Uncovering the Mechanism(s) of Deep Brain Stimulation

Li Gang, Yu Chao, Lin Ling, Stephen C-Y. Lu

Inspiring Technical Laboratory, College of Precision Instruments & Opto-Electronics Engineering, Tianjin University, Tianjin 300072, CHINA

E-mail: Ligang59@163.com

Abstract. Deep brain stimulators, often called “pacemakers for the brain”, are implantable devices which continuously deliver impulse stimulation to specific targeted nuclei of deep brain structure, namely deep brain stimulation (DBS). To date, deep brain stimulation (DBS) is the most effective clinical technique for the treatment of several medically refractory movement disorders (e.g., Parkinson’s disease, essential tremor, and dystonia). In addition, new clinical applications of DBS for other neurologic and psychiatric disorders (e.g., epilepsy and obsessive-compulsive disorder) have been put forward. Although DBS has been effective in the treatment of movement disorders and is rapidly being explored for the treatment of other neurologic disorders, the scientific understanding of its mechanisms of action remains unclear and continues to be debated in the scientific community. Optimization of DBS technology for present and future therapeutic applications will depend on identification of the therapeutic mechanism(s) of action. The goal of this review is to address our present knowledge of the effects of high-frequency stimulation within the central nervous system and comment on the functional implications of this knowledge for uncovering the mechanism(s) of DBS.

1. Introduction

Deep brain stimulators, often called “pacemakers for the brain”, are implantable devices which continuously deliver impulse stimulation to specific targeted nuclei of deep brain structure, namely deep brain stimulation (DBS). The deep brain stimulator device has 4 contact electrodes, which are stereotactically placed into the targeted nucleus of basal ganglia or thalamus. The electrodes are connected to the pulse generator by a wire that is tunneled down to the pulse generator from the brain. The pulse generator typically is placed in the subcutaneous tissue of the chest, much the same as a cardiac pacemaker. Stimulation parameters include electrode selection, stimulation pulse amplitude, frequency, and pulse width can be adjusted to achieve the maximum effect and the minimum side effects.

Deep brain stimulation (DBS) has recently evolved from a highly experimental technique to a well-established therapy for the treatment of medically refractory movement disorders including dystonia, essential tremor, and Parkinson’s disease. DBS results in clinical benefits analogous to those achieved by surgical lesions of the nucleus where the electrode is implanted, which has transformed the use of functional neurosurgery for the treatment of movement disorders [1]. Thalamic deep brain stimulation (DBS) for intractable tremor has virtually replaced ablative lesions of the thalamus [2]. And DBS of the subthalamic nucleus (STN) or globus pallidus internus (GPI) has largely replaced pallidotomy in the treatment of the cardinal motor features of Parkinson’s disease (PD) [3].
Although the clinical benefits of DBS have been well documented, fundamental questions remain about the therapeutic mechanism(s) of action. Because of the similarity in therapeutic outcomes achieved with DBS and lesions, it has been argued that high-frequency electrical stimulation (HFS) inactivates the structures being stimulated. Recordings made in the stimulated nucleus show inhibition and/or decreased activity during and after the stimulus train. However, recordings made in different nuclei of the stimulated nucleus indicate that the output of the stimulated nucleus is increased during DBS. In turn, there exist two general philosophies on the effects of DBS: (1) DBS generates a functional ablation by suppressing or inhibiting the structure being stimulated; or (2) DBS results in activation patterns in the stimulated network that override pathological network activity [4].

2. Inhibitory effects of DBS

Many experimental results show that increasing the stimulation frequency should result in an increased effect on the target structure of the neurons stimulated [5, 6, 7]. But, it appears not to be the case for the effects of DBS in the treatment of movement disorders. Figure 1 suggests that there may be different mechanisms involved in mediating stimulation effects at high-stimulation frequencies. In addition, due to the phenomenological similarity between the effects of DBS and lesioning, it appears logical to assume that DBS inactivates the structures being stimulated. Several studies have examined neuronal activity during stimulation or in the period after the end of stimulation.

