ELSEVIER

Clinical Neurophysiology 115 (2004) 1239–1248

www.elsevier.com/locate/clinph

Invited review

Uncovering the mechanism(s) of action of deep brain stimulation: activation, inhibition, or both

Cameron C. McIntyre[a], Marc Savasta[b], Lydia Kerkerian-Le Goff[c], Jerrold L. Vitek[a,*]

[a]*Department of Neurology, Emory University School of Medicine, Woodruff Memorial Research Building, Suite 6000, 1639 Pierce Drive, Atlanta, GA 30322, USA*

[b]*Neurochimie et Neuroplastisté Fonctionnelles, INSERM U318, Université Joseph Fourier, CHU de Grenoble, Departement de Neurologie, BP 217, 38043 Grenoble Cedex 9, France*

[c]*Laboratoire de Neurobiologie Cellulaire et Fonctionnelle, CNRS, 31 Chemin Joseph Aiguier, 13402 Marseille Cedex 20, France*

Accepted 20 December 2003

Abstract

High-frequency deep brain stimulation (DBS) of the thalamus or basal ganglia represents an effective clinical technique for the treatment of several medically refractory movement disorders. However, understanding of the mechanisms responsible for the therapeutic action of DBS remains elusive. 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. Four general hypotheses have been developed to explain the mechanism(s) of DBS: depolarization blockade, synaptic inhibition, synaptic depression, and stimulation-induced modulation of pathological network activity. Using the results from functional imaging, neurochemistry, neural recording, and neural modeling experiments we address the general hypotheses and attempt to reconcile what have been considered conflicting results from these different research modalities. Our analysis suggests stimulation-induced modulation of pathological network activity represents the most likely mechanism of DBS; however, several open questions remain to explicitly link the effects of DBS with therapeutic outcomes.

Keywords: Movement disorder; Parkinson's disease; Essential tremor; Dystonia; High-frequency stimulation; Thalamus; Basal ganglia

1. Introduction

The modern era of deep brain stimulation (DBS) began in the late 1980s with the pioneering work of Benabid and colleagues at the University of Grenoble, France (Benabid et al., 1987, 1991). Their realization that chronic high-frequency stimulation (HFS) results in clinical benefits analogous to those achieved by surgical lesioning transformed the use of functional neurosurgery for the treatment of movement disorders (Gross and Lozano, 2000). Thalamic DBS for intractable tremor has virtually replaced ablative lesions of the thalamus (Benabid et al., 1996). Moreover, 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) (resting tremor, rigidity, bradykinesia) (Obeso et al., 2001). In addition, multiple pilot studies have begun to examine the utility of DBS for dystonia (Coubes et al., 2000; Yianni et al., 2003), epilepsy (Hodaie et al., 2002), and obsessive-compulsive disorder (OCD) (Gabriels et al., 2003).

The general therapeutic stimulation parameters for DBS (monopolar cathodic; 1–5 V stimulus amplitude; 60–200 μs stimulus pulse duration; 120–180 Hz stimulus frequency) have been derived primarily by trial and error (Rizzone et al., 2001; Moro et al., 2002; Volkmann et al., 2002; O'Suilleabhain et al., 2003). This trial and error selection of the stimulation parameters has been effective because of the near immediate effects of DBS on the control of tremor and parkinsonian motor symptoms. However, new therapies utilizing DBS technology will not allow such ease of titration. The beneficial effects of stimulation can take weeks to months to manifest in dystonia and OCD, and it is unclear what stimulation amplitudes, pulse durations, and frequencies are most effective for these new therapeutic directions. Therefore, future advances in DBS technology

* Corresponding author. Tel.: +1-404-727-7177; fax: +1-404-712-8576.
E-mail address: jvitek@emory.edu (J.L. Vitek).

1388-2457/$30.00
doi:10.1016/j.clinph.2003.12.024

are dependent on addressing fundamental questions on the therapeutic mechanism(s) of action (Montgomery and Baker, 2000; Dostrovsky and Lozano, 2002; Vitek, 2002; McIntyre and Thakor, 2002).

Four general modalities: neural modeling, neural recording, neurochemistry, and functional imaging, have been employed to address the effects of DBS within the central nervous system. Neural modeling experiments have been conducted to address action potential generation directly resulting from the stimulation (Grill and McIntyre, 2001; McIntyre et al., in press). Neural recording experiments have been conducted during and after HFS to address changes in neuronal activity (Dostrovsky and Lozano, 2002; Anderson et al., 2003; Hashimoto et al., 2003). Microdialysis experiments have been conducted to address changes in neurotransmitter levels (Bruet et al., 2001; Windels et al., 2000, 2003), and in situ hybridization histochemistry has been used to address changes in gene expression induced by HFS (Salin et al., 2002). Functional imaging experiments have been conducted to address the effects of DBS from a systems level perspective by examining changes in cortical activity induced by the stimulation (Zonenshayn et al., 2000). When considered individually the results from these different modalities have suggested mechanisms of action for DBS that would appear mutually exclusive (Vitek, 2002). However, when results from each modality are considered together a more complete understanding of the effects of DBS can be developed, with each line of study providing an integral piece of the puzzle.

Understanding the effects of DBS presents investigators with a paradox of how stimulation (traditionally thought to activate neurons) can result in similar therapeutic outcomes as lesioning target structures in the thalamus or basal ganglia. In turn, there exist two strongly debated general philosophies on the effects of DBS: (1) DBS generates a functional ablation by suppressing or inhibiting the stimulated nucleus or (2) DBS results in activation of the stimulated nucleus that is transmitted throughout the network. Based on these fundamental philosophies, 4 general hypotheses have been developed to explain the mechanisms of DBS. (1) Stimulation induced alterations in the activation of voltage-gated currents that block neural output near the stimulating electrode (Depolarization Blockade) (Beurrier et al., 2001). (2) Indirect regulation of neuronal output via activation of axon terminals that make synaptic connections with neurons near the stimulating electrode (synaptic inhibition) (Dostrovsky et al., 2000). (3) Synaptic transmission failure of the efferent output of stimulated neurons as a result of transmitter depletion (synaptic depression) (Urbano et al., 2002). (4) Stimulation-induced modulation of pathological network activity (Montgomery and Baker, 2000). While the therapeutic mechanisms that underlie DBS most likely represent a combination of several phenomena (Benabid et al., 2002; Vitek, 2002), the goal of this review is to address which of these general hypotheses best explains the available data from functional imaging, neurochemistry, neural recording, and neural modeling experiments.

2. Effects of DBS as revealed by neural modeling

Limitations in experimental techniques and the complex response of neurons to extracellular stimulation, has hampered our understanding of the effects of DBS. The use of multi-compartment cable models of neurons coupled to extracellular electric fields has provided the opportunity to study the effects of stimulation on neural activity in a highly controlled environment. The foundational principals of modeling extracellular stimulation date back to McNeal (1976) and have been used extensively in the study of peripheral nerve stimulation (Rattay and Aberham, 1993). More recently, investigations have addressed the biophysical mechanisms of action potential initiation (API) during extracellular stimulation within the central nervous system, as well as the effects of changes in stimulus parameters on activation patterns (Rattay, 1999; McIntyre and Grill, 1999, 2000, 2002; Grill and McIntyre, 2001; McIntyre et al., in press).

