Chapter 34
Functional Neurosurgery: Past, Present, and Future

A. L. Benabid, M.D., Ph.D., S. Chabardes, M.D., E. Seigneuret, M.D., P. Pollak, M.D., V. Fraix, M.D., P. Krack, M.D., J. F. LeBas, M.D., Ph.D., S. Grand, M.D., and B. Piallat, Ph.D.

Functional neurosurgery has its roots in the past. Stereotaxy was initially designed to treat movement disorders. Since the 1940s, ablative lesions have been made in various parts of the central nervous system (CNS). During the 1950s and 1960s, there was a period of optimization of stereotactic procedures (mechanical, chemical, thermic, electrolytic, etc.) and of targets (pallidum and thalamus). From the 1960s to the 1980s, the thalamic target Vim was elected as the target of choice to treat tremors, but at the same time, the medical treatment with levodopa was introduced, which sent thalamotomy and pallidotomy to the archives. Neuromodulation for pain was established at the end of a long journey. Transcutaneous stimulation was initially applied by William Sweet and then to peripheral nerves, spinal cord, sensory thalamus, periventricular gray, and finally to the cortex where stimulation of the premotor cortex quickly imposed itself as a good method after its introduction by Tsubokawa et al. (18) in 1991.These various steps established the concept of neuromodulation and justified the development of specific chronic electrodes and generators.

The joint venture between DBS and movement disorders could then begin. The levodopa treatment had spectacular results but severe limitations such as dyskinesias appearing after several years, and ablative surgery had complications such as motor deficits or dysarthria and cognitive alterations when they performed bilaterally. This called for alternative methods such as grafts, staged lesions with implanted electrodes (which allowed the creation progressive lesions at the bedside), and attempts at stimulation (in the centrum medianum-parafascicularis [CM-Pf] for tremors [1] and multiple sclerosis [4]).

LUCK AND SERENDIPITY

This quest for alternatives to ablative surgery that could be adaptable, even reversible, associated with minimal side effects and nonpermanent deficits, set a context for open-mindedness. In 1987, during a Vim thalamotomy for essential tremor, electrical stimulation was used as a method to locate the best place to make a lesion. Stimulation could recognize the structures and particularly those that were potential sources of complications, such as the internal capsule, responsible for motor deficits, or the ventral posterior lateral thalamus, which could be responsible for sensory deficits, leading to permanent pain or Dejerine-Roussy syndrome.

Stimulation at a low frequency did not change the intensity of the tremor, and on the contrary, it could increase it or even drive it when the frequency was around the band of six Hz. Surprisingly, frequencies more than 100 Hz were able to block the tremor significantly, and sometimes totally, in a reversible manner because the tremor returned almost immediately when the stimulation was turned off. This paradoxical lesion-like effect of high-frequency stimulation (HFS) was then used on empirical rounds as a complement of the panel of investigational methods we had at hand at the moment to investigate the site of the lesion. After awhile, it became evident and highly suggestive that this could be used as a method. When a patient, initially treated for essential tremor by electrocoagulation of the Vim nucleus on one side, came and asked for a contralateral operation because a tremor had appeared, we proposed that he undergo the insertion of an electrode that would be connected to an implantable stimulator to

replicate chronically what we had observed acutely during the stereotactic surgery (2) rather than a lesion.

The results were immediately impressive, and since that time, no other lesion has been performed in our neurosurgical department. The discovery that the effects of stimulation depend on frequency was based on the recognition that the observed effect was in close relationship with the frequency. A retrospective review of the literature could show that this had been previously observed, as well as had the impairment of the tremor, when stimulation was related into the operative record, but the critical relationship with the frequency and the necessity to stimulate more than 100 Hz to obtain the effect was never recognized. However, it was easy to observe during the intraoperative period that stimulation was able to abolish Parkinsonian rest tremor as well as essential tremor at frequencies higher than 100 Hz and to demonstrate a U-shaped relationship when the voltage needed to abolish the tremor, which is quite an easy symptom to observe, is plotted against frequency. At frequencies less than 100 Hz, an effect can be observed at higher voltages (approximately 5–10 volts), whereas Parkinsonian tremor is usually influenced at higher frequencies with much lower voltages (approximately one or two volts) within the range of 100 to 2500 Hz. After treatment with frequencies in that range, the tremor required increased voltages, which corresponded to the finding that the human body is not sensitive to much higher frequencies, allowing the use of cell phones as well as the exposure to the electromagnetic environment. At frequencies around 130 Hz, the tremor stops within a few seconds when turning on the stimulation and reversibly recurs shortly after a few seconds, when the stimulation was turned off.

