Intraoperative Microrecordings of the Subthalamic Nucleus in Parkinson's Disease

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Abstract: Microelectrode recordings of single unit neuronal activity were used during stereotactic surgery to define the subthalamic nucleus for chronic deep brain stimulation in the treatment of Parkinson's disease. By using five parallel trajectories, often two to three microelectrodes allow us to recognize subthalamic nucleus (STN) neuronal activity. STN neurons were easily distinguished from cells of the overlying zona incerta and the underlying substantia nigra. During a typical exploratory track, we can observe a very low background noise in the zona incerta and almost complete absence of single cell recording. Penetration of the electrode tip into the STN is characterized by a sudden increase in background activity and single cell activity of spontaneously active neurons. The exit of electrode tip out of the STN corresponds to a decrease in background noise and a loss of single cell activity. Spontaneous neuronal activity increases again when the electrode tips enters the substantia nigra pars reticulata (SNr); however, the activity is less rich than in the STN, indicating a more cell-sparse nucleus. STN neurons are characterized by a mean firing rate of 42.30 ± 22.00 spikes/sec (mean $\pm$ SD). The STN cells exhibited irregular or bursty discharge pattern. The pattern of single cell activity in the SNr is a more regular tonic activity that can easily be distinguished from the bursting pattern in the STN. The most useful criteria to select a trajectory are (1) the length of an individual trajectory displaying typical STN activity, (2) the bursting pattern of activity, and (3) motor responses typical of the sensorimotor part of the nucleus. In conclusion, microelectrode recording of the subthalamic area improves the accuracy of targeting the STN. © 2002 Movement Disorder Society

Key words: Parkinson's disease; intraoperative microrecording; subthalamic nucleus; stereotaxic surgery; deep brain stimulation

The subthalamic nucleus (STN) plays an important role in the control of movement by exerting a glutamatergic excitatory influence on the output structures of basal ganglia: the pars reticulata of the substantia nigra (SNr) and the internal part of the globus pallidus (GPi). From the review of Parent and Hazrati,[1] it appears that the STN, like the striatum, is a major structure through which cortical signals are transmitted to the output nuclei of the basal ganglia. During the past decade, experimental animal models of Parkinson's disease have allowed extensive investigation of the functional consequences of the degeneration of the dopaminergic nigrostriatal pathway on the activity of STN neurons. The most significant alterations are an increase in the neuronal firing rate and a change in the firing pattern,[2–4] glucose metabolism,[5] and mitochondrial enzyme activity in the subthalamic nucleus and its efferent structures.[6–8] By using electrophysiological recordings, Bezard and colleagues[3] have shown that STN neurons may enhance their activity during the course of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine hydrochloride (MPTP) treatment, even before the first appearance of clinical signs.

It is well established now that the subthalamic nucleus plays a critical role in the pathophysiology of Parkinson's disease. STN lesions have been shown to induce an improvement in parkinsonian motor symptoms in monkeys rendered parkinsonian by systemic injections of MPTP.[9,10] Because the beneficial effect of STN lesions is accompanied by the appearance of abnormal movements,[9,10] it was difficult to propose lesional surgery for the treatment of Parkinson's disease. To

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avoid the side effects, we have replaced ablative lesions with high-frequency stimulation (HFS), which has been shown to reverse the three cardinal motor symptoms, ie, akinesia, rigidity, and tremor, in primate models of parkinsonism[11–13] and in severe parkinsonian patients.[14–16] Moreover, the threshold of current intensity inducing positive effects does not induce side effects.[11,12,15,17] From the results of these studies, it appears that STN-HFS is functionally equivalent to STN lesion, although its precise mechanism remains unclear. In our previous studies, we have shown that STN-HFS induced a significant decrease of neuronal activity in the STN and its efferent targets, the output structures of basal ganglia.[18–20]

PATIENTS AND METHODS

Since 1993, we implanted 153 patients, mostly suffering from severe akinesia and rigidity with or without tremor. In a few patients, tremor was the main indication for surgery. All patients had disabling motor fluctuations and/or dyskinesias.