To examine the effects of DBS, McIntyre et al. (in press) combined a finite element model of the electric field generated by a DBS electrode and a multi-compartment cable model of a thalamocortical (TC) relay neuron (Fig. 1A). When stimulating with extracellular electrodes it is possible to elicit both direct and indirect effects on local cells. The direct effects occur as a result of the field application to the neural membrane and result in regions of depolarization and hyperpolarization along each neural process (Rattay, 1986; McIntyre and Grill, 1999). The indirect effects occur as a result of activation of afferent inputs from the extracellular stimulus and their subsequent synaptic action on local cells. Experimental and modeling results have shown that afferent inputs have a low threshold for activation during extracellular stimulation (Baldissera et al., 1972; Jankowska et al., 1975; Gustafsson and Jankowska, 1976; Dostrovsky et al., 2000; McIntyre and Grill, 2002). Therefore, the response of the TC relay neuron was determined with a distribution of inhibitory and excitatory synaptic conductances on the dendrites that were activated in response to each stimulus in the train (McIntyre et al., in press).

Fig. 1 shows examples of the somatic and axonal firing of TC relay neurons (tonic activity level of 33 Hz) before, during and after a 500 ms train of 'therapeutic stimulation' (3 V cathodic stimuli, 0.1 ms in duration at 150 Hz). The stimuli were supra-threshold for activation of the white neuron 1.5 mm from the electrode generating axonal output in a one-to-one ratio with the stimulus frequency while the cell body showed suppression of activity (Fig. 1A). The stimuli were sub-threshold for generation of efferent output in the black neuron 2 mm from the electrode, and resulted in suppression of the tonic activity during the stimulus train in both the soma and axon (Fig. 1A). In both

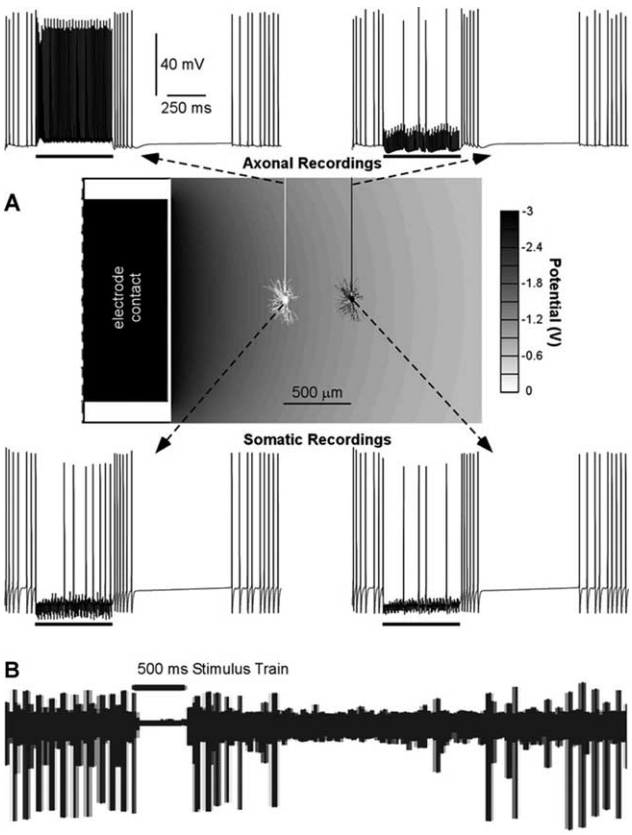

Fig. 1. Effects of DBS on model thalamocortical (TC) relay neurons. (A) Neuron models drawn to scale and superimposed on the potential distribution generated by the electrode model. Somatic and axonal recordings of two tonically active TC relay neurons before, during and after a 500 ms train of −3 V, 0.1 ms stimuli at 150 Hz (designated with black bars). The stimulus was supra-threshold for direct activation of the white neuron (1.5 mm from the electrode center), but sub-threshold for direct activation of the black neuron (2 mm from the electrode center). Both neurons received stimulation induced trans-synaptic inputs during the stimulus train. (B) Human intra-operative recording of a thalamic neuron before and after microstimulation (5 μA, 0.15 ms stimuli at 100 Hz) through the recording electrode (Dostrovsky and Lozano, 2002). Modified from McIntyre et al. (in press).

cases, stimulation induced trans-synaptic inputs were applied that resulted in a cascade of activity patterns following termination of the stimulus train. First there was a rebound of activity, followed by a period of quiescence (~650 ms), followed by a return to 33 Hz firing. Recent experimental recordings in humans have shown a very similar response in thalamic neurons following cessation of short duration high-frequency stimulus trains (Dostrovsky et al., 2002; Dostrovsky and Lozano, 2002) (Fig. 1B).

These results show that DBS generates a complex pattern of activation and inhibition in the local cells that surround the electrode. The model predicts that the activity recorded in the cell body is not necessarily representative of the spiking output generated in the axon, and the efferent output of local cells to DBS is dependent on the positioning of the neuron with respect to the electrode. Our preliminary results also suggest that the response of local cells to HFS is relatively independent of the neuron type (i.e. TC relay neurons, STN or GPi projection neurons, or motoneurons) (McIntyre, unpublished observations). In turn, the modeling data suggest that the majority of local cells within ~2 mm of the electrode will generate efferent output at the stimulus frequency when using therapeutic stimulation parameters (McIntyre et al., in press). However, neurons sub-threshold for direct excitation will exhibit suppression of their intrinsic firing patterns regulated by stimulation induced trans-synaptic inputs.

3. Effects of DBS as revealed by neural recording

Due to the phenomenological similarity between the effects of DBS and lesioning, it appears logical to assume that DBS inactivates the structures being stimulated. However, the neural recording literature on the effects of DBS fall into two contradictory sets with one indicating that DBS inhibits the stimulated nucleus and the other indicating that DBS excites the stimulated nucleus. In vivo neural recordings made in the stimulated nucleus show decreased activity during and after HFS (Benazzouz et al., 1995, 2000; Boraud et al., 1996; Dostrovsky et al., 2000; Wu et al., 2001; Tai et al., 2003). In vitro examinations of the effects of HFS show a frequency dependent suppression of activity that coincides with the frequency dependent therapeutic response of DBS (Beurrier et al., 2001; Kiss et al., 2002; Magarinos-Ascone et al., 2002; Garcia et al., 2003). However, based on the concept of de-coupled somatic and axonal firing of projection neurons during HFS, recordings from efferent target nuclei of the stimulated nucleus may provide the most pertinent neural recording data on the effects of DBS. In vivo recordings made in efferent nuclei indicate that the output of the stimulated nuclei is increased by DBS (Anderson et al., 2003; Hashimoto et al., 2003; Maurice et al., 2003).