The pragmatic concept that HFS mimics the effects of lesion was further applied to another target for ablative surgery in 1992 (16), after pallidotomy had been reintroduced by Laitinen and Hariz. Pallidal HFS applied to this revived target could reduce levodopa induced dyskinesias, which is the most sensitive symptom to respond to either pallidotomy or to the stimulation. It became clear that a neuroplasticity-like effect could also be observed. The score of the dyskinesia induced by a dopa challenge was decreased at 6 months, even more decreased at 1 year, and difficult to observe 2 years after surgery. This apparent neural plasticity could be also observed when the dyskinesias were induced by stimulation of subthalamic nucleus (STN) with a tendency to become less easily induced along time.

In 1998, GPi HFS was used to treat dystonias. It had been known for a few years that pallidotomy was able to improve the symptoms. There was a gradient in the response between the different varieties of dystonia: the generalized primary dystonia caused by mutation of the gene DYT1 was the most sensitive, whereas the dystonias secondary to a lesion, such as anoxia, anaphylactic accident after the use of the drug, or anesthetic complications of surgery were less responsive.

In 1999, capsulotomy was replaced by HFS in the treatment of obsessive-compulsive disorder (OCD), which raised the interesting question of the differential effect of HFS on fibers, where usually excitation-like responses were regularly observed, as opposed to the cellular targets, where only HFS was able to mimic lesions. Nuttin et al. (13) applied HFS within the anterior limb of the internal capsule. Clinical improvement was obtained with the highest voltage available (10 volts) with a rather large pulse width. This suggested that diffusion was able to reach the cellular targets and, particularly, the nucleus accumbens because the efficient contact was usually the lowest one and because of the higher parameters. Because of this finding and the physiopathological relationship it has with the behavioral and neuropsychological disorders, Sturm et al. (17) deliberately targeted this structure to treat OCDs. In this occasion, the pragmatic concept of HFS-mimicking lesion had been applied to a putative surgical target, suggested by the results of fundamental research in animals.

The breakthrough came in 1990 when Bergman et al. (3) showed that in MPTP Parkinsonian monkeys, the electrolytic lesion of the STN could be a possible therapeutic target in human Parkinson's disease. This target is also interesting because it is clearly visible on coronal sections of T2-weighted magnetic resonance imaging, above the substantia nigra reticulata, medial to the internal capsule and the internal pallidum, lateral to the most anterior part of the red nucleus, and below the thalamus.

After the suggestion based on experimental evidence, we performed an electrode implantation of STN with chronic electrodes. The effects were impressive, allowing an important alleviation of the major symptoms such as akinesia, rigidity, and tremor and extended to the axial rigidity. The effect was immediate and reversible, efficient also on OFF-period dystonia. It is important to point out that with electrode implantation of STN, contrary to GPi stimulation where the drug dosage is grossly kept constant, it was possible to decrease the treatment doses by an average of 60% and there was an improvement of approximately 70% of dyskinesias in duration and disability. This allowed us to consider that even patients having preoperative dyskinesias could benefit from this kind of stimulation because the drug could be decreased and dyskinesias could disappear. There is still a delicate equilibrium to reach between the decrease of the drugs and the setting and tuning of the stimulators, at least during the first year, to avoid dyskinesias. These effects are stable for more than 5 years (9), not only for tremor, rigidity, and akinesia, but also, to a lesser extent, for all symptoms including midline symptoms (postural instability and gait) and quality of life while still providing an improvement of more than 50% at the fifth year after surgery. However, symptoms such as speech and writing were not so strongly improved, reaching an average of 50% as compared to the 65% improvement of the motor symptoms.

