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Human Central Nervous System Circuits Examined in Patients with Parkinson's Disease Using the Electrodes Implanted for Deep Brain Stimulation

Joao Costa[1,2], Francesc Valldeoriola[2] and Josep Valls-Sole[2]
[1]Institute of Molecular Medicine, Lisbon Faculty of Medicine
[2]Neurology Department, Hospital Clínic, Centro de Investigación Biomédica en Red sobre
Enfermedades Neurodegenerativas (CIBERNED) and Institut d'Investigacio Biomedica
August Pi i Sunyer (IDIBAPS), Facultad de Medicina, Universitat de Barcelona
[1]Portugal
[2]Spain

1. Introduction

Epidural or subdural electrodes are often used in humans in order to identify eloquent structures by stimulation or recording. Neurosurgeons are able to use the motor maps gathered more than 50 years ago by Penfield and Jasper (1954) for delineation of the functions of non-lesioned cortical tissue. These and other contributions have been made during surgical procedures in humans by either applying direct cortical stimulation (Woolsey et al., 1979; Burke and Hicks, 1998) or recording from the spinal cord tracts after cortical or peripheral nerve stimulation (Burke and Hicks, 1998; Di Lazzaro et al., 2006). Peroperatory neurophysiological monitoring offers also great opportunities for learning from using neurophysiological techniques, at the same time as helping the surgeon to reach a better outcome (Rainov et al., 1997; Horikoshi et al., 2000; Deletis and Sala, 2008).

These procedures have not only helped to improve the surgical procedure but they have allowed the use of neurophysiological tests to expand our knowledge on human central nervous system circuitry and functional connectivity. Nowadays, stereotactically placed electrodes with therapeutic aims such as deep brain stimulation (DBS), offer the possibility to reach structures that could not be otherwise targeted in humans and investigate further physiological aspects of brain circuits. For these purposes, authors have used the DBS electrodes inserted either in the nucleus ventralis intermedius of the thalamus (Vim), the globus pallidus internus (GPi), the subthalamic nucleus (STN), the pedunculopontine nucleus (PPN) or others in which the results of research are still scarce (Weinberger et al., 2008; Galati et al., 2008; Shimamoto et al., 2010; Alessandro et al., 2010). The information brought by these studies has already shed some light on the functioning of some central nervous system circuits. However, many questions remain to be answered and further research on the subject is required to 1) understand fully the physiological mechanisms underlying the beneficial effects of chronic repetitive high frequency DBS, and 2) strengthen our knowledge on human brain circuitry and connectivity.

In this chapter, we revise the contributions that have been made to various physiological questions by the use of the electrodes implanted for therapeutic purposes in patients with Parkinson disease (PD) or dystonia. We have not included works on clinical effects of deep brain stimulation or clinical correlations, unless they were considered relevant for understanding physiological processes. The reader interested on clinical aspects may look for recent reviews on the topic (Limousin and Martinez-Torres, 2008; Lozano and Schneider, 2008; Benabid et al., 2009; Foltynie et al., 2010).

2. Recording

2.1 Neuronal spikes and local field potentials
2.1.1 Localization of targets
During the surgical procedure, at the operating room, it is possible to perform direct microelectrode recording of neuronal activity along the structures crossed by the electrode to reach the target nucleus. This is part of routine practice in most centers to help in localizing the target basal ganglia (Hutchison et al., 1998; Benazzouz et al., 2002; Sterio et al., 2002a; Molinuevo et al., 2003; Mrakic-Sposta et al., 2008). An example of such recordings taken from a patient along the trajectory of the electrode to the STN is shown in Figure 1.
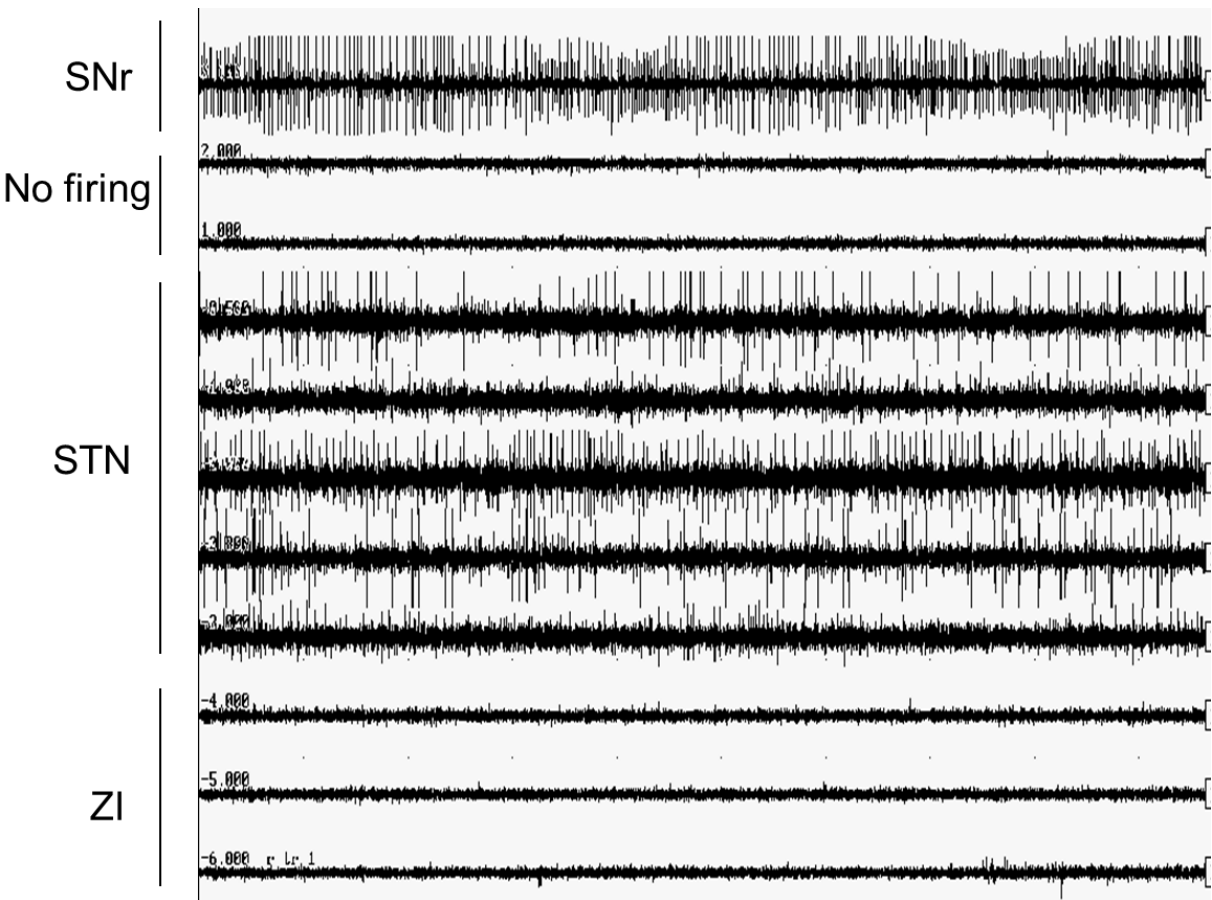

Fig. 1. Neurophysiological recording of various sites while inserting the electrode. From the bottom to the top: The electrode in the zona incerta (ZI) records almost no activity. When it enters the subthalamic nucleus (STN), the spikes become grouped in various bursts. Exiting the nucleus, there is a zone with no activity and then a continuous firing of spikes at a relatively high frequency, when the electrode enters the substantia nigra pars reticulata (SNr).

The possibility exists of recording from different nuclei in the circuitry. It is known, for instance, that the globus pallidus externus (GPe) shows a typical pauser neuronal firing, with activity in bursts. Sani et al. (2009) hypothesized that the characteristics of such firing might be different in patients with different disorders. They examined pause characteristics in 224 GPe units in patients with primary generalized dystonia, PD and secondary dystonia. The results showed that the characteristics of the pauses recorded in the GPe in awake humans distinguished primary dystonia from PD and secondary dystonia. Patients with primary dystonia had longer pause length, shorter interpause interval and higher mean pause frequency than PD patients. Interpause interval was also shorter in primary than in secondary dystonia. These results indicated an increased phasic input from striatal D2 receptor positive cells in primary dystonia.

A method to help localizing the border between the STN and the substantia nigra pars reticulata (SNr) has been shown by Lafreniere-Roula et al. (2009). These authors stimulated at low and high frequency through the electrode intended for the STN. When the electrode was at the border area between the STN and the SNr, they observed that high frequency stimulation caused a long lasting pause in the SNr firing but not in the STN. This is, therefore, an interesting technique to be used as a landmark for the STN electrode positioning. The same authors found inhibition in the GPi, similar to that induced in the SNr, although there were differences in threshold (Lafrenière-Roula et al., 2010), and suggested that such activity depression could contribute to the therapeutic effects of high frequency stimulation. A wavelet-based measure for quantitative assessment of neural background was used by Snellings et al. (2009) to show increase background levels within the STN that would help in identifying better the nucleus boundaries.

In our institution, we use the following criteria to consider electrode placement: For the GPi or the STN we consider signs of appropriate placement: 1) the observation of neuronal activity linked to limb movements, 2) a good therapeutic response such as improvement of bradykinesia, rigidity or tremor with intraoperatory high frequency stimulation, and 3) the absence of capsular, visual or ocular effects with the high frequency stimulation or its presence only when the stimulus intensity is increased above therapeutic threshold. For the Vim, we consider the finding of tremor cells within the boundaries of the nucleus and the disappearance of tremor when stimulating in the absence of motor or sensory side effects.