The work of Hashimoto et al. (2003) addressed the effects of STN HFS on neuronal activity of the GPi and globus pallidus externus (GPe) in non-human primates rendered parkinsonian by the unilateral intracarotid administration of the neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP). Following MPTP treatment, the monkeys developed a stable hemi-parkinsonian state characterized by contralateral rigidity and bradykinesia. A scaled down version of the clinical Medtronic DBS electrode was implanted in the STN and stimulation parameters were determined that provided the greatest therapeutic benefit.

Neuronal activity was recorded extracellularly from the GPe and GPi before, during and after therapeutic STN stimulation. Simultaneous stimulation in STN and single unit recording in GPi and/or GPe was accomplished using template subtraction of the stimulus artifact (Hashimoto et al., 2002). Peri-stimulus time histograms were constructed and mean discharge rates were determined. The results showed short-latency excitations at 2.5–4.5 ms and 5.5–7.0 ms after each stimulus pulse (Fig. 2). These short-latency

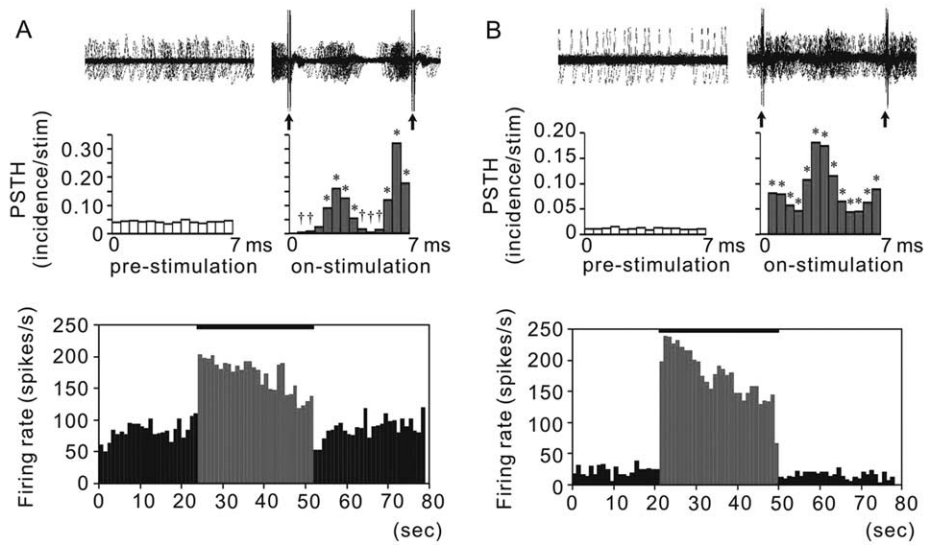

Fig. 2. Neural recordings during DBS. (A) Neuronal responses occurring during STN stimulation in a GPe cell. (B) Neuronal responses occurring during STN stimulation in a GPi cell. A signal overlay of 100 sweeps was made by triggering at 10 ms intervals in the pre-stimulation period and by triggering on the stimulation pulse in the on-stimulation period. Peri-stimulus time histograms (PSTH) were reconstructed from successive 7 ms time periods. The mean firing rate was calculated every 1 s based on the PSTH to illustrate the time course of the firing rate. Modified from Hashimoto et al. (2003).

responses were present with stimulation parameters effective for the alleviation of rigidity and akinesia (bipolar stimulation; 3 V; 136 Hz), and resulted in a significant increase in the mean discharge rate and the development of a more regular pattern of neuronal activity (Hashimoto et al., 2003).

The experimental setting of Hashimoto et al. (2003) closely reproduced the DBS system used in humans. Their results demonstrate that stimulation of the glutamatergic STN output produces short-latency excitatory responses that tonically increased the average firing rate and altered the pattern of neuronal activity in both GPi and GPe. In addition, the recent results of Anderson et al. (2003), who stimulated in the GPi and recorded in thalamus of non-human primates, also found results consistent with activation of the GABAergic GPi output. Their results showed a reduction in thalamic discharge frequency during GPi HFS in 77% of the responsive thalamic cells. Taken together, these data support the hypothesis that DBS increases the output of the stimulated nucleus, which directly effects neuronal activity in output nuclei.

4. Effects of DBS as revealed by microdialysis and changes in gene expression

In vivo microdialysis and in situ hybridization histochemistry have recently been employed to investigate the cellular and molecular effects of DBS. High-frequency stimulation of the STN of rats with or without 6-hydroxydopamine-induced lesion of nigral dopamine (DA) neurons has been used to quantify changes in the DA, glutamatergic, and GABAergic systems of the basal ganglia. STN HFS has been reported to increase striatal DA release and metabolism in intact rats and in rats with partial lesion of nigral DA neurons (Bruet et al., 2001; Meissner et al., 2002, 2003) (Fig. 3). However, positron emission tomography (PET)

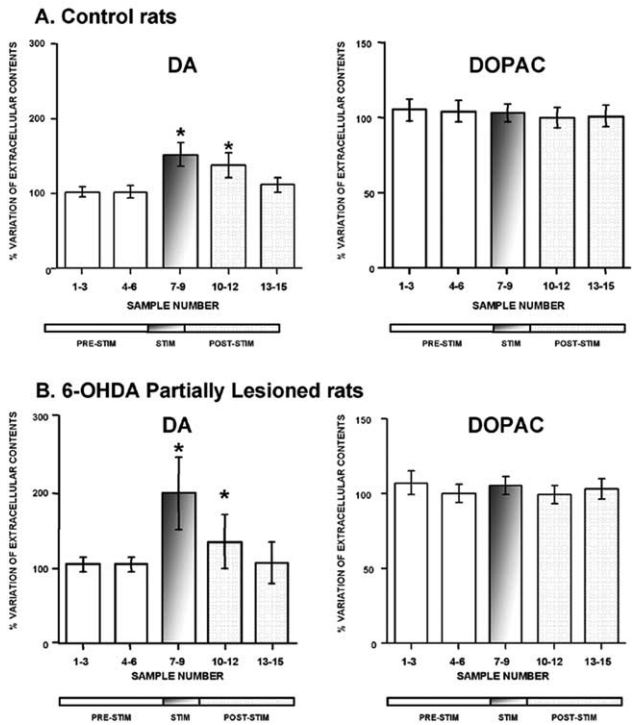

Fig. 3. Extracellular DA and DOPAC collected in striatum ipsilaterally to stimulation in control (A) or in 6-OHDA partially lesioned rats (B). Dialysate fractions were collected at 20 min intervals. Each bar represents the mean of 3 successive dialysates ± SEM expressed in percentage and calculated from 12 control rats or 6 hemiparkinsonian rats. The fractions of the pre-stimulation period were collected to ascertain basal values. $^{*}P < 0.05$, $^{**}P < 0.01$. Modified from Bruet et al. (2001).

studies of the D2/D3 ligand raclopride did not provide evidence for increased striatal DA concentration under effective DBS in patients with advanced PD (Hilker et al., 2003). Therefore, modulation of dopaminergic activity may not be a main mechanism of STN HFS action on parkinsonian symptoms, at least in the later stages of the disease when the number of intact DA neurons is presumably too small to provide a clinically relevant increase in striatal DA.