For electrophysiological recordings, stimulation tests, and implantation of chronic stimulating electrodes in the STN, patients were placed in a stereotaxic frame. Anteroposterior and lateral x-ray films were obtained at an average magnification coefficient of 1.05. Contrast ventriculography was performed by freehand tapping of the frontal horn of the ventricle through a twist drill. Serial images were obtained during and after injection of contrast medium (Iopamiron, Schering). This method allowed a very precise delineation of the midline of the third ventricle and of the anterior (AC) and posterior (PC) commissures. The coordinates of STN were calculated from the lateral x-ray view according to a proportional geometric scheme based on the AC–PC line. In addition, STN was seen on magnetic resonance imaging (MRI) as a well-delineated hypointense signal on a T2-weighted coronal view. This image, when drawn on the STN Talairach diagram, derived from coronal and lateral contrast ventriculography, corresponded in location to the STN area in the Schaltenbrand atlas.[21]

Electrophysiological recordings of neuronal activities were done under local anesthesia, and medication was stopped 6 to 12 hours before surgery. A microdrive allowed five simultaneous parallel trajectories, with four trajectories each 2 mm apart from a central one. Tungsten bipolar microelectrodes (FHC, Bowdoinham, USA) with an impedance between 2 and 6 MΩ (measured at 1,000 Hz) were introduced into each trajectory for single unit recordings. Neuronal activity was recorded at various sites along the trajectory by using the NeuroTrek system (AlphaOmega, Nazareth, Israel) equipped with five isolated preamplifiers to record five simultaneous

channels. The acquisition program contains a spike discriminator, which allows the recording of only single unit neuronal activity.

The relation of STN neuronal activity to passive manipulation of different body parts was studied. It consisted of the examination of passive joint movements, muscle palpation, and orofacial light touch. The presence or the absence of neuronal responses was determined by listening to the recorded cellular activity by using audio amplification.

For each trajectory, electrical stimulation was tested every 2 mm from 2 to 8 mm below the AC–PC line, by using the NeuroTrek system that is equipped with an isolated stimulator. During the stimulation tests, the same parameters as for chronic stimulation were used (frequency, 130 Hz; pulse width, 0.06 msec; current intensities, variable). Stimulation tests were carried out by means of the five microelectrodes separately. For each site, we determined the threshold of current intensity inducing the improvement of motor symptoms and the threshold inducing side effects. The effect of microstimulation was assessed by clinical semiquantitative evaluation of rigidity during passive movements of the wrist.

ELECTROPHYSIOLOGICAL IDENTIFICATION OF THE STN

By using the system of five parallel trajectories, generally two or three microelectrodes, sometimes up to five, enter the STN and display a typical STN activity over several millimeters. Only spikes with a signal-to-noise ratio higher than 2:1 were analyzed. The patterns of ongoing discharge of STN neurons were stable over relatively long periods. STN neurons were easily distinguished from cells of the overlying zona incerta and the underlying substantia nigra. During a typical exploratory track, the first recorded structure is the thalamus in which the majority of cells exhibit a burst discharge pattern. The background noise then decreases in the zona incerta. Penetration of the electrode tip into the STN is characterized by a sudden increase in the level of background noise, reflecting an increased density of active neuronal cell bodies. Spontaneously active neurons are recorded as single cell activity, typically with one or several spikes being recorded from the tip of the microelectrode all through the STN (Fig. 1). The exit of electrode tips out of the STN corresponds to a decrease in background noise and a decrease in incidence of spontaneous neuronal activity compared with STN when the electrode tips enters the SNr.