The study of those long-term effects of stimulation at HFS of STN in Parkinson’s disease teaches us two lessons: First, the good result comes from the neurologist’s adequate indications (5), and the improvements obtained by this electrical stimulation of STN as compared with the preoperative scores should be similar to the improvement obtained by medication alone. This response to levodopa has proven to be one of the major predictors of the efficiency of this stimulation. Second, the beneficial effect depends strongly on the correct placement of electrodes by the neurosurgeon. Around the STN nucleus are several neuronal structures or fiber bundles, which are or may easily be reached and affected by HFS, inducing, therefore, side effects that act as limiting factors. It is particularly clear that motor contractions are elicited by the excitation of descending corticospinal fibers, which run laterally to the STN, and the extension to the posterior fibers of the lemniscus medialis was responsible for all the induction of paresthesias. These criteria provide the neurosurgeon with a sort of quality index, which would help in comparing one team to other more experienced teams, taking into account the specificity of their patient and, particularly, their levodopa response.

Some side effects are of particular importance and must be related as precisely as possible to their proper causes. Confusion is observed in approximately 20% of the cases, and it has been observed that it appears during surgery at the time when the second set of guide tubes is inserted and crosses the border of the lateral ventricle where the body of the caudate nucleus resides. The comparison of three groups of patients operated with an electrode approach parallel to the midline, with an entry point 25 mm from the midline that leads the electrodes close to the recessus of the lateral ventricle containing the caudate nucleus, or using a more lateral penetration between 40 and 45 mm from the midline with the track traveling the white matter, showed that the incidence of this confusion was two times more frequent when it involved the caudate nucleus in one of its most compacted parts. In all cases, this confusion was temporary, lasting only the 3 days to 3 months required for the bilateral traumatic injury of the caudate nucleus to heal.

Depression and suicide have been reported. Depression occurs in approximately 20% of cases, and the frequency of suicide varies among teams. In our institution, we have performed 260 cases of bilateral STN implantation and have had only one patient commit suicide. These differences might be due to the involvement of the limbic STN, and this has to be confirmed by further observation. This is probably not the most determining factor: the strong decrease (60%) on the levodopa therapy needs to be considered because dopamine has a psychotonic affect, and the patients might be presenting a withdrawal syndrome. The profound changes in patients' lives and their readjustment to the society are extremely important because of the significant improvement of their performances. When, after surgery, they are reinjected, sometimes rather brutally, into the real world, the patients speak of a second birthday and describe themselves as adults being born and thrown into the external surroundings. This calls for an even more careful selection of the patient and for pre- and postoperative psychological support. The issue of neural cognitive decline has been raised, and it is important to relate that in our series, using various batteries of neural cognition, there is no change in these scores, such as the Mattis, the Beck, and the frontal scores. On the contrary, using the PDQ scales, there is definitely an improvement of the quality of life, also sustained for a long time.

Spectacular side effects such as acute depression, as well as laughter, are reported. It is of crucial importance to be able to locate the right structure that is responsible for these effects. Is it the limbic part of the subthalamic nucleus? Or is it the substantia nigra reticulata? The latter is unlikely because this target is implanted to treat pharmacoresistent epilepsies and has not been observed in these cases. The mapping of the area around STN shows a comparison of the spatial distribution of the contacts providing the best clinical improvement with the spatial distribution of motor contraction, paresthesias, or visual flashes caused by the diffusion to fiber tracks of the stimulation. It is quite often that this diffusion is caused by an increase in HFS voltage, which was required because of the non-optimal position of the electrode, to reach the place of the theoretical target at the price of the induction of side effects. One can get through the side effects to ensure the best results.