Dopamine denervation-mediated changes in the basal ganglia include increased activity in STN, SNr, and GPi (or rat EP) combined with decreased activity in GPe (or rat GP). STN HFS applied for 2 h in freely moving rats with prior extensive DA denervation antagonized the DA lesion-induced increase in SNr and EP activity as revealed by GAD67 mRNA levels (Salin et al., 2002) (Fig. 4). These effects can be compared to previous data showing that PD patients with subthalamotomy present a significant decrease in glucose metabolism in SNr and GPi (Su et al., 2001) and that STN lesion in experimental rat and primate models of PD prevent changes in markers of neuronal activity in these structures (Guridi et al., 1996; Delfs et al., 1995). Coupled with the reduced gene expression of cytochrome oxidase subunit I (marker of neuronal metabolic activity) in the STN after STN HFS (Salin et al., 2002), this suggests that STN lesion and STN HFS have similar effects.

However, several lines of evidence suggest the comparison between STN lesion and STN HFS is not especially clear. First, STN HFS did not counteract the DA lesion-mediated change in GAD67 gene expression in the GP (Salin et al., 2002), a main target of STN projections. Second, microdialysis studies have shown that STN HFS in intact rats increases extracellular glutamate levels in both SNr and GP (Windels et al., 2000) (Fig. 5). These results support the hypothesis that STN HFS increases STN glutamatergic outflow, in compliance with the above neural modeling (Fig. 1) and neural recording (Fig. 2) results. However, it should be noted that the primary source of extracellular glutamate is non-vesicular glutamate release from cystine-glutamate antiporter (Baker et al., 2002), so the actual contribution of synaptic release glutamate on the effects of

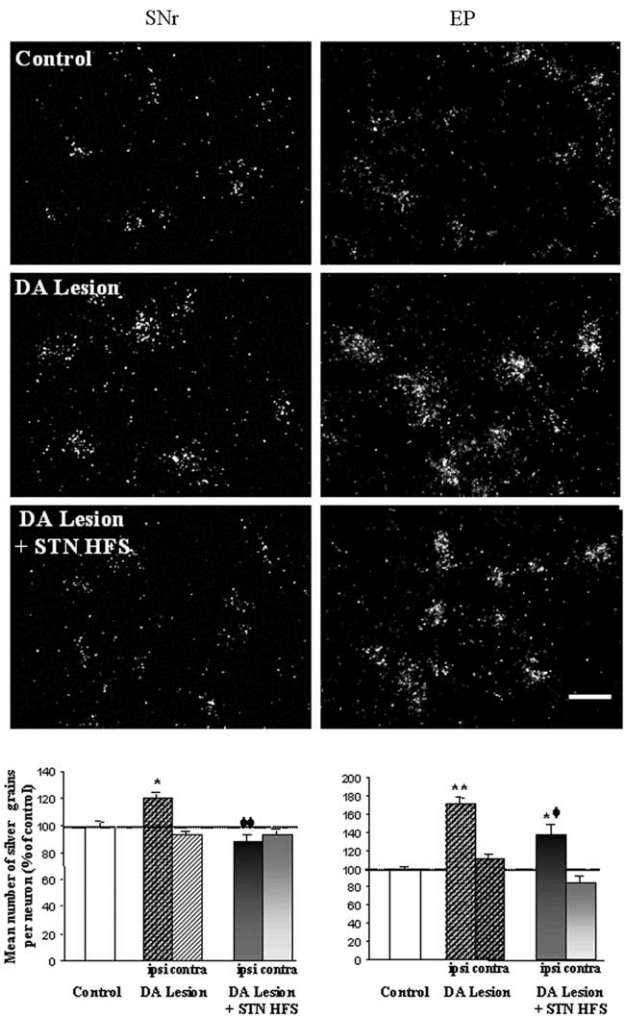

Fig. 4. Dark-field photomicrographs and quantitative analysis showing the effects of high-frequency stimulation of the subthalamic nucleus on the increase in GAD67 mRNA expression induced by 6-hydroxydopamine lesion of nigral dopamine neuron in the substantia nigra pars reticulata (SNr) and entopeduncular nucleus (EP). The photomicrographs concern the side ipsilateral to surgery. Scale bar: 50 μm. Modified from Salin et al. (2002).

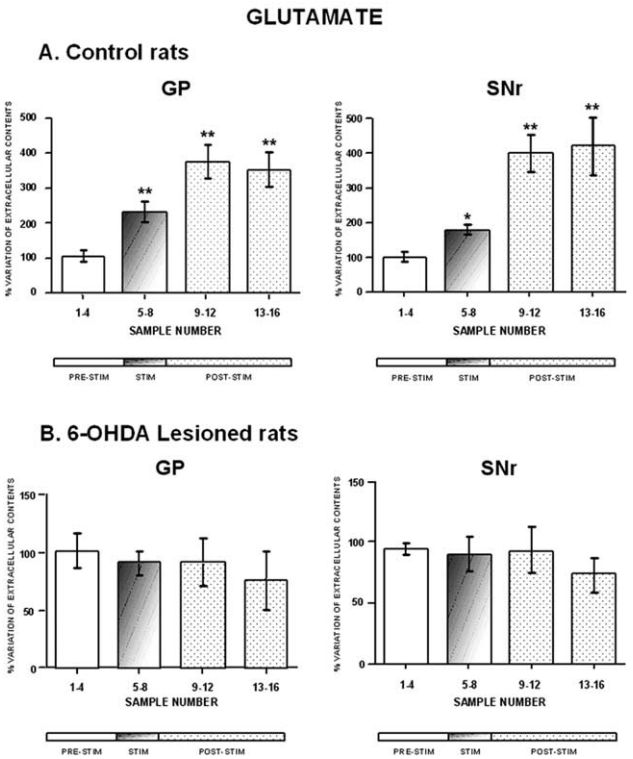

Fig. 5. Extracellular glutamate collected in GP and SNr ipsilaterally to stimulation in control (A) or in 6-OHDA totally lesioned rats (B). Dialysate fractions were collected at 15 min intervals. Each bar represents the mean of 4 successive dialysates ± SEM expressed in percentage and calculated from 12 control rats or 6 hemiparkinsonian rats. The fractions of the pre-stimulation period were collected to ascertain basal values. $^{*}P < 0.05$, $^{**}P < 0.01$. Modified from Windels et al. (2000).

