Subthalamic Neuronal Responses to Cortical Stimulation

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ABSTRACT

Background: Deep brain stimulation of the subthalamic nucleus alleviates motor symptoms in Parkinson's disease patients. However, some patients suffer from cognitive and emotional changes. These side effects are most likely caused by current spread to the cognitive and limbic territories in the subthalamic nucleus. The aim of this study was to identify the motor part of the subthalamic nucleus to reduce stimulation-induced behavioral side effects, by using motor cortex stimulation.

Methods: We describe the results of subthalamic nucleus neuronal responses to stimulation of the hand area of the motor cortex and evaluate the safety of this novel technique.

Results: Responses differed between regions within the subthalamic nucleus. In the anterior and lateral electrode at dorsal levels of the subthalamic nucleus, an early excitation (~5–45 ms) and subsequent inhibition (45–105 ms) were seen. The lateral electrode also showed a late excitation (~125–160 ms). Focal seizures were observed following motor cortex stimulation.

Conclusions: To prevent seizures the current density should be lowered, so that motor cortex stimulation-evoked responses can be safely used during deep brain stimulation surgery. ©2011 *Movement* Disorder Society

Key Words: cortical stimulation; deep brain stimulation; neurophysiology; Parkinson's disease; subthalamic nucleus

Deep brain stimulation (DBS) of the subthalamic nucleus (STN) alleviates motor symptoms in Parkinson's disease (PD) patients.[1–3] However, in a substantial number of patients the improvement of motor symptoms is accompanied by cognitive and/or limbic alterations.[4–8] These behavioral side effects are thought to be caused by stimulation of the associative and limbic areas in the STN.[9] Therefore, the optimal target is the dorsolateral part of the STN, supposedly the STN motor area.[10] Optimization, to identify the motor part, is currently done by intraoperative neurophysiologic measurements, such as spontaneous neuronal firing, neuronal kinesthetic responses, and beta-power in the local field potential.[11–13]

Earlier, Nishibayashi et al.[14] applied subdural motor cortex stimulation (MCS) in humans in order to identify the motor area of the globus pallidus internus and externus. This report provides insight in the cortically-evoked responses of the human STN neurons. The aim of this study was to identify the STN motor area by using MCS to reduce stimulation-induced behavioral side effects. In this study, we tested the feasibility of identifying the STN motor part by motor cortex stimulation and evaluated the safety of this novel approach.

Patients and Methods

Patients

The study was approved by the Medical Ethical Committee of the Maastricht University Medical Center and all patients gave written informed consent. Patients were informed about the additional burr hole, subdural placement of the stimulation electrode, and its additional potential complications, such as the risk of a bleeding or a seizure. Inclusion and exclusion criteria were the same as for standard DBS STN. In total,

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Table 1. The different motor cortex stimulation protocols used in all patients and the responsiveness of the subthalamic neurons to the applied protocol

Monopolar/ bipolar	Anodal/ cathodal	Amplitude (times MEP level)	STN response
Monopolar	Anodal	0.33	No
		0.5	No
		0.67	No
		1	No
		1.5	No
	Cathodal	0.5	No
		1	No
Bipolar		0.33	No
		0.67	No
		1	Yes (partial)
		2	Yes

The stimulation protocols that evoked a STN response were only used in the fifth patient.
MEP, motor-evoked potential; STN, subthalamic nucleus.