This stresses the difficulty to localize precisely the electrodes and the need to develop better imaging methods and raises some complementary questions: Where is the actual efficient target? Is it STN? Substantia Nigra? Is it even the Zona incerta? The clinical efficiency depends highly on the precision of insertion of the electrode within the theoretical target. The theoretical target is defined as the point in space, which has as coordinates the average values of the coordinates of the best contacts providing the best improvement. In our series of patients, 400 contacts were checked clinically to provide the optimal benefits for each patient. The average coordinates of this target are anterior to posterior commissure (AC-PC) 5.22 ± 0.65 one-twelfth degree of AC-PC distance (25.24 ± 3.26mm), −1.21 ± 0.66 one-sixth degree of thalamus height (17.36 ± 1.54 mm), and 11.58 ± 1.79 mm from midline.

The calculation of the distance of each contact to this target allows the prediction of which contact will be chosen under clinical grounds, and it just happens that the closest contact is the one that is chosen in approximately 54.9% of the cases. The second closest is chosen in 40.6% of the cases, giving the two closest contacts to the target a 95% probability of being chosen. This provides a rather easy method to analyze and comment on the position of an electrode in front of clinical results, which might possibly be non-optimal.

Currently, one of the most important questions raised is where is the efficient target? In other words, where is the place where the results are the best? Currently one may say that STN is more likely to be the target of choice, according to our data. Surrounding structures may then induce side effects. We nevertheless must take into account

the fact that the best active contact in a given patient is a compromise between the best clinical improvement and the most acceptable side effects. The conclusion of this first part is the establishment that HFS is functionally equivalent to a lesion, with the difference of being adaptable and reversible. HFS of brain structures induces a functional inhibition mimicking the effects of lesions in all three targets used for Parkinson's disease. But are there other indications? Are we facing a new physiological concept, and if so, what is the mechanism?

What are the New Indications?

HFS is applicable to OCD, epilepsy, cluster headache, tardive dystonias, depression, tics, and possibly obesity and anorexia. We have to resist the temptation to use it too often and to apply it unwisely to an indication without having a minimum of data on the pathophysiological mechanism involved and on the different targets available. HFS is a tool, not a panacea.

HFS FOR EPILEPSY

The use of HFS for epilepsy is based on the existence of a nigral control of epilepsy, which has been established and proven in animal experiments (7). Substantia nigra reticulata projects ã-aminobutyric acid (GABA)-ergic outputs onto the superior colliculus. The injection of GABA agonists or of N-methyl-D-aspartic (NMDA) acid antagonists within the substantia nigra reticulata, as well as the injection of the antagonists in the superior colliculus, results in an antiepileptic effect in various animal models. This has been the basis of proposing HFS of STN in patients suffering from a pharmacoresistent epilepsy and not candidate for resective surgery because of the location of the area to be resected (such as the motor strip) or because of bilateral lesions. Because of the anatomical organization of the target, which is situated above the substantia nigra reticulata and exerts a glutamatergic control over it, it was also logical to implant the electrode into STN, which was performed in our institution in five patients.

In four of them, the results were extremely encouraging. For instance, in the first patient, a 5-year-old girl, operated now 7 years ago for motor epilepsy with post-ictal deficits and with a frequency of about 330 ± 225 seizures per month, the improvement consisted of a decrease of the seizures by about 90%, a decrease in the intensity and severity of the seizures, and the seizures being replaced by very limited cloni without any behavioral consequence. It is important to define who the responders are and who the nonresponders are, which is the basis for the current control study we are engaged in with patients with a genetic abnormality (“ring” chromosome 20 responsible for generalized epilepsy, partly levodopa sensitive). This approach will lead to the identification of homogeneous groups of patients who do respond to stimulation.

HFS FOR OBSESSIVE COMPULSIVE DISORDER

As mentioned above, HFS has been applied early to replace lesion into the internal capsule (13), the preliminary results of which tend to indicate the existence of a target that could be situated at the level of the nucleus accumbens or more posteriorly. In 2002, Mallet et al. (11) reported two cases of Parkinsonian patients who had Obsessive Compulsive Disorder (OCD) symptoms concomitantly. They received surgery for their Parkinson’s disease, which improved, but they also had a significant improvement of the Yale-Brown Obsessive Compulsive Scale (Y-BOCS) for their OCD symptoms. On this basis, a multicentric study has been started, targeting patients with OCD refractory to cognitive behavioral therapy and to one and two inhibitors of capture of serotonin for several months. Preliminary

results show that in the STN target, as well as in the accumbens nucleus, which is targeted by Sturm et al. (17), there is a very significant improvement, frequency, and stimulation related, which is visible in the operating room, therefore facilitating tremendously the choice of the microelectrode to be replaced by the chronic implantable four contacts electrode.