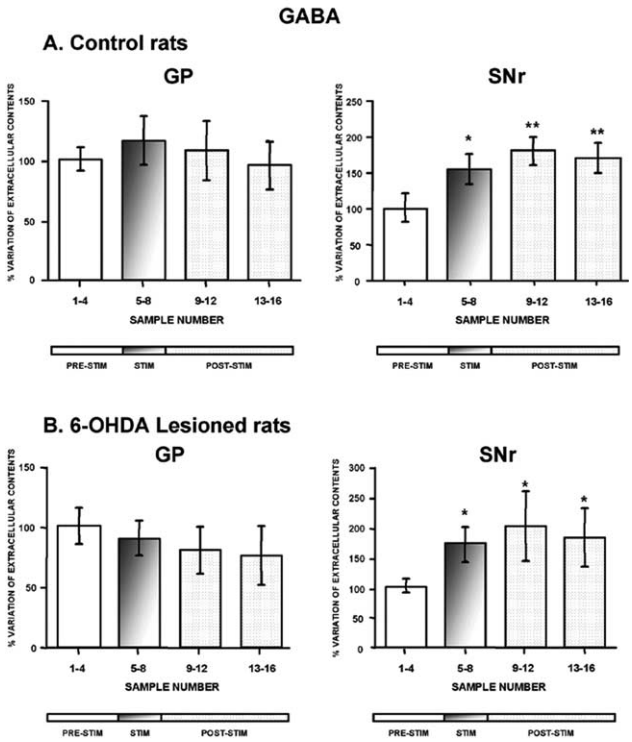

Fig. 6. Extracellular GABA collected in GP and SNr ipsilaterally to stimulation in control (A) or in 6-OHDA totally lesioned rats (B). Dialysate fractions were collected at 15 min intervals. Each bar represents the mean of 4 successive dialysates ± SEM expressed in percentage and calculated from 12 control rats or 6 hemiparkinsonian rats. The fractions of the pre-stimulation period were collected to ascertain basal values. $*P < 0.05$, $**P < 0.01$. Modified from Windels et al. (2000).

STN HFS remains to be determined. Third, contrary to STN HFS, an STN lesion dramatically decreases extracellular glutamate (Savasta, unpublished observation). Finally, evidence has been provided that STN HFS does not significantly modify the DA lesion-induced increase in extracellular glutamate levels in both SNr and GP, but resulted in significantly increased GABA levels in the SNr selectively (Windels et al., 2000; Savasta et al., 2002) (Fig. 6).

Recent microdialysis studies suggest the primary effects of STN HFS may be related to the selective increase in extracellular GABA levels rather than to glutamate-mediated mechanisms. Lesioning the GP, which markedly reduces extracellular GABA levels in SNr, suppressed stimulation-evoked increases in GABA in both intact and dopamine-depleted rats (Windels et al., 2002). These data can be compared to the electrophysiological finding that STN HFS increases the mean firing rate of GP neurons in the rat (Benazzouz et al., 1995) and GPe neurons in the monkey (Hashimoto et al., 2003). Windels et al. (2003) reported that changes in extracellular glutamate and GABA occur at frequencies above 60 Hz, corresponding to the frequency range for therapeutic benefit in Parkinson's patients (Moro et al., 2002). The increase in extracellular GABA in SNr was proportional to stimulus frequency from 60 to 350 Hz. However, such a frequency response curve cannot solely be explained by the increase of glutamate in GP activating the inhibitory pallidonigral pathway because the glutamate increase was maximal at 130 Hz. These results suggest that the increasing effect on extracellular GABA in SNr was also due to an increasing recruitment of GABAergic fibers that run in close proximity to the STN. Thus, the effectiveness of DBS may be dependent, in part, on activation of GABAergic tracts close to STN. In summary, the neurochemistry studies on the effects of STN HFS suggest a complex cascade of events throughout the entire basal ganglia network, many of which are not consistent with results generated by an STN lesion.

5. Effects of DBS as revealed by functional imaging

DBS is ideally suited to functional imaging because it generates consistent and controllable stimulation of the brain that yields reproducible clinical effects. Over the last 10 years there have been several DBS-related PET studies, and more recently functional magnetic resonance imaging (fMRI) has also been employed (Zonenshayn et al., 2000; Jech et al., 2001). The great benefit of functional imaging is that data can be obtained from essentially the entire brain simultaneously, thus providing a means for measuring system level responses to changes in the experiment. Advances in our understanding of the physiological basis for fMRI and PET signals (Logothetis et al., 2001) present the opportunity to critically address changes in neural activity of DBS patients with and without stimulation.

There exists a long list of functional imaging studies that have addressed the effects of DBS (see comprehensive reviews by Zonenshayn et al., 2000; Carbon and Eidelberg, 2002; Ceballos-Baumann, 2003). However, 3 studies on the effects of thalamic DBS in patients with essential tremor (ET) have generated similar results and provide a fundamental first step in understanding the network effects induced by DBS (Rezai et al., 1999; Ceballos-Baumann et al., 2001; Perlmutter et al., 2002). Studying patients with ET provides a standard control, as motor activity is identical in the resting state with stimulation on or off. Therefore, this experimental paradigm avoids interfering effects of rest tremor in interpreting the hemodynamic changes that occur with/without therapeutic stimulation. Each study found increased cortical activity with the patient at rest during application of therapeutic stimulation parameters, consistent with activation of thalamic efferents during DBS. The fMRI study of Rezai et al. (1999) found activation of thalamus, basal ganglia, and somatosensory cortex. The PET study of Ceballos-Baumann et al. (2001) found increases in motor cortex and decreases in vestibular cortex, and the PET study of Perlmutter et al. (2002) found activation of thalamus and supplementary motor area. In agreement with the above neural modeling, neural recording, and neurochemical data these functional imaging studies suggest that DBS does not

simply block the stimulated nucleus, but instead generates efferent output that is transmitted to non-stimulated nuclei.

6. DBS mechanisms of action

Presently, there exist 4 general hypotheses to explain the therapeutic mechanism(s) of DBS: Depolarization blockade (Beurrier et al., 2001); Synaptic inhibition (Dostrovsky et al., 2000); Synaptic depression (Urbano et al., 2002); and Stimulation-induced disruption of pathological network activity (Montgomery and Baker, 2000). Depolarization blockade and synaptic inhibition represent attractive hypotheses to explain the similarity between the therapeutic benefit of ablation and DBS for the treatment of movement disorders. Recordings representative of somatic activity in the stimulated nucleus support both of these hypotheses (Benazzouz et al., 1995, 2000; Boraud et al., 1996; Dostrovsky et al., 2000; Bikson et al., 2001; Beurrier et al., 2001; Kiss et al., 2002; Magarinos-Ascone et al., 2002; Lian et al., 2003). However, the limitation of the depolarization blockade or synaptic inhibition hypotheses is that they do not take into account the possible independent activation of the efferent axon of projection neurons. Theoretical results show suppression of somatic activity but high-frequency axonal output during DBS of projection neurons (McIntyre et al., in press). Strength-duration results suggest DBS mainly acts upon axonal elements (Holsheimer et al., 2000a,b; Kiss et al., 2003). And, in vivo experimental recordings in efferent nuclei show high-frequency inputs during DBS (Anderson et al., 2003; Hashimoto et al., 2003). Therefore, while synaptic inhibition and/or depolarization blockade may play a role in the suppression of somatic activity, the functional output of projection neurons during DBS does not appear to be primarily mediated by these phenomena.