2.1. The effect of stimulated structure

2.1.1. HFS inhibits STN activity. The subthalamic nucleus (STN) has come under focus in Parkinson disease (PD) from recent advances in the understanding of the functional organization of the basal ganglia (BG) and is now recognized as the target of choice for the neurosurgical treatment of advanced PD. Therefore, much data about STN-HFS has been reported. Most of these results which were recorded immediately after cessation of HFS consistently show a post-stimulus period of reduced neuronal firing followed by the slow recovery of spontaneous activity. In rat brain slice preparations, high-frequency electrical stimulation produces extended inactivation of voltage-gated sodium and calcium channels in STN neurons. In rats, Benazzouz and colleagues [9] found that a 5 s high-frequency stimulation train in the STN induced a decrease in STN neuronal activity for 30–90 s after the stimulation was stopped. Study on patients also showed that stimulation at higher frequencies (50–200 Hz) and with higher currents produced inhibition lasting for 50 to over 500 msec after the stimulus train in many cells (figure 2) [10]. Similarly, many others articles demonstrated that HFS at frequencies >50 Hz in the STN of patients undergoing functional stereotactic procedures [11, 12, 13], in the STN of rats in vivo [14, 15] and in rat STN slices in vitro [16, 17, 18] produces a period of neuronal silence of hundreds of milliseconds to tens of seconds.

In order to understand the actual actions of HFS, a few recordings were performed during HFS. Figure 3 compares extracellular STN recordings during brief STN-HFS in patients off medication and in the murine model of Parkinsonism. They all show reduced STN activity [12, 13, 15]. At 5–14 Hz, STN-LFS evokes inhibition or no response, but the higher the frequency of stimulation, the higher the
percentage of neurons presenting an inhibitory response. Magarinos-Ascone et al. conclude that HFS inhibits STN activity. Histological analysis of the expression of cytochrome oxidase subunit I (CoI) mRNA indicated that long-term HFS decreases by ~10–35% expression of CoI mRNA in the stimulated STN of control and lesioned rats, whether anaesthetized or awake [15, 18].

2.1.2. HFS inhibits Gpi/SNr and thalamus activity. In animal and human studies, long-duration high-frequency stimulation of either the Gpi can produce a long-lasting period of neuronal silence (several hundred milliseconds) after the period of stimulation that eventually recovers back to baseline [19]. In monkeys treated with 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), Boraud and co-workers reported that high-frequency stimulation of the Gpi for 20 s at therapeutic intensities resulted in a decreased firing rate but not in a block of activity, and the effect persisted for 2-3 s [20]. In Gpi and SNr, single low-intensity stimuli produce a short-lasting inhibition (25-50 ms) in most cells and at frequencies over 50 Hz, there is an almost complete block of firing during the train of stimulation (figure 3) [11]. Similarly, Jonathan and colleagues found that high-frequency, low-intensity stimulation in Gpi and SNr frequently resulted in inhibition after the termination of the train and this inhibition was usually on the order of a few hundred milliseconds [10].