HFS FOR CLUSTER HEADACHES

It has been observed using positron emission tomography (PET) scan (12) that during a cluster headache attack, there is a high activity focus situated in the posterior hypothalamic area close to the midline. On this basis, Franzini et al. (6) reported that the implantation of a chronic electrode to stimulate in this area was able to spectacularly suppress, also in reversible manner, the vascular manifestations.

This shows how new targets could be designed on the basis of functional imaging, providing at the same time, the spatial organization of the neuronal structure to be implanted and the evidence that in this pathological situation, the activity is increased, as proven by the PET scan. One might also expect that the progress in functional magnetic resonance imaging might suggest new surgical targets based not only on the coordinates, but also on the role of a given target within current systems and networks.

HFS FOR EATING DISORDERS

Can we treat obesity and anorexia nervosa? It has been evidenced in experimental animal studies that the lesion of the ventromedial nucleus of the hypothalamus would increase the food intake in already satiated animals, whereas low-frequency stimulation excites the ventromedial hypothalamic nucleus and then decreases the food intake in fasting animals. On this basis, we have undertaken animal experiments where the lesion was replaced by electrical HFS and where the site of the intended lesion was implanted with electrodes. Low-frequency stimulation reproduced the previously mentioned effects, whereas HFS mimicked the effect of lesions and increased the food intake of animals already fed. This opens a new field of activity and possibly of research, but we have to be extremely careful before we go into applications. Obesity cases should be limited to malignant obesity of life-threatening cases because of the impact of weight on basic functions, such as breathing. Anorexia is an even more delicate condition to test because, most of the time, the patients do not want to cooperate with the proposed treatment and will not give informed consent. This touches the borderline of psychosurgery.

MECHANISM: SOLVING THE PARADOX

HFS and low-frequency stimulation have similar excitatory effects on axons and fibers, fully complying with the classical physiology. On the contrary, with HFS in somatic structures, there is consistently an effect that resembles the effect obtained if we would destroy the neuronal structure (except that this is adjustable and reversible). This effect has been observed in all used targets such as Vim nucleus, CM-Pf, GPi, STN, and, more recently, the subcaudate cortex. It is not the purpose of this paper to detail the current and often conflicting data in a very active field of research. Trying to solve this problem, we make a proposal for a putative generalized model taking into account most of these data. Stimulation within or in the vicinity of fiber tracks will consistently induce the expected side effects fitting the concept of excitation (flashes in the visual track, muscular contraction in the internal capsule, paresthesias in the lemniscus medialis, monocular deviation in the third nerve fibers and conjugated gaze deviation

when the fibers of the corticonuclear projections are involved). If stimulation is delivered within nuclei when the inhibition of the cell firing by not yet clarified mechanisms at the level of the somatic membrane, excitation of fibers in the vicinity of the cells would have different effects, depending on where they come from and where they go. Incoming fibers could be activated, participating to a mechanism of jamming, which would make the neuronal structure unable to transmit and process information, and therefore not transmitting or producing an abnormal electrical activity, which is observed in the components of the basal ganglia (bursting or oscillations) in various pathologies. However, the fibers originating from the cell within the nucleus and that will project on the next neuron would be excited at the synaptic level; this would produce the release of a transmitter ending in postsynaptic excitation. Recent experimental data of our laboratory show that HFS of cells in culture (prolactinoma GH3 producing Prolactin and PC12 cells producing dopamine, norepinephrine, and epinephrine) was able to induce significant decreases in the production and release of the neurotransmitters when stimulation was performed at a high frequency, whereas at a low frequency, there was either no change or a slight increase of neurotransmitter production.