The concept of de-coupled somatic and axonal activity during HFS provides a resolution to conflicting neural recording results and is supported by two fundamental effects of extracellular stimulation. First, action potential initiation from extracellular stimulation occurs in the axon (Nowak and Bullier, 1998a,b; McIntyre and Grill, 1999). In general, cathodic stimuli generate membrane depolarization in regions near the electrode and membrane hyperpolarization in regions that flank the region of depolarization. However, because of the 3D branching and termination patterns of the dendritic arbor, soma-dendritic complexes near the electrode exhibit both depolarization and hyperpolarization (McIntyre et al., in press). Depending on the neuron's orientation and positioning with respect to the electrode, it is common for the cell body to be directly hyperpolarized by the stimulus pulse. However, the first few nodes of Ranvier are typically depolarized by the stimulus pulse because of the short internodal spacing of the axon compared to the spatial distribution of field generated by DBS electrodes (McIntyre et al., in press). In turn, action potential initiation occurs in the axon. The second effect of extracellular stimulation that supports the de-coupling of activity in the axon and cell body during HFS is the activation of trans-synaptic inputs. The threshold for activation of axonal terminals (or afferent inputs) projecting to the region around the electrode is lower than the threshold for direct activation of local cells. Summation of an overall inhibitory synaptic effect on the cell body can suppress somatic firing (Dostrovsky et al., 2000). However, because action potential initiation occurs in the axon, the efferent output of neurons supra-threshold for direct activation by the applied field are relatively unaffected by the trans-synaptic inhibition.

How then can stimulation that results in efferent output of neurons around the electrode mimic the therapeutic effects of ablation? One possibility is that neurons activated by the stimulus train are unable to sustain high-frequency action on

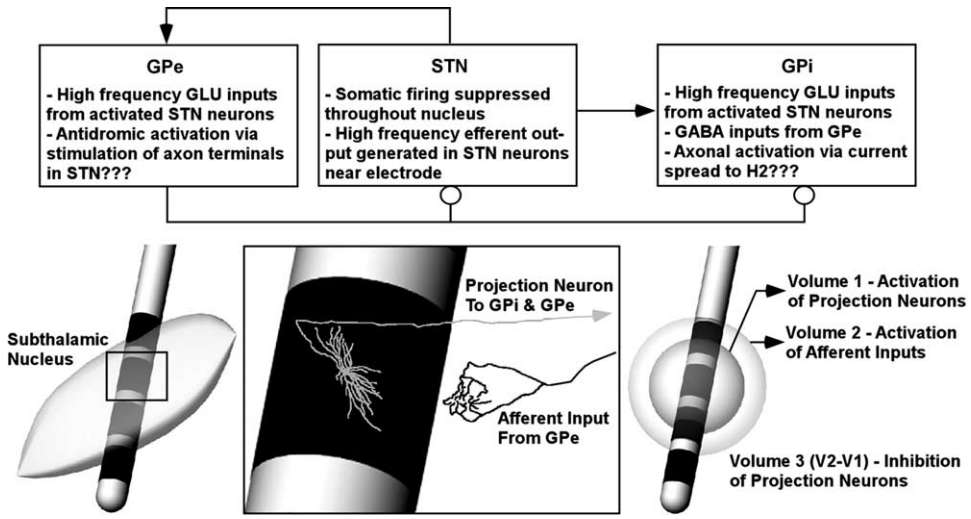

Fig. 7. Hypothetical summary of the effects of STN DBS. See text for details. (Top) network summary of stimulation effects induced in the subthalamic nucleus (STN), external segment of the globus pallidus (GPe), and the internal segment of the globus pallidus (GPi). This list is highly simplified and not exhaustive of present knowledge. (Bottom) pictorial summary of the stimulation effects generated in STN.

efferent targets due to depletion of neurotransmitter (Synaptic Depression) (Wang and Kaczmarek, 1998; Zucker and Regehr, 2002; Urbano et al., 2002). However, several in vivo experimental studies have shown increases in transmitter release and sustained changes in firing of neurons in efferent nuclei consistent with activation of neurons around the electrode and subsequent synaptic action on their target during HFS (Windels et al., 2000, 2003; Anderson et al., 2003; Hashimoto et al., 2003). Therefore, the only general hypothesis on the mechanisms of DBS that is consistent with all of the available data on the effects of DBS is stimulation-induced modulation of pathological network activity.

Fig. 7 shows a hypothetical summary of the effects of STN DBS. Within STN there exist two general volumes of activation induced by the applied field. The smaller volume 1 represents the activation of projection neurons. The larger volume 2 represents the activation of afferent inputs. The difference of these two volumes represents a volume of projection neurons, subthreshold for direct activation by the applied field, suppressed by the stimulation induced trans-synaptic inputs. However, most projection neurons within volume 2 will exhibit suppression of somatic firing independent of their efferent output. As a result of STN stimulation GPe and GPi will receive high-frequency glutamatergic inputs. It is also possible that a large number of GPe neurons will be antidromically activated via stimulation of their afferent inputs in STN. In addition, spread of the stimulation to the lenticular fasciculus (H2) and activation of GPi axons would be likely with electrodes in the dorsal STN. In turn, STN DBS should generate network wide changes in neural activity. However, while DBS may override pathological activity patterns, the activity patterns induced by DBS are not normal. Therefore, it remains an open question to link the effects of DBS with explicit therapeutic mechanisms. Nonetheless, while ablation and DBS result in similar therapeutic outcomes, it is likely that they achieve their results via different mechanisms.

Acknowledgements

This work was supported by grants from the National Institute of Health (NS-37019), Institut National de la Santé et de la Recherche Médicale, Centre National de la Recherche Scientifique, European Community (Grant No. QLK6-1999-02173, Fifth Programme Cadre de Recherche et de Développement Technologique) and a post-doctoral fellowship supported by the Medtronic Corporation.

References

Anderson ME, Postupna N, Ruffo M. Effects of high-frequency stimulation in the internal globus pallidus on the activity of thalamic neurons in the awake monkey. J Neurophysiol 2003;89:1150–60.

Baker DA, Xi ZX, Shen H, Swanson CJ, Kalivas PW. The origin and neuronal function of in vivo nonsynaptic glutamate. J Neurosci 2002; 22:9134–41.

Baldissera F, Lundberg A, Udo M. Stimulation of pre- and postsynaptic elements in the red nucleus. Exp Brain Res 1972;15:151–67.

Benabid AL, Pollak P, Louveau A, Henry S, de Rougemont J. Combined (thalamotomy and stimulation) stereotactic surgery of the VIM thalamic nucleus for bilateral Parkinson disease. Appl Neurophysiol 1987;50:344–6.

Benabid AL, Pollak P, Gervason C, Hoffmann D, Gao DM, Hommel M, Perret JE, de Rougemont J. Long-term suppression of tremor by chronic stimulation of the ventral intermediate thalamic nucleus. Lancet 1991; 337:403–6.

Benabid AL, Pollak P, Gao D, Hoffmann D, Limousin P, Gay E, Payen I, Benazzouz A. Chronic electrical stimulation of the ventralis intermedius nucleus of the thalamus as a treatment of movement disorders. J Neurosurg 1996;84:203–14.