2.2. The effect of downstream effect.
STN HFS induced (i) a significant decrease in STN neuronal activity, (ii) a significant decrease in firing rate of SNr neurons in intact animals and in rats with 6-OHDA-induced SNc lesions or with ibotenic acid lesion of the GP, and (iii) a significant increase in the firing rate of the VL [9]. Benazzouz and coworkers [9, 21] showed that stimulation in STN caused long-lasting inhibition (100 seconds) of SNr and Gpi neurons after a 130 Hz, 5-second train and increased firing in GPe. Similarly, Burbaud and colleagues [14] also reported inhibition of SNr whereas the inhibition did not usually outlast the period of stimulation. Burbaud et al. and Tai et al. have shown that brief STN-HFS (100–130 Hz, lasting for 20–120 s) in control or lesioned rats in vivo either decreases SN pars reticulata (SNr) firing rates or has no effect [14, 15] and causes modest inhibition (12%) in half of the EP neurons recorded [14]. Contemporarily, Benazzouz and colleagues also showed that the large majority of SNr neurons (91%) and EP (80%) tested in their study presented a significant decrease or
suppression of their spontaneous activity in response to the application of high-frequency stimulation (130 Hz, 0.3 mA for 5 s) at the STN level [22]. And at the same time, they found that the majority of tested neurons in these nuclei (83% for VM and 91% for VL) presented an excitatory response to STN HFS and that this effect was frequency-dependent. These results can be explained by the fact that STN HFS induces a deactivation of basal ganglia output structures that liberated motor thalamic nuclei (VL and VM) from the tonic GABAergic influence [23].

Additional support for inhibitory effects was derived from positron emission tomography studies demonstrating similar changes in cortical metabolic activity after pallidotomy and GPi DBS[24, 25] and electrophysiological studies describing decreased neuronal activity in the substantia nigra pars reticulata (SNr) and entopeduncular nucleus (GPi in primates) after STN stimulation in rats[9, 21]. Limousin et al. have shown that STN HFS, which produced a significant improvement in movement performance, was accompanied by an increase in cortical activity of the supplementary motor area, dorsolateral prefrontal cortex and cingulate [26].

3. Activatory effects of DBS

However, although many studies have confirmed that high-frequency stimulation results in depression of the output from the region stimulated, several recent studies have not confirmed this finding, or have even found the opposite to be true.

3.1. Activatory effects as revealed by neural recording

Studies of chronic stimulation in parkinsonian monkeys have demonstrated increased mean discharge rates of neurons in the GPi during chronic stimulation in the STN that occurs coincident with improvement in parkinsonian motor signs [27]. Unpublished observations by Hashimoto and co-workers also showed that there was a marked shift in the percentage of neurons with increased mean discharge rates in GPi at parameters that produced improvement in motor symptoms and a tonic activation pattern of GPi neurons during STN stimulation comparing with the irregular pattern of neuronal activity present before stimulation. Hashimoto and co-workers reported excitation of GPi neurons with STN stimulation in MPTP-treated monkeys [28]. In monkeys with parkinsonism induced by 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), during STN-HFS at a frequency that can alleviate parkinsonian signs (136 Hz or 185 Hz, lasting for 25–35 s), the majority of GPi neurons (85%) respond with a sequence of inhibition–excitation–inhibition–excitation [29]. Latencies of the excitatory responses are compatible with activation of subthalamo–nigral [30] or subthalamo–pallidal [31] neurons, thus strongly suggesting that STN-HFS activates output STN neurons. In addition, Montgomery and associates reported inhibition of thalamic neuronal activity during high-frequency stimulation in GPi, consistent with increased output from the stimulated site [32].

3.2. Activatory effects as revealed by others

Another line of evidence to support the hypothesis that stimulation may increase output from the stimulated site is derived from observations in PD patients during stimulation in GPe. Many researchers have observed that stimulation in the external segment of the globus pallidus (GPe) improves parkinsonian motor signs in patients with PD [33, 34, 35]. Acute stimulation in GPe with a radiofrequency lesioning probe, before making a pallidal lesion, dramatically improved bradykinesia and abolished rigidity in parkinsonian patients [33, 37]. Improvement in bradykinesia and rigidity during stimulation in GPe has also been reported by using chronically implanted leads [34]. In addition, Microstimulation-evoked movement which can occur at multiple sites in the nervous system including the motor cortex [19], thalamus [37], and deep cerebellar nuclei [39] also showed that stimulation leading to increased output from the stimulated structure.

