the midcommissural point [MCP], 2.47 mm inferior to the anterior commissure–posterior commissure [AC-PC] line, and 11.72 mm lateral to the midline) [2]. In the parallel processing model, GPi and SNr are pooled together as output structures of the BG, which suggests that the SNr target could be as good as GPi. Actually SNr HFS does not improve PD symptoms. This part of the BG functional scheme needs to be redefined. It is possible that the zona incerta (ZI), which lies immediately above the STN or fiber bundles (Forel fields), rather than neuronal clusters could be involved.

Conclusions

In patients with advanced PD and severe 'off' period disability, the quality of life after DBS improves to the level of a large population of patients with mild PD. A decrease in the social isolation of the patients is the real success of STN stimulation. It is worth taking the relatively small risk and operating on patients before their quality of life has reached a too low level. A better social life is the result of improvement in 'off' drug motor symptoms and dyskinesias, as they interfere with social functioning, not only because of their disabilitating nature but also because of the stigma associated with these symptoms.

DBS at a high frequency mimics the effects of lesions, is reversible, adaptable, and leaves open future options (neural grafts, the use of encapsulated cells [76•] or stem cells [75••], or new solutions, such as the application of growth factors [glial-derived neurotrophic factor (GDNF) or others], chronic infusion [77••] or gene therapy [78••]).

The mechanisms of action of DBS are still to be deciphered and, although they closely mimic the effects of a lesion, they might have a complex nature, probably involving both jamming and neuronal silencing as well as axon stimulation.

Demonstration of the efficacy of this technique for PD has opened new avenues of putative use (epilepsy [81••,82], obsessive compulsive disorders [83,84], cluster headache [85••] and possibly obesity) and makes DBS at high frequency a new potent tool for functional neurosurgery even beyond the field of movement disorders [86].

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- • of special interest
- •• of outstanding interest

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