Benabid AL, Benazzous A, Pollak P. Mechanisms of deep brain stimulation. Mov Disord 2002;17(Suppl 3):S73–4.

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

Benazzouz A, Gao DM, Ni ZG, Piallat B, Bouali-Benazzouz R, Benabid AL. 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 2000;99: 289–95.

Beurrier C, Bioulac B, Audin J, Hammond C. High-frequency stimulation produces a transient blockade of voltage-gated currents in subthalamic neurons. J Neurophysiol 2001;85:1351–6.

Bikson M, Lian J, Hahn PJ, Stacey WC, Sciortino C, Durand DM. Suppression of epileptiform activity by high-frequency sinusoidal fields in rat hippocampal slices. J Physiol 2001;531:181–91.

Boraud T, Bezard E, Bioulac B, Gross C. 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 1996;215:17–20.

Bruet N, Windels F, Bertrand A, Feuerstein C, Poupard A, Savasta M. 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 2001;60: 15–24.

Carbon M, Eidelberg D. Modulation of regional brain function by deep brain stimulation: studies with positron emission tomography. Curr Opin Neurol 2002;15:451–5.

Ceballos-Baumann AO. Functional imaging in Parkinson's disease: activation studies with PET, fMRI and SPECT. J Neurol 2003; 250(Suppl 1):15–23.

Ceballos-Baumann AO, Boecker H, Fogel W, Alesch F, Bartenstein P, Conrad B, Diederich N, von Falkenhayn I, Moringlane JR, Schwaiger M, Tronnier VM. Thalamic stimulation for essential tremor activates motor and deactivates vestibular cortex. Neurology 2001;56: 1347–54.

Coubes P, Roubertie A, Vayssiere N, Hemm S, Echenne B. Treatment of DYT1-generalised dystonia by stimulation of the internal globus pallidus. Lancet 2000;355:2220–1.

Delfs JM, Ciaramitaro VM, Parry TJ, Chesselet MF. Subthalamic nucleus lesions: widespread effects on changes in gene expression induced by nigrostriatal dopamine depletion in rats. J Neurosci 1995;15: 6562–75.

Dostrovsky JO, Lozano AM. Mechanisms of deep brain stimulation. Mov Disord 2002;17(Suppl 3):63–8.

Dostrovsky JO, Levy R, Wu JP, Hutchison WD, Tasker RR, Lozano AM. Microstimulation-induced inhibition of neuronal firing in human globus pallidus. J Neurophysiol 2000;84:570–4.

Dostrovsky JO, Patra S, Hutchison WD, Palter VN, Filali M, Lozano AM. Effects of stimulation in human thalamus on activity of nearby thalamic neurons. Soc Neurosci Abstr 2002;6214.

Gabriels LA, Cosyns PR, Meyerson BA, Andreewitch S, Sunaert SG, Maes AF, Dupont PJ, Gybels JM, Gielen F, Demeulemeester HG. Long-term electrical capsular stimulation in patients with obsessive-compulsive disorder. Neurosurgery 2003;52:1263–74.

Garcia L, Audin J, D'Alessandro G, Bioulac B, Hammond C. Dual effect of high-frequency stimulation on subthalamic neuron activity. J Neurosci 2003;23:8743–51.

Gross RE, Lozano AM. Advances in neurostimulation for movement disorders. Neurol Res 2000;22:247–58.

Grill WM, McIntyre CC. Extracellular excitation of central neurons: implications for the mechanisms of deep brain stimulation. Thalamus Rel Syst 2001;1:269–77.

Guridi J, Herrero MT, Luquin MR, Guillen J, Ruberg M, Laguna J, Vila M, Javoy-Agid F, Agid Y, Hirsch E, Obeso JA. Subthalamotomy in parkinsonian monkeys. Behavioural and biochemical analysis. Brain 1996;119:1717–27.

Gustafsson B, Jankowska E. Direct and indirect activation of nerve cells by electrical pulses applied extracellularly. J Physiol 1976;258:33–61.

Hashimoto T, Elder CM, Vitek JL. A template subtraction method for stimulus artifact removal in high-frequency deep brain stimulation. J Neurosci Methods 2002;113:181–6.

Hashimoto T, Elder CM, Okun MS, Patrick SK, Vitek JL. Stimulation of the subthalamic nucleus changes the firing pattern of pallidal neurons. J Neurosci 2003;23:1916–23.

Hilker R, Voges J, Ghaemi M, Lehrke R, Rudolf J, Koulousakis A, Herholz K, Wienhard K, Strum V, Heiss WD. Deep brain stimulation of the subthalamic nucleus does not increase the striatal dopamine concentration in parkinsonian humans. Mov Disord 2003;18:41–8.

Hodaie M, Wennberg RA, Dostrovsky JO, Lozano AM. Chronic anterior thalamus stimulation for intractable epilepsy. Epilepsia 2002;43: 603–8.

Holsheimer J, Demeulemeester H, Nuttin B, de Sutter P. Identification of the target neuronal elements in electrical deep brain stimulation. Eur J Neurosci 2000a;12:4573–7.

Holsheimer J, Dijkstra EA, Demeulemeester H, Nuttin B. Chronaxie calculated from current-duration and voltage-duration data. J Neurosci Methods 2000b;97:45–50.

Jankowska E, Padel Y, Tanaka R. The mode of activation of pyramidal tract cells by intracortical stimuli. J Physiol 1975;249:617–36.

Jech R, Urgosik D, Tintera J, Nebuzelsky A, Krasensky J, Liscak R, Roth J, Ruzicka E. Functional magnetic resonance imaging during deep brain stimulation: a pilot study in 4 patients with Parkinson's disease. Mov Disord 2001;16:1126–32.

Kiss ZH, Mooney DM, Renaud L, Hu B. Neuronal response to local electrical stimulation in rat thalamus: physiological implications for mechanisms of deep brain stimulation. Neuroscience 2002;113: 137–43.

Kiss ZH, Anderson T, Hansen T, Kirstein D, Suchowersky O, Hu B. Neural substrates of microstimulation-evoked tingling: a chronaxic study in human somatosensory thalamus. Eur J Neurosci 2003;18:728–32.

Lian J, Bikson M, Sciortino C, Stacey WC, Durand DM. Local suppression of epileptiform activity by electrical stimulation in rat hippocampus in vitro. J Physiol 2003;547:427–34.

Logothetis NK, Pauls J, Augath M, Trinath T, Oeltermann A. Neurophysiological investigation of the basis of the fMRI signal. Nature 2001; 412:150–7.

Magarinos-Ascone C, Pazo JH, Macadar O, Buno W. High-frequency stimulation of the subthalamic nucleus silences subthalamic neurons: a possible cellular mechanism in Parkinson's disease. Neuroscience 2002;115:1109–17.

Maurice N, Thierry AM, Glowinski J, Deniau JM. Spontaneous and evoked activity of substantia nigra pars reticulata neurons during high-frequency stimulation of the subthalamic nucleus. J Neurosci 2003;23:9929–36.