The putative model is therefore based on the following statements: Both HFS and low-frequency stimulation excite axons passing by the stimulation site, whereas low-frequency stimulation excites the bodies. HFS may inhibit neuronal firing and induce jamming of the neuronal message either normally or incorrectly. Axons originating from the stimulated neurons should be excited and convey spikes, leaving the cell bodies traveling to the synapses, where they release empty vesicles, devoid of neurotransmitters, making these synapses “firing blanks.” HFS inhibits intracellular protein processes, and the intimate mechanism remains to be elucidated.

WHAT IS THE FUTURE OF HFS?

There is no better future for a method than being replaced by a better method. What could be the challengers: neural grafts, stem cells, gene therapy, or growth factors? Should lesions be revisited?

There is a research field to plow, and the distant future is still fuzzy. In the near future, improvements can be made. Better knowledge of the effect of HFS, correct evaluation of potential neuroprotection, better stimulation methods, and gene transfer have been initiated after the publication of experimental data (10), showing that the glutamatergic subthalamic nucleus could be turned into a GABA-ergic nucleus leading to the reversal of the cascade of events associated with dopamine cell generation and increased glutamatergic activity within STN.

Gill et al. (8) published the effect of direct brain infusion of GDNF in the pallidum of parkinsonian patients who showed a significant improvement of their motor disorder. A further multicenter study is needed to confirm that. There are potential methodological problems that cast a doubt on this conclusion.

Is there a neuroprotective effect of STN stimulation? This is based on the hypothesis that HFS decreases or shuts down the hyperproduction of glutamate, which is hypothesized as being one on the functional substances driving the basal ganglia to a wrong functioning because it is known that glutamate outputs might participate in the neurodegenerative process. It is known that there is glutamate neurotoxicity through NMDA receptors, that is, NMDA enhances neurotoxicity of methamphetamines, and neurotoxicity is attenuated by an NMDA antagonist ([MK801, CPP, etc.). The inhibition of STN by either lesioning or HFS could decrease this to glutamate production and should interrupt or even stop the degenerative process.

To date, experiments in rats (14,15) support this hypothesis, as are monkey experiments (unpublished data. In humans, the observation of the UPDRS score in the off-medication/off-stimulation situation shows, in one series, that 25% of 89 patients still aggravate regularly over a long period, as classically described in this disease, 36% of them have been stable within the range of 10% over 5 years, and 38% of them improve their UPDRS. There is a strong improvement during the first year of their UPDRS score from 57.5% to 38%, and half of them (19% of the total population) have this improvement continuing for 5 years. However, remaining effects of either stimulation or of medication could be responsible for this prolonged effect, and therefore these data do not serve as proof of neuroprotection. This should be proven using nonclinical parameters (PET scan data).

Is it possible to implant several electrodes in one target to better cover each symptom and maybe to cover several symptoms? According to this hypothesis, modeling of the electrical field of stimulation shows that it could be possible by selectively activating subsets of contacts to shape the isopotentials to the shape of the target of interest, providing a better improvement of the symptoms as well as a reduced number of side effects. This has justified the development, in conjunction with the LETI, of a programmable implantable multiplexer. Similarly, one can think of implanting several electrodes in several targets, such as GPi and STN in dystonia. A better detection of the target could take advantage of spike discrimination using an unsupervised spike sorting software, which is being developed in our laboratory. The exploration of targets with microelectrodes or various targets in various pathologies provides an opportunity to collect samples, allowing polysomics analyses (genomics and proteomics using transcriptome as well as surface enhanced laser desorption ionization-time of flight mass spectrometry), which are able to detect on nano samples a wide range of small proteins, which are currently being identified.

CONCLUSION

High-frequency DBS of basal ganglia is the current surgical alternative in the treatment of advanced Parkinson's disease. It has already several applications to other diseases, and future indications are being investigated. Its mechanisms are not fully understood but produce functional inhibition, with multiple complex components, from the cell to the gene. The physiology of electrical stimulation in general, or even at larger scale the biological effects of electricity, should be further investigated.

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