In 2002, various authors reported their observations on the preferred technical approach to reach the anatomical location for the electrodes to be implanted in the STN, GPi or Vim (Benazzouz et al., 2002; Lanotte et al., 2002; Starr et al., 2002; Saint-Cyr et al., 2002). However, good outcome measures of the surgical procedure should consider not only the precise localization of the appropriate target but, also, the lowest occurrence of residual symptoms and the lowest occurrence of side effects (Guehl et al., 2007).

Recognizing the target structure is a very important task at the time of electrode implantation. Knowing where the stimuli are actually applied or where they are more effective is another important piece of information for feedback. An attempt at knowing where the stimuli were actually applied through the STN electrode for the best clinical outcome was made by Maks et al. (2009). These authors used neuroimaging to measure the theoretical volume of tissue activated (VTA) by clinically defined best therapeutic stimulation parameters. They showed that therapeutic benefit was mainly achieved when the majority of VTA was in the area of the STN, mainly at its dorsal region, but outside the atlas defined boundaries of the nucleus. This, therefore, underlines the importance of the axons surrounding the STN for therapeutic efficacy. A similar observation was made by

Herzog et al. (2007) using electrodes implanted in the thalamus for the treatment of tremor. These authors observed a better effect on tremor using leads that were located closer to the STN rather than in the thalamus itself.

2.1.2 Assessment of activity and connectivity

Once in the target nucleus, the microelectrode can record both neuronal spikes and local field potentials (LFPs) originating in the same nucleus or in neighbouring neuronal groups. Such recordings have been used to characterize the physiological relationship between the target nuclei and its surroundings, as well as to provide evidence for disease-related neurophysiological abnormalities and their modulation by treatment (pharmacological and/or DBS).

Microelectrode recordings from within the STN show relatively rich background and spontaneously firing single neurons. Interestingly, however, if spikes are removed (obtaining a 'despiked' trace), the analysis of the STN signal still provides for the possibility to identify a pattern of activity typical of the STN (Danish et al., 2008). Various authors have reported high firing rates of neuronal spikes in PD patients in both, the STN (Rodríguez-Oroz et al., 2001; Sterio et al., 2002a), and the GPi (Hutchison et al., 1997; 2003), fitting well with the hypothesized hyperactivity of the indirect circuit of the basal ganglia in PD patients (Alexander and Crutcher, 1990; Wichmann and DeLong, 1996). An interesting finding has been recently reported by Novak et al. (2009) to provide a cue to understand why patients with unilateral STN DBS show bilateral benefit. These authors found that during high frequency STN DBS, there was an increase in multiunit spiking activity in the contralateral STN, an observation that provides also many questions to be answered in future studies. Apart from increased firing frequency, Levy et al. (2001; 2002) observed that neuronal spikes recorded from PD patients with tremor showed a prominent oscillatory pattern, which was substantially modified under dopaminergic activity. In the case of dystonia, however, the hypothesized low frequency firing rate of the GPi neurons has not always been found. While Vitek et al. (1999) reported firing rates lower than in PD in 3 patients with dystonia and one patient with hemiballismus, other authors have suggested that anesthesia played an important role in decreasing neuronal firing rate (Hutchison et al., 2003). The effect of anesthesia has not always been confirmed (Sanghera et al., 2003) and, according to Pralong et al. (2005), the lower firing rate of GPi neurons is independent of the type of anesthetic drug used.

Tremor is usually treated with thalamic high frequency stimulation both in PD and in essential tremor (ET). To see if there were differences between the two disorders in regard to the spontaneous neuronal firing in thalamic neurons, Chen et al., (2010) analyzed the recordings from the ventral oral posterior and the ventral intermediate nuclei. These authors concluded that there were significant differences between the two disorders, with decreased ventral oral posterior firing frequency in ET and increased neuronal firing rates in the ventral intermediate nucleus in patients with PD. The authors speculated on the possible pathophysiological implications of their findings.

Neuronal activity can be recorded also as LFPs, which have been confirmed to be time-locked to spikes generated in neighbouring neurones by recording spike-triggered LFP averages (Kuhn et al., 2005a) or examining coherence with multiunit recordings (Weinberger et al., 2006). The analysis of the LFPs may help confirming that the electrode is between the dorsal and ventral borders of the STN (Miyagi et al., 2009).

The LFPs can be recorded from the macroelectrode leads left externalized after surgery prior to connection to the impulse generator and, therefore, they can be analyzed while patients perform cognitive or motor tasks (Brown and Williams, 2005). Three prevailing frequency bands have been identified in the LFPs recorded from the basal ganglia: <8, 8-30 and >60 Hz. The band dominating the spectrum in the 'off' medication stage is the frequency in the alpha-beta range (8-25 Hz), while in the 'on' medication state baseline frequencies are higher (70-80 Hz). Brown et al. (2002) reported an increase in the amplitude of the frequency band of 25 Hz in the GPi of 2 PD patients that occurred prior to completion of a bimanual timing task. Because of a strong correlation between band amplitude changes and task duration, the authors suggested that modulation of this GPi frequency band could be involved in the prediction of movement timing. The band of 8-30 Hz predominates in the STN and GPi of PD patients withdrawn from their dopaminergic medication and is, therefore, considered antikinetic, likely contributing to the bradykinesia.

The high frequency LFP oscillations can only be recorded with normal levels of dopaminergic activity, while the band of 8-30 Hz is suppressed by dopaminergic treatments, behaviourally relevant stimuli and voluntary movement. Therefore, it seems that the subthalamo-pallidal-thalamo-cortical circuit undergo an opposite modulation by dopaminergic activity that may be a fundamental feature of the pathophysiological mechanisms of bradykinesia in PD (Brown, 2003). Actually, a correlation has been reported between the efficacy of the pair of leads used for chronic stimulation and the energy of the beta and gamma frequency band detected initially with LFP recordings during movements (Ince et al., 2010; Zaidel et al., 2010).

Foffani et al. (2003; 2005) described a distinct 300 Hz band in the STN that was more consistently seen during movement than at rest and more robust after apomorphine treatment. The authors suggested that such high frequency band represented a distinct mode of operation of the STN that could be a pathophysiological clue for PD. However the same group reported a similar high frequency band in the STN of two patients with diagnosis other than PD (one with dystonia and another with ET), hence suggesting that this finding may represent a broader feature of human STN function rather than being specific for PD (Danish et al., 2007).

Various loops are likely to run between the cortex and the basal ganglia that can be segregated by the amplitude of the frequency band. Williams et al. (2002) examined coherence between neuronal oscillatory activity recorded from electrodes inserted into the STN (8 patients) or the GPi (2 patients) and the EEG activity. They found significant coherence in three major frequency bands: 2-10 Hz, 10-30 Hz and 70-85 Hz, which differed in their cortical topography. Cortical activity led by around 20 ms the basal ganglia activity in frequencies <30 Hz, while it was the other way around with frequencies in the 70-85 Hz band.

An exaggerated synchronization in the band between 8 and 35 Hz (alpha/beta) might be implicated in the pathophysiology of Parkinson's disease. The power in this band decreased with dopamine treatment, as shown by several authors in the analysis of STN-LFP oscillations (Giannicola et al., 2010). The same effect has been obtained with STN DBS (Kuhn et al., 2008; Bronte-Stewart et al., 2009; Giannicola et al., 2010) although the intensity of the effect has not been the same in all reports. The abnormally enhanced beta band oscillations are encountered in certain sites of the STN and some authors have found a correlation between localization of the electrode in sites of the STN where there was a predominating beta band and the efficacy of STN DBS in alleviating the patient's symptoms (Ince et al.,

2010; Zaidel et al., 2010). Interestingly, the activity was transiently suppressed between 200 and 600 ms after transcranial magnetic stimuli (TMS), regardless of it being applied to the motor cortex or to the supplementary motor area (Gaynor et al., 2008). The effect was seen even with subthreshold intensity for elicitation of a motor evoked potential and, therefore, the authors dismissed the possibility for peripheral reafferentation as the cause of the transient interruption. This observation could underline the beneficial effects of repetitive TMS (rTMS) in patients with PD but the differences between L-Dopa, STN DBS and rTMS point out to the existence of other contributory mechanisms.

The high frequency oscillatory activity (gamma band) is more prominently recorded in patients treated with L-Dopa, suggesting that this may be an important correlate of dopaminergic activity. Although initially considered to be related to the L-Dopa induced dyskinesias, an increase power in the gamma band was actually seen at movement onset in patients in the OFF medication state, to increase significantly in the 'on' medication state (Androulidakis et al., 2007). Therefore, there is evidence that the L-Dopa related increase in gamma band power is a sign of restoration of physiological pattern of oscillatory activity in Parkinson's disease. An abnormally low ratio between beta and gamma activity has been found in the STN during tremor (Weinberger et al., 2009), suggesting that the balance between these two oscillatory frequency bands may be associated with the clinical manifestation of tremor.

Kuhn et al. (2006a) examined event-related desynchronization (ERD) by recording LFPs from the STN region in 8 PD patients 'off' dopaminergic medication. Patients were instructed to either extend the wrist or to imagine performing the same task without any overt movement. They found that imagining a motor action was accompanied by ERD of oscillatory beta activity in the region of the STN that was similar in frequency, time course and degree to the ERD occurring during real execution of movement. The event-related synchronization (ERS) occurring after completion of movement was significantly smaller in movement imagination than in movement execution. According to these observations, neuronal activity in an area around the STN might have a role in trial-to-trial motor learning and in the re-establishment of postural set after movement.