In rats in vivo, STN-HFS (60–130 Hz) provoked a significant increase of glutamate content in both GPe and SNr, as measured using microdialysis [39, 40], which suggests that the stimulation is driving STN neurons or exciting the glutamatergic efferent axons in the STN. STN-HFS can influence the activity of dopaminergic neurons either directly [30, 41] or indirectly via collaterals of SNr cells.
Whenever tested, STN-HFS has been found to increase dopamine content or metabolism in the ipsilateral striatum in control and partially dopaminenederated rats [42, 43]. During the STN-HFS period (130 Hz for 1 h), the ipsilateral extracellular content of dopamine increases by up to 200% in 6-hydroxydopamine lesioned rats bearing partial destruction of the SN pars compacta (SNc) and by less in control rats (168%) [42]. But similar results have not be confirmed in patients. In patients greatly ameliorated by the stimulation, increasing blood flow, regional cerebral metabolic rates and blood oxygenation in the ipsilateral GPe [44, 45, 46] induced by STN-HFS also suggest that STN-HFS should drive the rest network of the basal ganglia.

4. Mechanism of action of DBS
Presently, there exist four general hypotheses to explain the therapeutic mechanism(s) of DBS: (1) stimulation-induced alterations in the activation of voltage-gated currents that block neural output near the stimulating electrode (depolarization blockade) [17]; (2) indirect inhibition of neuronal output by means of activation of axon terminals that make synaptic connections with neurons near the stimulating electrode (synaptic inhibition) [48]; (3) synaptic transmission failure of the efferent output of stimulated neurons as a result of transmitter depletion (synaptic depression) [49]; and (4) stimulation-induced disruption of pathologic network activity [50].

Depolarization blockade and synaptic inhibition represent two of the earliest hypotheses to explain the similarity between the therapeutic benefit of ablation and DBS for the treatment of movement disorders. Single-unit recordings of local cells in the stimulated nucleus support both of these hypotheses [17, 51, 52, 53, 54, 55]. A depolarizing block means that the membrane is so depolarized that spikes become smaller and smaller and finally can no longer be evoked, owing to inactivation of the voltage-gated Na⁺ current. Filali et al. [24] and Tai et al. [27] have excluded this hypothesis, because the STN spike amplitude does not change in the initial part of the train and the firing rate does not increase before activity decreases. In addition, the response of the soma does not necessarily represent the output of the axon during HFS [56]. Therefore, while synaptic inhibition and/or depolarization blockade may be occurring in the soma, the functional effect of these phenomena may have limited significance in the therapeutic mechanism(s) of DBS.

In turn, synaptic depression represents an attractive connection between the functional effects of DBS and ablation. However, several in vivo experimental studies have shown increases in transmitter release and changes in firing of efferent nuclei consistent with activation of neurons around the electrode and subsequent synaptic action on their targets during HFS [29, 57, 58]. Therefore, while some level of synaptic depression is undoubtedly occurring throughout the stimulated network of neurons, this phenomenon does not appear to be sufficient to block signal transmission between nuclei.

The abnormal motor activity effectively controlled by DBS is most likely generated by altered patterns, increased neuronal synchronization, and low-frequency rhythmic oscillation of neurons within the basal ganglia and thalamus [59, 60, 61]. It is possible that DBS overrides these altered patterns and low-frequency oscillatory activity and replaces it with tonic high-frequency output, which may be more easily compensated by the remaining elements of the basal ganglia-thalamocortical network [29, 56, 50, 62]. In addition, in untreated patients and primate models of parkinsonism, local field potentials that represent synchronous activity in many neurons are dominated in the STN and GPi by low-frequency oscillations in the 11–30 Hz band [63, 64, 65]. Treatment with L-dopa encourages synchronized oscillations at frequencies >70 Hz [66] and concomitantly improves parkinsonism. The reduction of a pathological 11–30 Hz rhythm and the introduction of a high-frequency rhythm [50, 67] are well consistent with the hypothesis of stimulation-induced disruption of pathologic network activity and maybe provide a common mechanism for therapeutic effects of L-dopa and deep brain stimulation [68].