5 PD patients with an age ranging between 55 and 70 years old were enrolled in this study.

Procedure

The procedure and results described below are from the fifth patient, because the stimulation protocols used in the other patients did not result in an STN response due to saturation of the amplifier in the first 2 patients and suboptimal MCS protocols in the remaining 2 patients (see Table 1). The day before the DBS procedure transcranial magnetic stimulation (TMS) was performed to localize the hand area of the motor cortex. The stereotactic procedure was performed under local anesthesia. Preoperatively, the patient was loaded with 15 mg/kg Diphantoine intravenously in 90 minutes. A strip of 4 electrodes (Model TS04R-SP10X-000; AD-Tech, Racine, WI, USA) was placed in the subdural space through a burr hole posterolateral to the hand area (identified by TMS). The strip electrode position was verified by performing a motor-evoked potential (MEP) registration at the contralateral hand and arm, and the stimulation amplitude threshold was obtained. Subsequently, 5 microelectrodes (MicroMacroElectrode; InoMed, Emmendingen, Germany) were simultaneously inserted toward the STN through a precoronal burr hole. After baseline recordings, cortical-evoked neuronal activity was measured using a multiple channel registration system (ISIS MER System; InoMed; stimulation settings: bipolar, monophasic, 0.2 ms, 15 mA). After acquiring the cortically-evoked responses, surgery was continued according to the standard procedure (Deep Brain Stimulation System, Model 3389; Medtronic, Columbia Heights, Minneapolis, MN, USA).[15] On the left side, the standard surgical procedure was performed without cortical stimulation. Three to 4 days after surgery, the electrodes were connected to an internal pulse generator (Kinetra, Model 7428; Medtronic).

Data Analysis

Data analysis was performed in Matlab (MathWorks, Natick, MA, USA). First, offset and drift were removed from the signal by a high-pass Butterworth filter at 5 Hz. Subsequently, the stimulation artifact was removed. To assess multi- or single-unit activity, each epoch was digitally filtered between 350 and 5000 Hz. Spike detection was performed using the envelope method.[16] To obtain single-unit activity, spike sorting was performed by computing the principal components, which were clustered using either K-means or the Gaussian mixture model and the expectation maximization algorithm.[17] After spike detection, peristimulus time histograms (PSTHs) from 100 ms before stimulation until 200 ms after stimulation were constructed from 200 sweeps, grouping all trials with a specific stimulation setting. Bins of 1 ms were used and bins 1 ms before and 2 ms after cortical stimulation were set to zero to avoid any remaining stimulation artifact to be mistaken for spikes. To determine significant excitatory and inhibitory responses from the PSTHs, changing points indicating increases and decreases of the PSTH were detected using the change point analyzer software.[18,19] The periods between 2 changing points were tested for having a significantly different firing rate compared to the 100 ms preceding stimulation. This was done using a 2-tailed t test with a 5% significance level. STN borders were determined by the intraoperative observations of the neurophysiologist and the postoperative analysis of the MER recordings.

Results

The STN was entered at a depth of 2 mm above the target and left at 2.5 mm below the target on the anterior and lateral trajectories. The central trajectory was within the STN from 0.5 mm to 3.5 mm below the target, while the medial trajectory did not go through the STN. The posterior channel was defect and could not be analyzed. We measured 8 neurons inside the STN at various locations in this patient. The neurons had an average firing rate of 47 $\pm$ 25 Hz. Four neurons had a bursting pattern, 3 neurons showed a random pattern, and 1 neuron showed a regular firing pattern.[20,21] Statistically significant responses in the STN were observed when MCS was performed with a single monophasic pulse (0.2 ms duration) at 15 mA and bipolar settings. Excitations ranged from a 30% to a 103% increase in firing rate relative to the 100 ms period preceding stimulation, while the inhibitory periods ranged from an 11% to a 76% decrease in firing rate (Fig. 1). After each cortical stimulus, a clear contraction of the contralateral hand musculature was observed. Both spontaneous unit activity and unit responses to cortical stimulation were recorded from target -1.5 until target $+2.5$ mm. Inside the STN, responses to MCS were found, while outside of the