In dystonia, Chu Chen et al. (2006), using a multielectrode that combined 4 platinum-tungsten fibers in a glass insulation with 4 circular contacts, reported the finding of a high power 3-12 Hz band in the analysis of LFP from the GPi, which has been considered relevant in the pathophysiology of dystonia (Silberstein et al., 2003; Liu et al., 2006). Again, computed spike-triggered averages demonstrated that the oscillations were actually generated by GPi neuronal spikes. Consistent with the expected basal ganglia functional activity, a significantly lower firing rate was found in the GPi neurons in dystonic patients than in PD patients (Tang et al., 2007). When recording from the STN of dystonic patients, Schrock et al. (2009) found a frequency of firing of 26.3 Hz (SD 13.6), which was lower than that in the PD patients (35.6 Hz, SD 15.2), but higher than published values for subjects without basal ganglia dysfunction. In Tourette's syndrome, Marceglia et al. (2010) reported the observation of bursting neuronal activity in the ventralis oralis (VO) complex of the thalamus, known to improve tics in patients with Tourette's syndrome. These bursts occurred at low frequencies (2-7 Hz) and in the alpha-band (8-13 Hz), while there was virtually absent beta band activity. Microelectrode recording was performed in the GPi by Zhuang et al. (2009) to explore the relationship between basal ganglia output and electromyographic activity during tics and demonstrate that the basal ganglia motor circuit is involved in tic movements. In 232 neurons, these authors found 45% of them that were related to either a burst of activity or a pause in ongoing tonic activity.

The correlation between LFP oscillatory changes and movements has been reported by many authors, supporting the hypothesis that the GPi and the STN are somehow involved in movement preparation in humans. An increase in high frequency activity (>60 Hz) has been found to occur before voluntary movement (Cassidy et al., 2002). Alegre et al. (2005) reported bilateral changes in the neuronal oscillatory activity of the STN during voluntary unilateral hand movements, suggesting that movement-related activity in the STN has a bilateral representation and probably reflects cortical input. Alegre et al. (2010) also reported, during movement observation, a bilateral beta reduction in subthalamic power, similar to that observed in the EEG, , and decreased cortico-STN coherence, suggesting that the basal ganglia might be engaged by the activity of the human mirror system. Likely, there are multiple circuits linking the motor cortex with the basal ganglia that are segregated by not only topography but also frequency (Lalo et al., 2008).

Interestingly, Paradiso et al. (2003) reported the finding of pre-movement potentials recorded from the STN similar to those recorded from the scalp. These authors found a bilateral slow rising negative pre-motor potential beginning at a latency of more than 2 seconds before onset of self-paced wrist extension movements. Further support for the implication of the cortico-basal ganglia-thalamocortical circuit in movement preparation has been brought recently by the same group. Purzner et al. (2007) reported a phase reversal of the pre-movement potential when simultaneously recorded the activity preceding self-paced or externally cued movements with scalp electrodes and STN electrodes. The possibility that rhythms of neuronal oscillatory activity determine the participation of the basal ganglia on movement preparation, movement execution and post-movement recovery was pointed out by Foffani et al. (2005), while Marceglia et al. (2006) suggested that the key factor could be the interaction between rhythms generated in different neuronal circuits.

There is some evidence for the human STN area to be involved in the processing or transmission of emotional information: Kuhn et al. (2005b) recorded LFPs through the STN electrode in 10 PD patients while viewing pleasant and unpleasant emotionally arousing and neutral pictures. They found a significant, unspecific, ERD in the alpha power (8 to 12 Hz), starting at about 0.5 seconds after stimulus presentation, and a later ERD (at about 1 to 2 seconds post-stimulus), that was larger in trials containing pleasant or unpleasant images than in those with neutral stimuli. These findings suggest some kind of link between the STN and limbic structures that could be a clue for understanding the pathophysiology underlying the mood changes observed in patients with PD and high frequency STN stimulation. The basal ganglia may be involved in the evaluation of changes in the environment and their significance, which could explain the behavioural impairment that can follow basal ganglia lesions or dysfunctions (Sauleau et al., 2009).

2.1.3 Responses of nearby neuronal groups

In search for an explanation of the effects of high frequency stimulation, investigators have used microelectrode recording of neuronal spikes and LFPs in response to local stimuli. Technical development has brought up the possibility of recording from one contact while stimulating by another at a few hundred microns distance only, allowing for the construct of a functional stereotactic mapping around the microelectrode. Dostrovsky et al. (2000) reported inhibition of the GPi neurons by high frequency stimulation through another electrode inserted in the same nucleus, between 250 and 600 microns apart. This was re-examined in 2007 by Pralong et al., who reported opposite effects of high frequency stimulation (100 Hz) over neurones located in different parts of the GPi nucleus, with a

pattern of local inhibition and distant excitation. A similar study was done in STN neurons by Filali et al. (2004), who reported an inhibitory effect of stimulation applied through another electrode located in the same nucleus at a distance of about 600 microns. Welter et al. (2004) reported that stimulation at frequencies over 40 Hz decreased firing frequency and increased burst-like activity of STN neurons in patients with PD. Montgomery (2006) reported on microelectrode recordings in the posterior VO nucleus of the thalamus during high frequency GPi DBS in a patient with dystonia. Eighty-eight percent of neurons showed brief but highly consistent increased firing in the first 1ms following stimulation. This was followed by inhibition in about half of the neurons, which occurred at about 3.5 to 5 ms, and a post-inhibitory rebound of enhanced activity in 25% of neurons.

The importance of stimulus intensity in determining effects on neuronal firing was demonstrated by Maurice et al. (2003) who reported that the firing rate of the SNr neurons increased with high intensity, and decreased with low intensity STN DBS. This observation suggests that the fibers connecting STN to SNr neurons may carry inhibitory or excitatory inputs depending on the firing frequency. Sterio et al. (2002b) demonstrated that the STN neurons were activated by stimuli applied to the GPi, with two different main effects: reduction of firing rate in neurons of the dorsal region of the STN, and facilitation in those of the ventral region of the STN. The latter had a behavior similar to that of the SNr neurons. The authors point out that this finding is just one example of the complexity of the basal ganglia loops, which overshadows the relatively simple and linear, although still useful, schematic connections predicted after the classical circuitry (Alexander and Crutcher, 1990; Wichmann and DeLong, 1996).

2.1.4 Effects of disease and treatment on neuronal activity in the basal ganglia

The possible association between characteristics of the neuronal firing in the STN and GPi and tremor, dyskinesias and other movement dysfunctions of PD patients has been studied by many authors in 'off' and 'on' medication state. The high frequency STN rhythm at about 300 Hz described by Foffani et al. (2003) was dopamine-dependent. It was more robust and larger after apomorphine, suggesting that modulation of this high frequency band may be underlying beneficial therapeutic effects in PD. The authors suggested that an absent 300-Hz STN rhythm during movement could be a pathophysiological clue for PD. Priori et al. (2004) reported that the main effects of L-Dopa and apomorphine were an increase in the power of the low frequency bands (2-7 Hz), and a decrease in the power of low-beta activity (13-20 Hz). Their findings were compatible with at least two STN neuronal oscillatory rhythms, separately modulated by antiparkinsonian medication: one at low frequencies and one in the beta range. Alonso-Frech et al. (2006) found basically the same results and suggested that the increase in the power of the 4-10 Hz frequency band could account for dopamine-induced dyskinesias in PD patients. This has been also pointed out more recently by Lee et al. (2007) who observed that a decrease in neuronal firing rate in the GPi preceded the onset of dyskinesias induced by the administration of apomorphine.

Kuhn et al. (2006b) calculated in 9 PD patients the STN LFP power over the frequencies of the most prominent spectral peak within the 8-35 Hz frequency band and of any peak in the 60-90 Hz band. They observed a dopamine-related reduction in peak activity in the 8-35 Hz band, which was positively correlated with the contralateral hemibody improvement on motor aspects of the unified Parkinson's disease rating scale (UPDRS) and with hemibody subscores of akinesia-rigidity, but not tremor. They also found a trend for negative correlations between peak 60-90 Hz LFP power and UPDRS hemibody score, suggesting

that positive correlations were relatively frequency specific. Peak amplitude or power of the frequency band may be not the only relevant aspect for the function of basal ganglia.

A few authors have examined whether STN DBS have the same effects as dopamine on neuronal firing and LFP oscillations. This has been assessed immediately after switching off the stimulator, when patients still benefit from STN DBS but there is no ongoing stimulation (Foffani et al., 2003; Priori et al., 2006). In those studies, the effects were limited to an increase in the power of very low frequency bands (1-1.5 Hz), while no effects were seen in the low beta band (13-20 Hz), high beta band (20-35 Hz), gamma band (60-90 Hz) or in the 300 Hz oscillations. However, Wingeier et al. (2006) were able to document in two patients a significant attenuation of the power of the beta band oscillatory activity recorded from the STN immediately after DBS, an effect that lasted for 15-25 s after DBS had been turned off. Therefore, more work is needed in this area to establish whether or not the effects induced by DBS on the neuronal oscillatory activity of the STN are the same or not as those induced by dopaminergic treatment.

The mechanisms by which DBS is effective in the symptomatic treatment of PD remain not fully elucidated. A prevailing theory is that, instead of just blocking the activity, the electrical stimuli interfere with the output from the STN, in such a way that the pathological activity is jammed. Carlson et al. (2010) found results consistent with this hypothesis when recording from the STN during therapeutically effective stimulation. These authors saw that the spontaneous firing was not arrested but the firing patterns were altered, with a predominant shift toward random firing.

2.1.5 Discussion

Neurophysiological recordings during surgery are routine practice for most departments carrying out stereotactic procedures for treatment of Parkinson's disease. Recording neuronal spikes helps in the assessment of the trajectory and, together with the magnetic resonance imaging (MRI) correlate of the electrode and the relevant anatomical structures, has provided cues for the assessment of the electrode position with most effective clinical results. Although landmarks have been defined and are helpful for orientation of the target, modification of the first tract is done in about 1/3 of patients in order to reach better outcomes for the specific individual. The relationship between movements of specific body parts and STN neuronal activity has led to recognize topographic specificity of neuronal groups within the STN, which may lead in the future to modification of the target to better suit specific purposes. One example is speech, a complex function that is not always improved and many times even worsens when the STN DBS has been implanted in the best location for improvement of motor function (Rodriguez-Oroz et al., 2005; Tornqvist et al., 2005). At present, when morbidity is low and patients can be relatively assured of an outstanding clinical benefit, the challenge for specialized teams is to search for alternatives that lead to still larger benefit by improving as many functions as possible and avoiding unwanted effects. The neurophysiological mapping of neuronal groups in the STN and other target nuclei could help to better locate the leads in the somatosensory area of the STN, avoiding associative and limbic areas.