5. Conclusion
Although we continue to debate the mechanisms underlying the effects of deep brain stimulation, there is no doubt that it has been made in surgical treatment of movement disorders by using deep brain stimulation; future studies directed at improving our understanding of the mechanism underlying the effect of deep brain stimulation will be important for the continued development and application of deep brain stimulator for the treatment of neurologic disease.

References
[1] Gross R E and Lozano A M 2000 Advances in neurostimulation for movement disorders J.Neurol Res. 22 247-258
[2] Benabid A L, Pollak P, Gao D, Hoffmann D, Limousin P, Gay E, Payen I and Benazzouz 1996 A Chronic electrical stimulation of the ventralis intermedius nucleus of the thalamus as a treatment of movement disorders J. Neurosurg 84 203-214
[3] Obeso J A, Olanow C W, Rodriguez-Oroz M C, Krack P, Kumar R and Lang A E 2001 Deep-brain stimulation of the subthalamic nucleus or the pars interna of the globus pallidus in Parkinson’s disease N Engl J Med 345 956-963
[4] McIntyre C C, Savastab M, Goffc L K and Viteka J L 2004 Uncovering the mechanism(s) of action of deep brain stimulation:activation, inhibition, or both Clinical Neurophysiology 115 1239-48
[5] Yeomans J S 1990 Principles of brain stimulation (Oxford: Oxford University Press)
[6] Ashby P, Strafella A, Dostrovsky J O, Lozano A and Lang A E 1998 Immediate motor effects of stimulation through electrodes implanted in the human globus pallidus Stereotact Funct Neurosurg 70 1–18
[7] Dostrovsky J O, Davis K D, Lee L, Sher G D and Tasker R R 1993 Electrical stimulation-induced effects in the human thalamus. In: Devinsky O, Beric A, Dogali M, editors. Electrical and magnetic stimulation of the brain and spinal cord. New York: Raven Press 219-229
[8] Wu Y R, Levy R, Ashby P, Tasker R R and Dostrovsky J O 2001 Does stimulation of the GPi control dyskinesia by activating inhibitory axons? Mov Disord 16 208-216
[9] Benazzouz A, Gao D M, Ni Z G, Piallat B, Bouali-Benazzouz R and Benabid A L 2000 Effect of high frequency stimulation of the subthalamic nucleus on the neuronal activities of the substantia nigra pars reticulata and ventrolateral nucleus of the thalamus in the rat J.Neuroscience 99 289-295
[10] Dostrovsky J O and L A M 2002 Mechanisms of Deep Brain Stimulation Movement Disorders 17 63-68
[11] Lozano A M, Dostrovsky J, Chen R and Ashby P 2002 Deep brain stimulation for Parkinson’s disease: disrupting the disruption Lancet Neurol 1 225-231
[12] Filali M, Hutchison W D, Palter V N, Lozano A M and Dostrovsky J O 2004 Stimulation-induced inhibition of neuronal firing in human subthalamic nucleus Exp.Brain Res 156 274-281
[13] Welter M L et al. 2004 Effects of high-frequency stimulation on subthalamic neuronal activity in parkinsonian patients Arch. Neurol 61 89-96
[14] Burbaud P et al.1994 Effect of subthalamic high frequency stimulation on substantia nigra pars reticulata and globus pallidus neurons in normal rats J. Physiol 88 359-361
[15] Tai C H et al. 2003 Electrophysiological and metabolic evidence that high-frequency stimulation of the subthalamic nucleus bridges neuronal activity in the subthalamic nucleus and the substantia nigra reticulata J.FASEB J.17 1820-30
[16] Garcia L et al. 2003 Dual effect of high-frequency stimulation on subthalamic neuron activity J. Neurosci 23 8743-51
[17] Beurrier C et al. 2001 High-frequency stimulation produces a transient blockade of voltage-gated currents in subthalamic neurons J. Neurophysiol 85 1351-56
[18] Salin P et al. 2002 High-frequency stimulation of the subthalamic nucleus selectively reverses
dopamine denervation-induced cellular defects in the output structures of the basal ganglia in the rat. *J. Neurosci* 22 5137-48