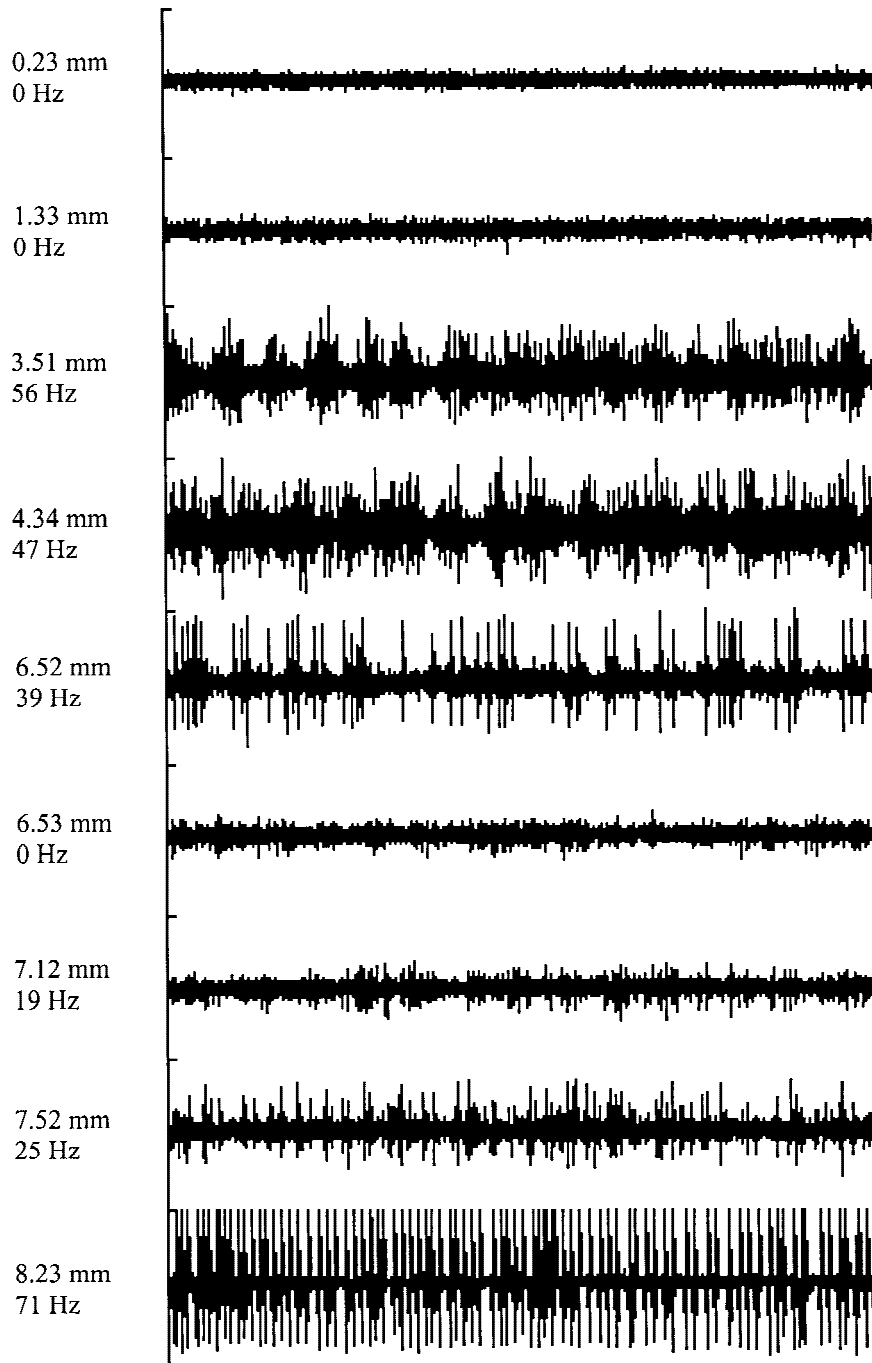STN neurons exhibited two different extracellular spike waveforms. Both mono- and biphasic waveforms