Unfortunately, the findings on frequency of spike recordings, band power of LFPs, or even cortico-STN oscillations cannot have a direct correlation with the pathophysiological mechanisms of the disease, since the setup in which these features are recorded implies the presence of interfering factors such as anesthetics, surgery-related stress, and others that may influence brain activity in general. However, measurements of neuronal firing and

LFPs allow for understanding better the effects of medication and repetitive stimulation on the behaviour of local neuronal activity and oscillatory loops. Many authors agree in that frequency bands at about the beta range decrease with dopamine. However, it is not always clear whether repetitive STN DBS modifies the recordings in the same way, and further work is certainly needed in this regard.

2.2 Intracranial recording through the implanted electrode
2.2.1 Characteristics of the evoked potentials

Intracranial electrodes can be used to record relatively large volume conduction action potentials from distant sources. The electrodes inserted in the thalamus, mainly with the purposes of arresting tremor in patients with PD or severe ET, are likely the most appropriate for recording the evoked potentials (EP) after somatosensory stimuli (). In general, the EPs recorded from DBS electrodes are polyphasic and of a latency 2 to 3 ms shorter than the cortical EPs (Figure 2). In most occasions, the subcortical EPs have been recorded from the thalamic Vim, where the electrodes are close to the source of activity. Klosterman et al. (2003) recorded the median nerve EPs from various sites along the pathway of the electrode. When recording from sites along the tract to the STN or the Vim, the EPs were of low amplitude with no high frequency oscillations (HFO). These characteristics did not change when the electrode entered the STN, while entering the Vim it
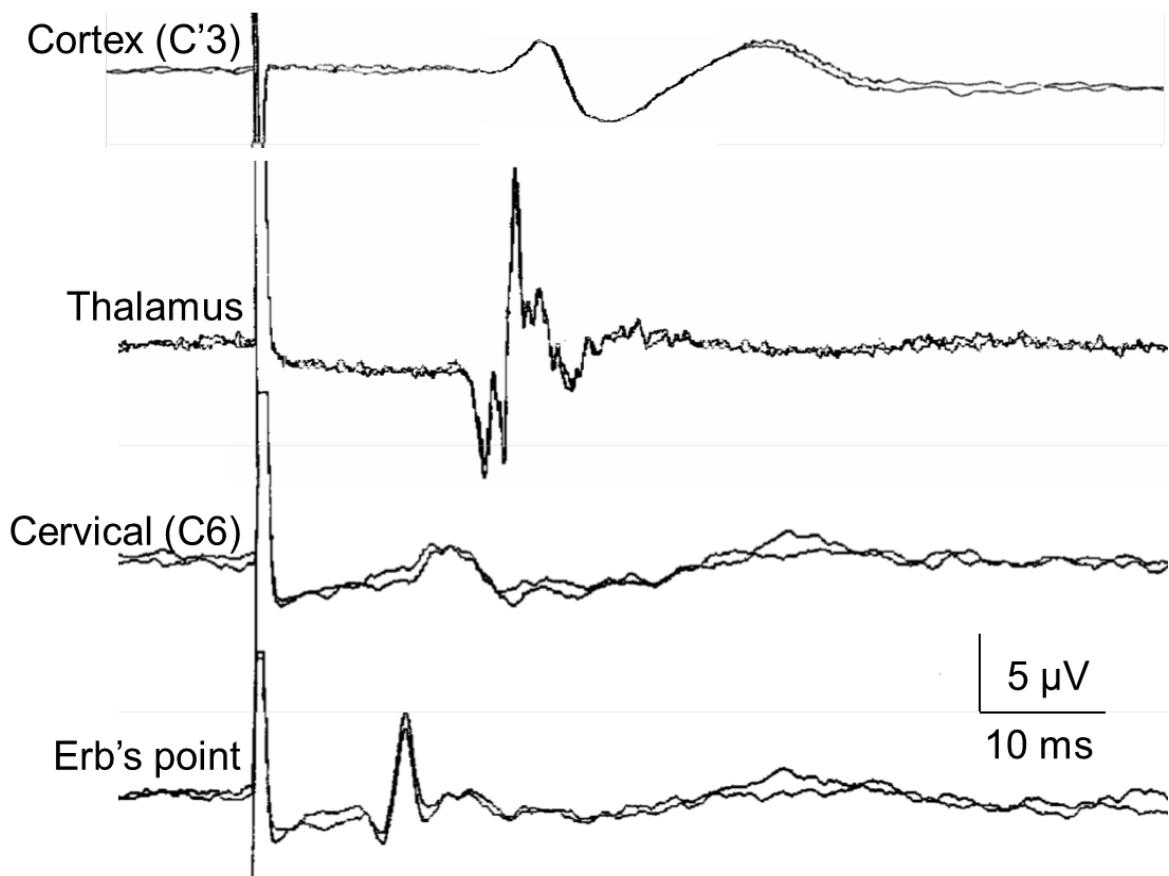

Fig. 2. Somatosensory evoked potentials recorded from Erb's point (Erb), cervical spinal cord (cervical), the nucleus ventral intermedius of the thalamus (thalamus) and the cortex to median nerve stimulation at the wrist.

was recognized by a sharp amplitude increase and the observation of HFOs. The latter were characterized by Hanajima et al. (2004a), who identified them with intrathalamic neuronal firing at intervals between 0.8 and 1.2 ms (a frequency of about 1000 Hz) and found the site of phase reversal at about the nucleus ventralis caudalis. The same authors (Hanajima et al., 2004b) recorded from the thalamic electrode a large somatosensory EP with a mean latency of 17.9+/-1.7 ms, which had a phase reversal at the level of the inter-commissural line. Assessment of phase reversal with bipolar recordings from two electrode leads may be potentially useful intraoperatory to establish the optimal position of the contacts relative to the sensory pathways, contributing to the choice of contacts for chronic stimulation. Laser stimulation has been reported recently to induce also intrathalamic evoked potentials (Kobayashi et al., 2009; Valeriani et al., 2009).

The small EPs recorded from the STN or along the tract are likely to be volume conduction from non-local generators, although Pesenti et al. (2003) proposed that the STN EPs can also be due to local field potentials elicited by muscle afferent inputs to the STN or to activity in thalamo-subthalamic projections. A few articles have been published on intracerebral recording from other nuclei than the thalamus. However, Kitagawa et al. (2007) recorded the somatosensory EPs from the thalamus and the subthalamic area, indicating that this could be a way to refine target localization. Balaz et al. (2008) recorded the P300 wave from the STN, suggesting that this nucleus is involved in cognitive executive functions.

2.2.2 Efferent and afferent gating in subcortical structures

Efferent or centrifugal gating is understood as the modulatory effect of movement on incoming sensory volleys (Grunewald et al., 1984; Cohen and Starr, 1987), while afferent or centripetal gating is understood as the competition between incoming afferent volleys to the brain (Schmidt et al., 1990; Nakajima et al., 2005). Both types of gating of EPs in humans have been documented to occur in part in subcortical structures by recording from the DBS electrodes. However, all authors agree in that a significantly larger effect is seen in scalp recordings than in subcortical recordings.

Regarding efferent gating, Valeriani et al. (2001) recorded the subcortical EPs during voluntary movement of the stimulated foot and saw a significant reduction of amplitude in all DBS recordings and in cortical somatosensory EP components following the P30 potential at the vertex but not at the contralateral temporal and ipsilateral parietal recordings. The authors speculated on the possibility that posterior tibial nerve stimulation generates two differently oriented dipoles in the contralateral hemisphere, one perpendicular to the mesial cortex and another radial to the convexity. Insola et al (2004) also reported that the movement-induced gating of somatosensory EPs occurs at a subcortical level by recording from the STN and GPi electrodes in 9 PD patients. The EPs recorded in those nuclei were triphasic (P1-N1-P2) and their latency ranged from 14 to 22 ms. When they were recorded during voluntary flexo-extension movements of the stimulated wrist, the subcortical EPs significantly decreased in the same way as the scalp N20, P22 and N30 potentials, while the response recorded in the Erb's point remained unchanged. Klosterman et al. (2002) investigated gating of intrathalamic somatosensory EPs in 10 PD patients during the surgical procedure. These authors applied median nerve stimuli to record EPs simultaneously with the intrathalamic and scalp electrodes in patients anesthetized with propofol. They compared conditions before and after application of the depolarising muscle blocker succinylcholine, i.e., with and without reafferent somatosensory inflow from background muscular tone and the repetitive muscle twitches

caused by the median nerve stimulation needed to induce the EPs. The authors found no changes in the sensory nerve action potentials recorded at the upper arm, but the primary cortical component (N20) was significantly increased under succinylcholine (+17%). This cortical release from gating was not paralleled, however, by an increased thalamic response; rather, the primary thalamic response (P16) showed a significant (-9%) amplitude reduction. Thus, the findings reported by these authors suggest a thalamo-cortical dissociation in the phenomenon of gating, when tested by causing muscle relaxation, with significantly more effect in the primary somatosensory cortex than in the thalamus.