[19] Stoney S D, Thompson W D and Asanuma H 1968 Excitation of pyramidal tract cells by intracortical microstimulation: effective treatment of stimulating current *J. Neurophysiol* 31 659-669

[20] Boraud T, Bezdard E, Bioulac B and Gross C 1996 High frequency stimulation of the internal globus pallidus (GPi) simultaneously improves parkinsonian symptoms and reduces the firing frequency of GPi neurons in the MPTP-treated monkey. *Neurosci Lett* 215 17-20

[21] Benazzouz A, Pallat B, Pollak P and Benabid AL 1995 Responses of substantia nigra pars reticulata and globus pallidus complex to high frequency stimulation of the subthalamic nucleus in rats: electrophysiological data *Neurosci Lett* 189 77-80

[22] Benazzouz A and Hallett M 2000 Mechanism of action of deep brain stimulation *Neurology* 55 13-16

[23] Gao D M, Benazzouz A and Bressand K, et al. 1999 High-frequency stimulation of the subthalamic nucleus suppresses experimental resting tremor in the monkey *Neuroscience* 88 201-212

[24] Limousin P, Greene J, Pollack P, Rothwell J, Benabid A L and Frackowiak R 1997 Changes in cerebral activity pattern due to subthalamic nucleus or internal pallidum stimulation in Parkinson’s disease *Ann Neurol* 42 283-291

[25] Davis K, Taub E, Houle S, Lang A, Dostrovsky J, Tasker R, and Lozano A 1997 Globus pallidus stimulation activates the cortical motor system during the alleviation of parkinsonian symptoms *Nat Med* 3 671-674

[26] Limousin P, Greene J, Pollak P, Rothwell J, Benabid A L and Frackowiak R 1997 Changes in cerebral activity pattern due to subthalamic nucleus or internal pallidum stimulation in Parkinson’s disease *Ann. Neurol* 42 283-291

[27] Hashimoto T, Elder C M, DeLong M R and Vitek J L 2001 Responses of pallidal neurons to electrical stimulation of the subthalamic nucleus is experimental primates *Sixth International Congress of Parkinson’s Disease and Movement Disorders, Barcelona, Spain* Abstract 277-231

[28] Hashimoto T, Elder C M, DeLong M R and Vitek J L 2001 Response of pallidal neurons to electrical stimulation of the subthalamic nucleus in experimental parkinsonism *Proceedings of the Society for Neuroscience, San Diego* 27 (abstr 750.5)

[29] Hashimoto T. et al. 2003 Stimulation of the subthalamic nucleus changes the firing pattern of pallidal neurons *J. Neurosci* 23 1916-23

[30] Hammond C et al 1978 Electrophysiological demonstration of an excitatory subthalamonigral pathway in the rat. *Brain Res* 151 235-244

[31] Nambu A et al. 2000 Excitatory cortical inputs to pallidal neurons via the subthalamic nucleus in the monkey *J. Neurophysiol* 84 289-300

[32] Montgomery E B, Baker K B and Rezai A R. 2001 Effects of GPi stimulation on human thalamic neuronal activity Neuromodulation: defining the future *The Cleveland Clinic Foundation, Cleveland, Ohio*

[33] Vitek J L, Bakay R A E, Hashimoto T, Kanoke Y, Mewes K, Zhang J Y, Rye D B, Starr P, Baron M S, Turner R, and DeLong M R 1998 Microelectrode-guided pallidotomy: technical approach and application for treatment of medically intractable Parkinson’s disease *J Neurosurg* 88 1027-43