FIG. 1. Examples of electrophysiological background noise and single cell activity recorded in the subthalamic nucleus and the surrounding region in one trajectory. Note that we start microrecording at 0 mm anterior commissure–posterior commissure line and that the level of background noise is very low. Penetration of the electrode tip into the subthalamic nucleus (STN) is characterized by an increase in the background activity with the appearance of spontaneously active neurons. The exit of electrode tips out of the STN is characterized by a decrease in background noise. When the electrode tip enters the substantia nigra, background activity increases again. Compared with STN, the substantia nigra pars reticulata activity typically is less rich, reflecting a lower density of active neuronal cell bodies. Moreover, the pattern changes from an irregular bursting activity with motor responses to a more regular, tonic pattern of discharge (not shown).

were observed. A majority of recorded cells was characterized by spikes with a mainly negative wave followed by a smaller positive deflection. The negative peak was wider than the positive peak. The spontaneous firing rate of all STN recorded neurons was 42.30 ± 22.00 spikes/sec (mean ± SD; range, 10–80 spikes/sec; n = 423). The STN recorded cells exhibited two types of discharge pattern: (1) a population of cells characterized mainly by a tonic activity with an irregular discharge pattern and occasional bursts (mixed pattern), and (2) another population of cells with a high tendency to discharge with bursts (burst pattern). In this second population of cells, periodic oscillatory bursts synchronous to the rest tremor were observed in patients with parkinsonian rest tremor.

SNr cells were characterized by symetrically biphasic

and large-amplitude spikes. The mean firing rate of SNr neurons was 30 ± 13 spikes(s) with a range of 8 to 80 spikes(s). Other groups reported a higher firing rate which was around 70 spikes(s).[22,23] The spontaneous activity in SNr recorded neurons was characterized by a tonic discharge pattern. Periodic burst activities were never observed even in patients with tremor.

In all our parkinsonian patients, STN neurons were tested for their responses to passive movements. Approximately 40% of the STN cells responded to passive manipulations of parts of the body on the contralateral side. The responding cells modulated their activities in response to manipulations of the contralateral arm or leg and only few cells responded to orofacial touch or light tapping. The majority of responding cells was activated by manipulation of one or two contiguous joints. Cells generally responded either to flexion or to extension.

For the majority of sites, wherever electrophysiological activities were characteristic of STN neurons, high-frequency electrical stimulation alleviated muscular rigidity, akinesia, and tremor in the contralateral limbs. In the majority of cases, these improvements in motor symptoms were accompanied by dyskinesias in the contralateral limbs, which abated when stimulation was stopped. Induction of dyskinesias during surgery generally predicted a good anti-akinetic effect of chronic subthalamic stimulation. At high intensities of stimulation (2 to 3 times the threshold, which reversed motor symptoms), side effects related to current diffusion to neighboring structures occurred such as tetanic muscle contraction (anteriorly and laterally), paresthesia (posteriorly), or ipsilateral ocular deviation (medially).

The final trajectory is selected based on the results of both microrecording and stimulation. The most useful criteria are the length of an individual trajectory displaying typical STN activity, the bursting pattern of activity, and motor responses for microrecording, and induction of dyskinesias, improvement in parkinsonism time-locked to stimulation at low stimulation intensity, and high threshold for side effects for microstimulation.

In conclusion, our results suggest that the high level of STN neuronal activity with irregular and bursty pattern is associated to parkinsonian rigidity and akinesia, whereas periodic oscillatory bursts are associated to parkinsonian tremor. Our stereotaxic approach of using five simultaneous parallel tracks with electrophysiological microrecording, allows us to explore the STN and its surrounding structures. With microelectrode recording, it is easy to target the STN, as it is surrounded by myelinated fibers. Moreover, the SNr, which forms the lower border, has a different pattern of activity (less spontaneous activity, no movement response, more regular) and can also be easily distinguished from the STN. Microelectrode recording improves the accuracy of the electrode implantation into the subthalamic nucleus.

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