Regarding afferent gating, Hsieh et al. (1995) performed a very early study in 5 patients with PD and one with Meige's syndrome undergoing thalamotomy. These authors examined the afferent gating induced by simultaneous stimulation of two fingers. Apart from intrathalamic recordings, these authors obtained direct recordings also from the sensory and motor cortices, and the cuneate nucleus. Electrical stimulation was applied to the II, III or V fingers individually, and also to pairs of either the II and III fingers or the II and V fingers simultaneously. The authors calculated the interaction between afferent volleys as the ratio of amplitude attenuation of the EP caused by the simultaneous stimulation to two fingers compared with the amplitude of the arithmetically summed EPs to the individual stimulation of each finger. The largest interaction was observed in the responses recorded in the scalp (P25 and P22), but a significant effect was also seen in the thalamic recordings. We have examined another form of afferent gating, i.e., the simultaneous activation of fibers by two different stimulus modalities: mechanical taps to the muscle and electrical stimulation to the digital nerves. Interactions between inputs of different sensory modality occur along the sensory pathway, including the thalamus. We investigated the interactions between mechanical taps and electrical nerve stimuli in 8 patients who had an implanted electrode for deep brain stimulation for symptomatic treatment of ET or PD (Costa et al., 2008). A hand-held electronic reflex hammer was used to deliver a mechanical tap to the skin overlying the first dorsal interosseous muscle, and trigger an ipsilateral digital median nerve electrical stimulus time-locked to the mechanical tap with a variable delay of 0 to 50ms. There were significant time-dependent interactions between the two sensory volleys at subcortical level. Thalamic SEPs were decreased in amplitude at inter-stimulus intervals (ISIs) from 10 to 40ms with maximum effect at 20ms, with no changes in peripheral responses. Our results are in line with those reported in other forms of gating and indicate that gating among two different somatosensory afferent volleys occurs at various levels of the central nervous system, and although it is predominating in cortical circuits there is already a significant effect taking place at a subcortical level.

2.2.3 Discussion

Having electrodes implanted in the basal ganglia and particularly in thalamic nuclei called for investigating physiological mechanisms involving sensory events. Most of the research in this area has dealt with thalamic EPs. Although the Vim does not contain the second order neurons activated by somatosensory inputs, the EPs to median or tibial nerve stimulation show consistently reproducible HFOs thought to reflect neuronal activity in the nearby nucleus ventralis caudalis of the thalamus. A few authors have used the electrodes in the STN or GPi to record EPs. In most instances, the authors agree in the fact that the EPs recorded in these nuclei have the same characteristics as those recorded outside the thalamus and are probably volume-conducted from distant sources.

Many investigators have devoted their efforts to examine the phenomenon of gating at the thalamic level. All authors coincide in that the two main forms of gating reported in the EPs (afferent and efferent) can already be demonstrated at thalamic level. However, gating increases in more rostral structures, in such a way that the EPs recorded from scalp electrodes show more effect than those of the thalamus. The whole picture indicates that gating is a multilevel effect that begins at a point caudal to the thalamus and increases along the path up to the site of generation of the scalp EPs.

Interestingly, while nerve stimulation causes well defined EPs in the Vim, we were unable to record such EPs to mechanical muscle taps. Only a slow shift of the baseline time-locked to the mechanical stimulus was apparent in some recordings, indicating that the afferent volley has reached a central nervous system structure where it generated an action potential that is volume conducted towards the electrode. A series of studies may be necessary to determine, for instance, whether or not direct electrical stimulation of muscle afferents does or does not generate Vim EPs. It would be interesting also to use other more natural forms of stimulation to assess their effects on thalamic neurons either by direct recording of EPs or by assessing the effects that such stimuli may induce in thalamic EPs generated by electrical stimuli. In the same line, research has not been done yet in other afferent pathways, such as visual or auditory. Challenges for future investigations using intrathalamic electrodes involve not only deepening in the mechanisms of gating but also in the role of the thalamus in mediating and processing the input from different sources of information.

3. Stimulation

3.1 Experimental procedures
3.1.1 Effects due to activation of circuits and tracts

Because patients are kept awake during most of the surgical time during implantation of electrodes for DBS, the immediate beneficial effects of electrical stimulation can be evaluated in situ by clinical neurological observations and tests. Nevertheless, Liu et al. (2005) have drawn the attention to the usefulness of monitoring the effects of DBS with surface electromyography from the affected muscles to assist electrode implantation and lesioning. According to the authors, there are several potential uses of intraoperative EMG monitoring. EMG can be used as the reference signal for other events, such as the oscillatory LFPs simultaneously recorded via the implanted electrodes, to quantify the effects of acute electrical stimulation on the motor symptoms and to detect unwanted muscle responses induced by direct stimulation of the motor tract.

The effects of stimulation through the DBS electrode may be evaluated in a neurophysiological environment that is more convenient than the operating room if the electrodes are left available for a few days for further testing before implantation of the stimulator. It is understood that the electric field generated by the current delivered through the electrode spreads beyond the target nuclei and affects surrounding structures (McIntyre et al., 2004; Butson et al., 2007). According to the general principles of the effects of stimulation of the neuropil (Nowak and Bullier 1998; Ashby et al., 1999), electrical stimuli are more likely to activate axons than cell bodies, fibers near the cathode than those near the anode, and fiber tracts that run parallel rather than those that run perpendicular to the electrode. Indeed, the effects obtained with just a single stimulus at the weakest possible intensity are usually those due to activation of axons in long tracts located in the vicinity of the target nuclei. Ashby and Rothwell (2000) have summarized nicely the possibilities for

neurophysiological studies using deep brain electrodes. Two structures have been used for recording: the brain and the muscle.

3.1.2 Effects on cortical activity

The EEG activity is modulated by stimuli applied through the electrodes inserted in the STN (Ashby et al., 2001). Single stimuli elicited a negative potential with an onset latency of approximately 3 ms, followed by later potentials at 5 and 8 ms, which were usually largest over the frontal region in 9 out of 11 sides. Medium latency (18-25 ms) and long latency (longer than 50 ms) responses were also reported. Short latency EPs had short chronaxie and refractory period, implying that they arose from the activation of low threshold neural elements, possibly myelinated axons. They were maintained without blocking at stimulation frequencies as high as 100 Hz. Cortical responses likely due to direct stimulation of axons running close to the electrode were reported by Baker et al. (2002) with latencies ranging from 8 to 400 ms. Medium-latency EPs, with an average onset of 14 +/- 3 ms and peak at 23 +/- 4 ms, were reported by MacKinnon et al. (2005) to low frequency STN stimulation (5-10 Hz). These authors showed that the distribution of the EPs recorded by scalp electrodes to stimuli applied through the STN electrode was similar to that of the EPs elicited by median nerve stimuli. One likely axonal bundle that may generate the EEG potentials after electrical stimulation through the electrode inserted in the STN is the pallido-thalamic tract, which contains highly myelinated axons and traverses the dorsal aspect of the STN. These authors, did not find a positive correlation between the cathodal contact that produced the largest EEG response and the one that produced the optimal clinical benefit, suggesting that the neural elements mediating the medium-latency EP are different from those responsible for clinical effects. However, Kuriakose et al. (2010) have recently suggested that one of the mechanisms by which the STN DBS causes a beneficial effect is through cortical activation. These authors examined the time course of cortical activation after controlled stimulation at the STN and suggested that cortical activation could be due to short-latency antidromic stimulation of cortico-subthalamic projections and the medium-latency facilitatory basal ganglia-thalamo-cortical interactions. No significant changes were observed in event related potentials in regard to amplitude in a standard oddball auditory paradigm (Kovacs et al., 2008), in spite of the improvement in the accuracy of the task. Interestingly, the P300 was recorded from the STN or its vicinity in 8 out of 14 leads examined by Balaz et al. (2008).

A few other observations of the effects of DBS have been reported in circuits involving the cortex. Fraix et al. (2008) reported a tendency to normalization of the contralateral silent period to TMS and short-interval intracortical facilitation during STN DBS. Herzog et al. (2008) reported improvement of integration of sensory inputs from the bladder with STN DBS 'on'. Using positron emission computed tomography (PET) they showed that urinary bladder filling led to an increased regional cerebral blood flow (rCBF) in the periaqueductal grey, the posterior thalamus, the insular cortex as well as in the right frontal cortex and the cerebellum bilaterally. These authors suggest that STN DBS facilitates the discrimination of different bodily states by supporting sensory perception and the underlying neural mechanisms.

Neuroimaging techniques have given some cues for understanding the relationship between basal ganglia nuclei and regions of the cortex using functional MRI (fMRI) (Jech et al., 2001; Perlmutter et al., 2002; Karimi et al., 2008) or rCBF with PET (Payoux et al., 2004, Grafton et al., 2006; Thobois et al., 2002; Strafella et al., 2003; Vafaee et al., 2004). In these studies, high frequency stimulation decreased the abnormal hyperactivity of the motor cortex at rest and increased activity in premotor areas during movement in PD patients. Measuring rCBF,

Payoux et al. (2009) showed opposite effects of GPi and GPe over the ipsilateral primary sensorimotor cortex. Using PET, Arai et al. (2008) observed effects of unilateral thalamic stimulation on the motor cortex of the side stimulated and on the GPi of the contralateral side, which could underline the observation of bilateral improvement after unilateral stimulation.