[34] Yelnik J, Damier P and Bejjani B P, et al. 2000 Functional mapping of the human globus pallidus: contrasting effect of stimulation in the internal and external pallidum in Parkinson’s disease *Neuroscience* 101 77-87

[35] Vitek J, Hashimoto T, Peoples J, DeLong M and Bakay R Acute 2004 stimulation in the external segment of the globus pallidus improves parkinsonian motor signs *Mov Disord.* 19 907-915
[36] Vitek J L, Hashimoto T and Kaneoke Y, et al 1994 Improvement of parkinsonian motor signs during electrical stimulation of the pallidum *Mov Disord* **9**(Suppl. 1) 102
[37] Vitek J L, Ashe J, DeLong M R and Kaneoke Y 1996 Microstimulation of primate motor thalamus: somatotopic organization and differential distribution of evoked motor responses among subnuclei *J. Neurophysiol* **75** 2486-95
[38] Schultz W, Montgomery E B Jr and Marini R 1979 Proximal limb movements in response to microstimulation of primate dentate and interposus nuclei mediated by brain-stem structures *Brain* **102** 127-146
[39] Windels F, Bruet N and Poupard A, et al 2000 Effects of high frequency stimulation of subthalamic nucleus on extracellular glutamate and GABA in substantia nigra and globus pallidus in the normal rat *Eur J. Neurosci* **12** 4141-46
[40] Windels F, et al 2003 Influence of the frequency parameter on extracellular glutamate and g-aminobutyric acid in substantia nigra and globus pallidus during electrical stimulation of subthalamic nucleus in rats *J. Neurosci. Res.* **72** 259-267
[41] Groenewegen H J and Berendse H W 1990 Connections of the subthalamic nucleus with ventral striatopallidal parts of the basal ganglia in the rat *J. Comp. Neurol.* **294**, 607-622
[42] Bruet N et al. 2001 High frequency stimulation of the subthalamic nucleus increases the extracellular contents of striatal dopamine in normal and partially dopaminergic denervated rats *J. Neuropathol Exp. Neurol.* **60** 15-24
[43] Meissner W et al. 2003 High-frequency stimulation of the subthalamic nucleus enhances striatal dopamine release and metabolism in rats *J. Neurochem.* **85** 601-609
[44] Ceballos-Baumann A O et al. 1999 A positron emission tomographic study of subthalamic nucleus stimulation in Parkinson disease: enhanced movement-related activity of motor association cortex and decreased motor cortex resting activity *Arch. Neurol.* **56** 997-1003
[45] Hershey T et al. 2003 Cortical and subcortical blood flow effects of subthalamic nucleus stimulation in PD. *Neurology* **61** 816-821
[46] Zhao Y B et al. 2004 Effects of bilateral subthalamic nucleus stimulation on resting-state cerebral glucose metabolism in advanced Parkinson’s disease *J.Chin Med. (Engl.)* **117** 1304-08
[47] Beurrier C, Bioulac B, Audin J and Hammond C 2001 High-frequency stimulation produces a transient lockade of voltage-gated currents in subthalamic neurons *J. Neurophysiol* **85** 1351-56.
[48] Dostrovsky J O, Levy R, Wu J P, Hutchison W D, Tasker R R and Lozano A M 2000 Microstimulation-induced inhibition of neuronal firing in human globus pallidus *J.Neurophysiol* **84** 570-574
[49] Urbano F J, Leznik E, Linas R R 2002 Cortical activation patterns evoked by afferent axons stimuli at different frequencies: an in vitro voltagesensitive dye imaging study *Thalamus Rel Syst* **1** 371-378
[50] Montgomery E B and Baker K B 2000 Mechanisms of deep brain stimulation and future technical developments *Neuro Res* **22** 259-266.
[51] Benazzouz A, Piallat B, Pollak F and Benabid AL 1995 Responses of substantia nigra pars reticulata and globus pallidus complex to high frequency stimulation of the subthalamic nucleus in rats: electrophysiological data *Neurosci Lett.* **189** 77-80
[52] Benazzouz A, Gao D M, Ni Z G, Piallat B, Bouali-Benazzouz R and Benabid A L 2000 Effect of high-frequency stimulation of the subthalamic nucleus on the neuronal activities of the substantia nigra pars reticulata and ventrolateral nucleus of the thalamus in the rat *Neuroscience* **99** 289-295
[53] Bikson M, Lian J, Hahn P J, Stacey W C, Sciotino C and Durand D M 2001 Suppression of epileptiform activity by high frequency sinusoidal fields in rat hippocampal slices *J.Physiol.* **531** 181-191
[54] Dostrovsky J O, Levy R, Wu J P, Hutchison W D, Tasker RR and Lozano AM 2000
Microstimulation-induced inhibition of neuronal firing in human globus pallidus 
*J. Neurophysiol.* **84** 570-574