McIntyre CC, Grill WM. Excitation of central nervous system neurons by nonuniform electric fields. Biophys J 1999;76:878–88.

McIntyre CC, Grill WM. Selective microstimulation of central nervous system neurons. Ann Biomed Eng 2000;28:219–33.

McIntyre CC, Grill WM. Extracellular stimulation of central neurons: influence of stimulus waveform and frequency on neuronal output. J Neurophysiol 2002;88:1592–604.

McIntyre CC, Thakor NV. Uncovering the mechanisms of deep brain stimulation for Parkinson's disease through functional imaging, neural recording, and neural modeling. Crit Rev Biomed Eng 2002;30: 249–81.

McIntyre CC, Grill WM, Sherman DL, Thakor NV. Cellular effects of deep brain stimulation: model-based analysis of activation and inhibition. J Neurophysiol 2004;91:in press.

McNeal DR. Analysis of a model for excitation of myelinated nerve. IEEE Trans Biomed Eng 1976;23:329–37.

Meissner W, Harnack D, Paul G, Reum T, Sohr R, Morgenstern R, Kupsch A. Deep brain stimulation of subthalamic neurons increases striatal dopamine metabolism and induces contralateral circling in freely moving 6-hydroxydopamine-lesioned rats. Neurosci Lett 2002;328:105–8.

Meissner W, Harnack D, Reese R, Paul G, Reum T, Ansorge M, Kusserow H, Winter C, Morgenstern R, Kupsch A. High-frequency stimulation of the subthalamic nucleus enhances striatal dopamine release and metabolism in rats. J Neurochem 2003;85:601–9.

Montgomery EB, Baker KB. Mechanisms of deep brain stimulation and future technical developments. Neurol Res 2000;22:259–66.

Moro E, Esselink RJ, Xie J, Hommel M, Benabid AL, Pollak P. The impact on Parkinson's disease of electrical parameter settings in STN stimulation. Neurology 2002;59:706–13.

Nowak LG, Bullier J. Axons, but not cell bodies, are activated by electrical stimulation in cortical gray matter. I. Evidence from chronaxie measurements. Exp Brain Res 1998a;118:477–88.

Nowak LG, Bullier J. Axons, but not cell bodies, are activated by electrical stimulation in cortical gray matter. II. Evidence from selective inactivation of cell bodies and axon initial segments. Exp Brain Res 1998b;118:489–500.

O'Suilleabhain PE, Frawley W, Giller C, Dewey RB. Tremor response to polarity, voltage, pulsewidth and frequency of thalamic stimulation. Neurology 2003;60:786–90.

Obeso JA, Olanow CW, Rodriguez-Oroz MC, Krack P, Kumar R, Lang AE. Deep-brain stimulation of the subthalamic nucleus or the pars interna of the globus pallidus in Parkinson's disease. N Engl J Med 2001;345: 956–63.

Perlmutter JS, Mink JW, Bastian AJ, Zackowski K, Hershey T, Miyawaki E, Koller W, Videen TO. Blood flow responses to deep brain stimulation of thalamus. Neurology 2002;58:1388–94.

Rattay F. Analysis of models for external stimulation of axons. IEEE Trans Biomed Eng 1986;33:974–7.

Rattay F. The basic mechanism for the electrical stimulation of the nervous system. Neuroscience 1999;89:335–46.

Rattay F, Aberham M. Modeling axon membranes for functional electrical stimulation. IEEE Trans Biomed Eng 1993;40:1201–9.

Rezai AR, Lozano AM, Crawley AP, Joy ML, Davis KD, Kwan CL, Dostrovsky JO, Tasker RR, Mikulis DJ. Thalamic stimulation and functional magnetic resonance imaging: localization of cortical and subcortical activation with implanted electrodes. Technical note. J Neurosurg 1999;90:583–90.

Rizzone M, Lanotte M, Bergamasco B, Tavella A, Torre E, Faccani G, Melcarne A, Lopiano L. Deep brain stimulation of the subthalamic nucleus in Parkinson's disease: effects of variation in stimulation parameters. J Neurol Neurosurg Psychiatry 2001;71:215–9.

Salin P, Manrique C, Forni C, Kerkerian-Le Goff L. 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 2002;15:5137–48.

Savasta M, Windels F, Bruet N, Bertrand A, Poupard A. Neurochemical modifications induced by high-frequency stimulation of subthalamic

nucleus in rats. In: Nicholsson L, editor. The basal ganglia, VII. Kluwer; 2002. p. 581–90.

Su PC, Ma Y, Fukuda M, Mentis MJ, Tseng HM, Yen RF, Liu HM, Moeller JR, Eidelberg D. Metabolic changes following subthalamotomy for advanced Parkinson's disease. Ann Neurol 2001;50:514–20.

Tai CH, Boraud T, Bezard E, Bioulac B, Gross C, Benazzouz A. Electrophysiological and metabolic evidence that high-frequency stimulation of the subthalamic nucleus bridles neuronal activity in the subthalamic nucleus and the substantia nigra reticulata. FASEB J 2003;17:1820–30.

Urbano FJ, Leznik E, Llinas RR. Cortical activation patterns evoked by afferent axons stimuli at different frequencies: an in vitro voltage-sensitive dye imaging study. Thalamus Rel Syst 2002;1:371–8.

Vitek JL. Mechanisms of deep brain stimulation: excitation or inhibition. Mov Disord 2002;17(Suppl 3):69–72.

Volkmann J, Herzog J, Kopper F, Deuschl G. Introduction to the programming of deep brain stimulators. Mov Disord 2002; 17(Suppl 3):181–7.

Wang LY, Kaczmarek LK. High-frequency firing helps replenish the readily releasable pool of synaptic vesicles. Nature 1998;394:384–8.

Windels F, Bruet N, Poupard A, Urbain N, Chouvet G, Feuerstein C, Savasta M. 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 2000;12: 4141–6.

Windels F, Bruet N, Poupard A, Feuerstein C, Bertrand A, Savasta M. Possible role of GABA in the therapeutical efficacy of high-frequency stimulation of the subthalamic nucleus in Parkinson's disease: a microdialysis study in rats. Mov Disord 2002;17(Suppl 5):207.

Windels F, Bruet N, Poupard A, Feuerstein C, Bertrand A, Savasta M. 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 2003;72:259–67.

Wu YR, Levy R, Ashby P, Tasker RR, Dostrovsky JO. Does stimulation of the GPi control dyskinesia by activating inhibitory axons? Mov Disord 2001;16:208–16.

Yianni J, Bain P, Giladi N, Auca M, Gregory R, Joint C, Nandi D, Stein J, Scott R, Aziz T. Globus pallidus internus deep brain stimulation for dystonic conditions: a prospective audit. Mov Disord 2003;18:436–42.

Zonenshayn M, Mogilner AY, Rezai AR. Neurostimulation and functional brain imaging. Neurol Res 2000;22:318–25.

Zucker RS, Regehr WG. Short-term synaptic plasticity. Annu Rev Physiol 2002;64:355–405.