3.1.3 Muscle responses

Ashby et al. (1998; 1999) were the first to report the effects of controlled external stimuli using the artifact of the implanted stimulator, picked up by cutaneous electrodes, as the trigger of the recording device a few months after the stimulator had been implanted. Single stimuli modulated voluntary EMG activity of contralateral muscles, inducing a short-latency facilitation, followed by a longer latency inhibition. The authors hypothesized that facilitation was due to activation of descending axons in the corticospinal tract of the capsula interna, which lies at a mean distance of about 4.5 mm in the mediolateral plane and 2 mm in the antero-posterior plane from the tip of the electrode implanted in the STN (Schaltenbrand and Wahren, 1977; Voges et al., 2002; Molinuevo et al., 2003). Ashby et al. (1999) reported also an inhibitory effect of DBS on the ongoing voluntary activity, revealed by a decrease ('dip') in the level of EMG activity. This silent period (SP) was thought to arise from the activation of large-diameter inhibitory thalamo-cortical fibres running parallel to the electrode. Hanajima et al., (2004c) observed that 3 ms after STN stimulation, the Motor Evoked Potential (MEP) amplitudes produced by TMS-induced anterior-posterior directed currents were significantly larger than control responses, while the responses to lateral-medial currents were unchanged. Similar facilitation also occurred after GPi stimulation, but not with thalamic stimulation. Therefore, single pulse STN DBS had a short latency facilitatory effect on motor cortex, which may be due to antidromic excitation of the cortico-STN fibers or transmission through the basal ganglia-thalamocortical pathway.

Kuhn et al. (2004) compared motor effects of activation of corticospinal neurons using either subcortical (direct electrical stimulation through the DBS electrode) or cortical (indirect stimulation of cortical neurons by TMS) stimuli. The study was done in 8 dystonic patients that underwent GPi DBS, using again the artifact of the stimuli issued by the implanted electrodes as triggers for the recording. Single pulse DBS activated a fast conducting monosynaptic pathway to alpha motoneurones. The contralateral MEPs had a significantly shorter onset latency and shorter duration compared to the responses induced by TMS. They reported the observation of a contralateral SP of short duration and no ipsilateral facilitatory or inhibitory motor effects. These results suggest that DBS of the GPi activates the corticospinal neurons at the level of the internal capsule to account for the MEP, and the thalamic fasciculus or cerebellothalamic fibers to account for the SP (see also Strafella et al., 1997 and Ashby et al., 1999). The absence of ipsilateral inhibition is consistent with a transcallosal pathway for the ipsilateral SP. In contrast, our group (Compta et al., 2006), who used the electrode implanted in the STN, reported ipsilateral SP with two short duration phases. This challenged the possibility that the ipsilateral SP is mediated through the corpus callosum since the stimuli were applied caudal to the transcallosal fibers. However, the possibility still exists that some parts of the ipsilateral SP are indeed mediated through transcallosal collaterals activated antidromically.

We found a long duration contralateral SP that had the peculiarity of having a burst separating it into two parts (Figure 3). The characteristics of the contralateral SP were explained on the bases of collision between the antidromic impulses generated through the DBS electrode and the descending volleys related to voluntary activity. Collision would have freed some neurons

from antidromic invasion of inhibitory collaterals and precisely the firing of these neurons with new premotor inputs would account for the burst of EMG activity breaking through the SP. Methodological differences could account for the different results reported by Kuhn et al. (2004) and our group (Compta et al., 2006). Kuhn et al. (2004) used electrodes inserted in the GPi, which is slightly more rostral, anterior and lateral than the STN, and could activate a different bunch of corticospinal axons than the electrode inserted in the STN. The same differences apply to the volley reaching the axons responsible for inhibitory effects via the thalamus. Whereas Compta et al. (2006) studied patients with Parkinson's disease, Kuhn et al. (2004) studied patients with generalized dystonia who are known to have a disorder of inhibition and an abnormally shorter SP (Ridding et al., 1995; Chen et al., 1997). Finally, Kuhn et al. (2004) applied the stimuli at a frequency of 5 Hz from the implanted generators, which allows for a relatively short time for analysis between two consecutive stimuli.
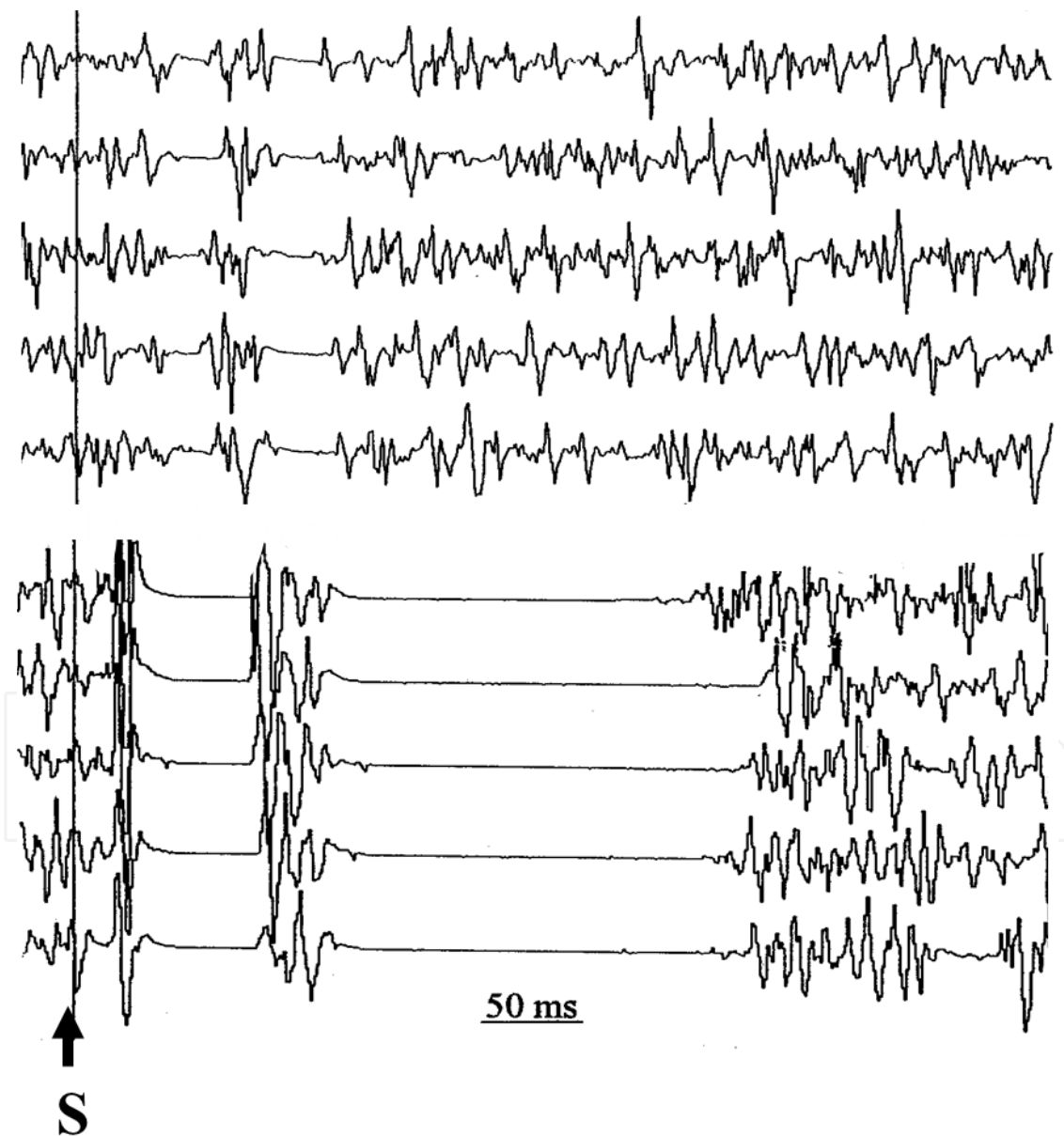

Fig. 3. Contralateral and ipsilateral silent periods induced by a single unilateral suprathreshold stimulus through the electrode inserted in the STN

Obviously, MEPs are not only obtained in hand muscles but in all muscles receiving innervation through fibers running in the capsula interna. This includes the cortico-bulbar tract. Fibers of the cortico-bulbar tract run in the genu of the capsula interna and are readily accessible to stimuli applied through the DBS electrode. Our knowledge of the distribution of cortical innervation to muscles innervated by cranial nerves is less accurate than for limb muscles because of various drawbacks of cortical stimulation such as the generation of large artefacts and the unavoidable elicitation of direct and reflex responses to activation of cranial nerves in the posterior fossa. We studied responses of cranial nerve innervated muscles to single STN DBS in 14 PD patients (Costa et al., 2007). The stimulus intensity used was 130% the resting threshold for an MEP in the thenar muscles. The inhibitory effects were also examined during sustained voluntary contraction of about 20% of maximum. As expected, unilateral stimuli induced strictly contralateral responses in thenar muscles at a mean latency of 20.1±2.0 ms. The MEPs obtained in the trapezius, deltoid and biceps muscles were also present in only the contralateral side, but the same stimulus induced always (i.e., a probability of 100%) bilateral MEPs in orbicularis oculi, orbicularis oris, masseter and sternocleidomastoid. The mean MEP latency ranged from 6.0 to 9.1 ms. The MEP latencies were significantly longer in facial nerve innervated muscles than in masseter and sternocleidomastoid muscles (Figure 4).
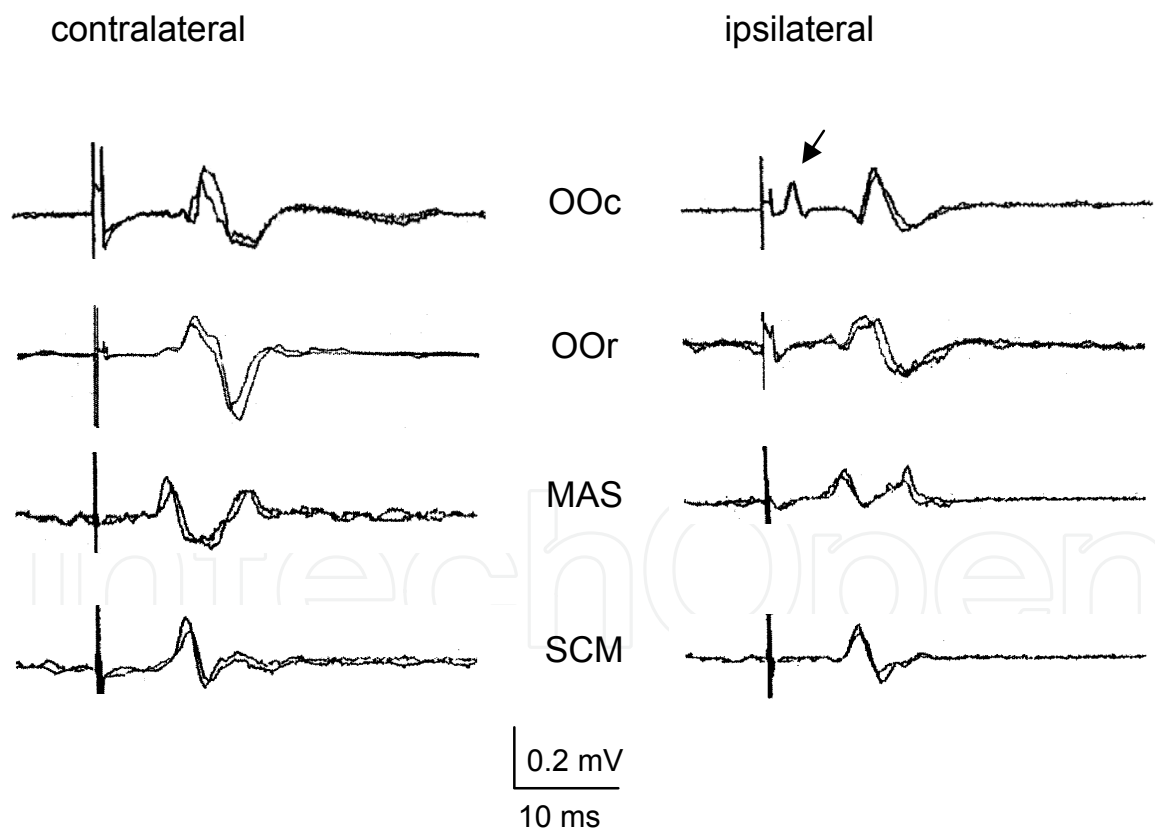