[55] Lian J, Bikson M, Sciortino C, Stacey W C and Durand D M 2003 Local suppression of 
epileptiform activity by electrical stimulation in rat hippocampus in vitro *J. Physiol.* **547** 427–434

[56] McIntyre C C, Grill W M, Sherman D L and Thakor N V 2004 Deep brain stimulation of 
thalamocortical relay neurons: model-based analysis of activation and inhibition *J 
Neurophysiol.*

[57] Anderson M E, Postupna N and Ruffo M 2003 Effects of high-frequency stimulation in the 
internal globus pallidus on the activity of thalamic neurons in the awake monkey *J. Neurophysiol.* **89** 1150-60

[58] Windels F, Bruet N, Poupard A, Feuerstein C, Bertrand A and Savasta M 2003 Influence of the 
frequency parameter on extracellular glutamate and gamma-aminobutyric acid in substantia 
nigra and globus pallidus during electrical stimulation of subthalamic nucleus in rats *J. 
Neurosci Res.* **2** 259-267

[59] Bergman H, Feingold A, Nini A, Raz A, Slovin H, Abeles M and Vaadia E 1998 Physiological 
aspects of information processing in the basal ganglia of normal and parkinsonian primates *Trends Neurosci* **21** 32–38

[60] Deuschl G, Raethjen J, Lindemann M and Krack P 2001 The pathophysiology of tremor *Muscle Nerv.* **24** 716-735.

[61] Vitek J L and Giroux M 2000 Physiology of hypokinetic and hyperkinetic movement disorders: 
model for dyskinesia *Ann Neurol.* **47**(suppl 1) 131-140

[62] Vitek J L 2002 Mechanisms of deep brain stimulation: excitation or inhibition *Mov Disord.* **17**(suppl 3) 69-72

[63] Nini A. et al. 1995 Neurons in the globus pallidus do not show correlated activity in the normal 
monkey, but phase-locked oscillations appear in the MPTP model of parkinsonism *J. 
Neurophysiol.* **74** 1800-05

[64] Brown P. et al. 2001 Dopamine dependency of oscillations between subthalamic nucleus and 
pallidum in Parkinson’s disease *J. Neurosci.* **21** 1033-38

[65] Levy R et al. 2002 Synchronized neuronal discharge in the basal ganglia of parkinsonian 
patients is limited to oscillatory activity *J. Neurosci.* **22** 2855-61

[66] Williams D et al. 2002 Dopamine-dependent changes in the functional connectivity between 
basal ganglia and cerebral cortex in humans *Brain* **125** 1558-69

[67] McIntyre C and Grill W M 2002 Extracellular stimulation of central neurons: influence of 
stimulus waveform and frequency on neuronal output *J. Neurophysiol.* **88** 1592–1604

[68] Brown P et al. 2004 Effects of stimulation of the subthalamic area on oscillatory pallidal 
activity in Parkinson’s disease *Exp. Neurol.* **188** 480–490