Fig. 4. Motor evoked potentials of cranial nerve innervated muscles to unilateral STN DBS electrode stimulation. Responses in the contralateral muscles are on the left side column while those of the ipsilateral muscles are on the right side column. OOc= Orbicularis oculi; OOr=Orbicularis oris; MAS= Maseter; SCM= sternocleidomastoid. Note the small short latency potential in the ipsilateral orbicularis oculi (inclined arrow)

Well defined SPs to single unilateral STN stimuli were present in both sides in the orbicularis oculi and masseter muscles in all patients, probably due to transient alpha motoneuron refractoriness after synchronized firing, blocking of the arrival of excitatory inputs to the motoneurons (Compta et al., 2006), and activation of thalamocortical inhibitory projections (Strafella et al., 1997). The amplitude of the MEP elicited during contraction was higher, and the duration of the SP was significantly longer, in the contralateral with respect to the ipsilateral sides. However, duration of the SP had no significant correlation with amplitude of the MEP.

3.1.4 Discussion

It seems obvious that chronic high frequency DBS causes its therapeutic effects by changing neuronal excitability in the area covered by the electrical field. Therefore, several authors have studied the effect in neurons in the vicinity. However, the mechanism of action of high frequency DBS is far from being clarified. Instead, the analysis of the effects of stimulation through one electrode lead and recording with a nearby electrode has brought new evidences for interconnections between nuclei of the basal ganglia. As expected, the observations suggest a more complex circuitry than a simple chain of nuclei with excitatory and inhibitory connections. In at least some connections, the frequency of inputs determines the sign of the effect while in others the exact site of the nucleus receiving the inputs is what makes a difference. This is likely reflecting that we are beginning to establish the temporal and spatial characteristics of the connectivity between basal ganglia nuclei and from the basal ganglia to output structures.

STN DBS induces consistent changes in cortical metabolism that can be summarized as a decrease of motor cortical activity at rest and an increase in cortical activity of the supplementary motor area and premotor cortex during active movements. However, the changes in metabolism do not necessarily show the function of the neurons undergoing such change, because they may involve both facilitatory and inhibitory neurons. Unfortunately, a good correlation between neuroimaging studies reflecting changes in metabolism and neurophysiology studies showing changes in cortical excitability has not yet been done.

There are effects of STN DBS on tracts with long projections that run close to the position of the electrode. We do not know if activation of those tracts contributes somehow to the clinical effects of DBS. Corticonuclear and corticospinal fiber tracts can be activated at relatively low intensity through the electrodes inserted in the STN or in the GPi. It is noteworthy that the effects on the motor tract of stimuli applied through the STN electrode seem not to be the same as those induced by stimuli applied through the GPi electrode (Kuhn et al., 2004; Compta et al., 2006). If these differences hold true in future works, they may be a hint to further understand the differential mechanisms of action of electrodes inserted in the two nuclei.

As with the MEPs elicited in hand muscles, the most likely physiological mechanism accounting for the generation of the MEPs in cranial nerve innervated muscles is activation of axons of the corticonuclear tracts within the internal capsule. However, in the case of the facial nucleus, Morecraft et al. (2001) have reported up to 5 projections from motor cortical areas to subsectors of the facial nucleus. Therefore, the MEPs obtained in cranial nerve innervated muscles by single pulse STN DBS could result from activation of just one of the many descending corticonuclear pathways, the function of which is largely unknown.

3.2 Effects of DBS on neurophysiological tests of clinical use.

Several studies have demonstrated that high frequency DBS improves the symptoms of PD patients. These effects have been documented and quantified using clinical scales. For instance, a clinical significant effect of the treatment is usually considered when there is more than 30% improvement in the UPDRS score. However, researchers have been interested in knowing how DBS modifies certain clinical neurophysiological abnormalities that may not have a direct clinical correlate but support in part pathophysiological mechanisms underlying parkinsonian symptoms and signs (Hallett, 1998; Rossini et al., 1998; Deecke, 2001; Valls-Solé and Valldeoriola, 2002). This has a double advantage: One is the quantitation and documentation of improvement through objective scales; the other is the determination of the neurophysiological abnormalities that are more closely related to clinical changes. Usually, the clinical and neurophysiological effects of DBS are compared with those of dopaminergic medication in a quadruple comparison: 'on' vs. 'off' medication and 'on' vs. 'off' stimulation.

3.2.1 Cortical physiology

One of the first observations on the neurophysiological effects of DBS was the change in contingent negative variation reported by Gerschlager et al. (1999) with bilateral STN DBS in PD patients. The contingent negative variation is a slow negative potential shift reflecting cognitive processes associated with the preparation and/or anticipation of a response that has been found to be reduced over the frontal and frontocentral regions in PD (Deecke, 2001). The increase in amplitude of the contingent negative variation with STN DBS 'on' (Gerschlager et al., 1999) suggests improvement of the impaired cortical functioning in PD, particularly within the frontal and premotor areas.

In a series of works on ERD preceding movement and ERS at movement termination, Devos et al. (2003, 2004, 2006) showed that STN DBS had also effects on the abnormally reduced and delayed cortical oscillatory activity patterns of PD patients, which have been considered a correlate of bradykinesia (Magnani et al., 1998; Brown and Marsden, 1999). The effects shown by Devos et al. with STN DBS (2003, 2004) were similar to those of an acute administration of L-Dopa. Interestingly, when recording ERD and ERS from the electrode inserted in the STN, the contacts that produced the best clinical results were also those showing the earliest mu and beta ERD and the strongest beta and gamma ERS.

The effects of STN or GPi DBS on motor cortex excitability have been studied by many authors. Chen et al. (2001) reported the effects of GPi DBS on several brain circuits that may exhibit functional abnormalities when examined with neurophysiological methods in PD patients. These included motor threshold, MEP recruitment curve, SP duration, short interval intracortical inhibition (SICI), long interval intracortical inhibition, and intracortical facilitation. The stimulators were set at the optimal parameters, at half the optimal stimulus intensity or switched off, in random order, while patients remained in their usual medication condition. No significant differences were found in most tests among the three conditions, the only exception being a reduction in the SP duration. Similar absence of modification of SICI was reported by Kuhn et al. (2003) during GPi DBS in patients with dystonia. However, switching off GPi stimulation led to an increase in motor threshold, and reduced the size of contralateral responses in the stimulus-response curves in relaxed muscles. On top of that, the authors reported no STN DBS related changes in spinal excitability, assessed by the H-reflex in the forearm muscles.

A different result was reported by Cunic et al. (2002) who examined the effects of STN DBS on cortical excitability in 9 PD patients, using the same protocol that Chen et al. (2001) and Kuhn et al. (2003) used for the GPi. These authors found that resting SICI, studied with paired-pulse TMS at the interstimulus interval of 2 ms, was restored to normal levels in the 'on' condition. Opposite to the results reported with GPi DBS, STN DBS did not induce changes in SP duration, motor threshold or MEP recruitment curve. Thus, in parallel to the differences found when recording hand muscle responses (Kuhn et al., 2004; Compta et al., 2006), it seems that the effects of STN DBS are different from those of the GPi DBS on motor cortex excitability changes accessible to neurophysiological testing with TMS. The effects of STN DBS on resting SICI were confirmed by Pierantozzi et al. (2002), who found an increase in SICI at intervals of 2 ms with STN and 2 and 3 ms with GPi. The improvement was similar to the one provided by apomorphine infusion. The authors suggest that improvement of SICI may be related to a recovery in modulation of thalamo-cortical motor pathway.

3.2.2 Subcortical circuits

Tisch et al. (2006a) measured changes in the excitability of the blink reflex after GPi DBS in 10 patients with dystonia. The abnormally enhanced excitability recovery after a conditioning stimulus (Kimura, 1973) was found to decrease progressively at intervals of 1, 3, and 6 months after surgery, suggesting that GPi DBS results in functional reorganization of the nervous system and a long-term increase in brainstem inhibition. Another dysfunction seen in the recording of the blink reflexes in PD patients is reduced prepulse inhibition (Schicatano et al., 2000; Valls-Solé et al., 2004). The pathophysiology of this phenomenon is not clarified but the abnormalities observed in PD may be due to a dysfunction in the connections between the basal ganglia and the brainstem nuclei, particularly the PPN (Pahapill and Lozano, 2000). We investigated the prepulse effects of single electrical STN DBS on the blink reflex induced in orbicularis oculi muscle by supraorbital electrical nerve stimulation in 7 PD patients (Costa et al., 2006). Five of them had an abnormally reduced prepulse inhibition to auditory and somatosensory stimuli. In all 7 patients, stimuli applied through the STN electrodes induced significant inhibition of the R2 at inter-stimuli intervals between 10 and 30 ms, with a mean percentage inhibition of 92% at 20 ms. Therefore, dysfunction of auditory and somatosensory prepulses in PD patients cannot be due to the machinery activated by DBS. We proposed that either the abnormal reduction in prepulse inhibition lies in a point of the circuit before reaching the structures activated by DBS, or STN DBS causes the prepulse by a different circuit than auditory and somatosensory stimuli.

The effects of DBS on spinal cord excitability have been reported for propriospinal circuits in the forearm (Tisch et al., 2006b) and in the leg (Potter et al., 2004). Tisch et al. (2006) reported a progressive improvement of the reciprocal inhibitory effect of a radial nerve stimulus on the median nerve H reflex, at 1,3, and 6 months of GPi DBS in patients with dystonia, and suggested that DBS causes functional reorganization of the nervous system that includes the spinal machinery. Potter et al. (2004) reported an increase of autogenic inhibition of the soleus H reflex, a propriospinal inhibitory phenomenon that has been found to be abnormal in PD (Delwaide et al., 1991). The authors measured the soleus H-reflex alone or conditioned by previous gastrocnemius nerve stimulation at ISIs of 2 to 10 ms in 10 PD patients. STN DBS induced an increase in the inhibitory effect of the conditioning stimulus that was significantly correlated with the clinical improvement of gait and posture. In a more recent work, the same group (Tisch et al., 2007) reported the absence of long-term potentiation-like

effect in patients with dystonia and GPi DBS. This has been considered a sign of abnormal plasticity in patients with dystonia (Quartarone et al., 2003). Therefore, this negative result could be reflecting the mechanism of action of pallidal DBS in dystonia.

Activity in descending tracts facilitates the soleus H reflex but such facilitation is abnormally decreased in patients with PD. This has been shown for auditory stimuli (Delwaide et al., 1993) and for TMS (Valls-Sole and Valldeoriola, 2002). Potter-Nerger et al. (2008) reported an improvement of the descending modulation of the H reflex by continuous high frequency STN DBS. Using single pulse STN DBS, we found in 11 PD patients that it modulates the amplitude of the soleus H reflex and therefore the net influence of the various mechanisms determining the excitability of the spinal alpha-motoneuron pool (Costa et al., 2011). Furthermore, the modulation of the H reflex was different according to the site of stimulation (ipsilateral vs. contralateral). In the case of contralateral single pulse STN DBS, the modulation of the soleus H reflex is distributed in an early and late facilitation phases, while in the case of ipsilateral single pulse STN DBS, there is a single early facilitation phase. Whether the modulation of the H reflex by STN DBS is the consequence of direct or indirect effects on the reticulospinal motor system is presently unknown.

The work of Tisch et al. and Potter et al. are just illustrative studies of one of the many positive effects reported during continuous high frequency STN DBS in the various abnormalities described in patients with PD, dystonia or ET (Sailer et al., 2007 for afferent inhibition; Potter et al., 2008 for audiospinal reactions; Yugeta et al., 2010, for the initiation and inhibition of saccades; Kronenbuerger et al., 2010 for eyeblink conditioning).

3.2.3 Discussion

In general terms, DBS causes changes in neurophysiological tests of clinical use that consist in a tendency to normalization, although in many occasions differences remain between patients with DBS 'on' and control subjects. This is consistent with clinical observations and points to a good correlate of some neurophysiological tests. This is particularly true for those tests related to planning and execution of voluntary movements such as the ERD or the cognitive negative variation. Changes in these tests demonstrate the influence of basal ganglia on cortical reactivity.

Less straightforward are the results of the assessment of motor cortical excitability at rest or during tonic voluntary contraction. Although there is no complete agreement among all authors, changes in SICI and in the SP duration seem not to result from activation of the same structure since most studies show that when there is reduction in SICI there is no effect on SP duration and viceversa. Interestingly, GPi and STN seem to give different results, reinforcing the possibility to identify distinctive neurophysiological outcome from the two nuclei.

The effects of DBS on subcortical circuits, including the brainstem and spinal levels, indicate a tendency to normalization of the results of neurophysiological tests. One of the subcortical circuits of interest in PD is the one responsible for prepulse inhibition (Fendt et al., 2001). The abnormally reduced prepulse inhibition in PD patients (Schicatano et al., 2000; Valls-Solé et al., 2004) reflects in part disturbed sensorimotor integration, but the normality of the effects when DBS is used as prepulse indicate that the defect does not lie ahead of the structures activated by the stimulus. We cannot assume that the circuit of prepulse inhibition is the same with DBS and with auditory or somatosensory stimuli. Actually, the STN is not part of the circuit of the prepulse. However, fibers connecting the GPi and the

PPN run close to the STN (Swerdlow et al., 2001) and might have been activated by the stimulus through the STN electrode. If this was the case, two explanations should be considered: One is that the dysfunction responsible for the loss of prepulse inhibition by acoustic and somatosensory inputs lies in circuits rostral to the PPN. One such possibility is the nucleus reticularis pontis caudalis, which receives inputs from the acoustic and somatosensory stimuli, and has reciprocal connections to the PPN. Another is that STN DBS induces its effects at a point beyond the PPN in the prepulse circuit. In favour of the first hypothesis is the fact that PD patients have an abnormal startle reaction due to dysfunction in nuclei of the reticular formation. In favour of the second hypothesis is the fact that STN DBS is known to cause inhibitory effects by way of activating afferents to the thalamic nuclei. Only further work in the area may help in answering the questions that remain unsolved by the findings reported so far.

4. Conclusion and future perspectives

The outstanding clinical neurophysiological investigation that is currently ongoing makes probably superfluous the task of guessing what can be expected in future years in this field. Nevertheless, the rapid growing understanding of both, the physiology and pathophysiology mechanisms of the different subcortical-cortical circuits, as well as the underlying clinical neurophysiological mechanisms of DBS, points to the possibility in the near future to: (1) Change the paradigm of DBS to another one were patients are treated with electrodes placed simultaneous in different nuclei (e.g. STN and PPN); (2) Allow for the simultaneous assessment of neuronal activity through recording of LFPs from DBS electrode leads and the consequent change in DBS stimulation parameters delivered by other DBS electrode leads, in a kind of real time individualised DBS therapy; (3) Begin to explore the possibility of improving non-motor symptoms through identification of new targets and stimulation parameters.

Many more studies than those reported here dealing with the effects of DBS have been published, bringing small or large pieces of information to increase our understanding of how the basal ganglia participate in the very many tasks that they are assigned. In this review, we attempted to focus on neurophysiological aspects of DBS not necessarily correlated with therapeutic effects. Understanding the physiological mechanisms accounting for some of the events seen with DBS is a growing field in which relevant contributions appear often in the literature and some of them might have done so while this chapter was in the review or publication processes. We hope, however, that this review reflects the state of our knowledge at the beginning of a new era in neurophysiology: that of direct recording and stimulation from deep brain electrodes. We hope also that it stimulates research in the field, the only way to eventually understand at least partially the function of the basal ganglia and subcortical motor circuits.

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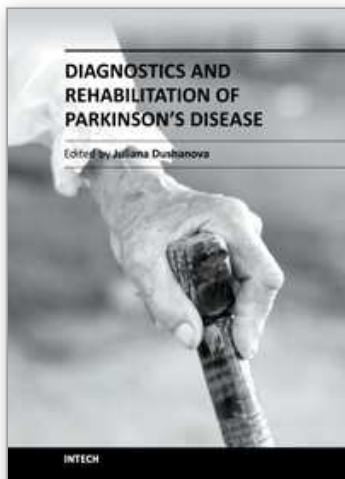
Diagnostics and Rehabilitation of Parkinson's Disease presents the most current information pertaining to news-making topics relating to this disease, including etiology, early biomarkers for the diagnostics, novel methods to evaluate symptoms, research, multidisciplinary rehabilitation, new applications of brain imaging and invasive methods to the study of Parkinson's disease. Researchers have only recently begun to focus on the non-motor symptoms of Parkinson's disease, which are poorly recognized and inadequately treated by clinicians. The non-motor symptoms of Parkinson's disease have a significant impact on patient quality of life and mortality and include cognitive impairments, autonomic, gastrointestinal, and sensory symptoms. In-depth discussion of the use of imaging tools to study disease mechanisms is also provided, with emphasis on the abnormal network organization in parkinsonism. Deep brain stimulation management is a paradigm-shifting therapy for Parkinson's disease, essential tremor, and dystonia. In the recent years, new approaches of early diagnostics, training programmes and treatments have vastly improved the lives of people with Parkinson's disease, substantially reducing symptoms and significantly delaying disability. Written by leading scientists on movement and neurological disorders, this comprehensive book should appeal to a multidisciplinary audience and help people cope with medical, emotional, and practical challenges.

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