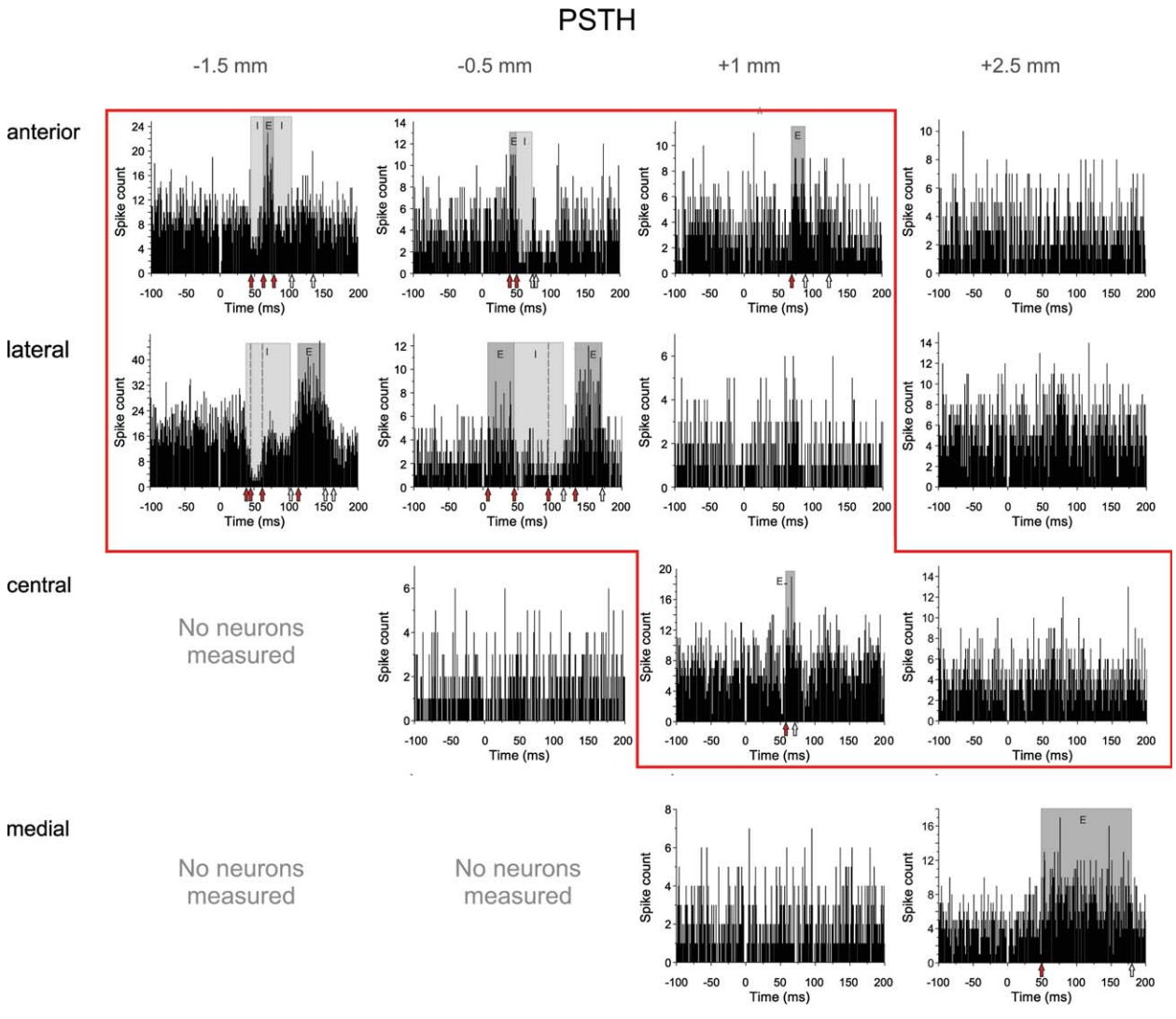

FIG. 1. PSTHs of neuronal recordings starting 0.5 mm after the electrode first enters the STN (1.5 mm above target) until the last electrode leaves the STN (2.5 mm below target). Recordings inside the STN are enclosed with a red window. MCS was performed with a bipolar electrode configuration using a monophasic pulse with an amplitude of 15 mA and a duration of 0.2 ms. The arrows at the x-axis indicate the significant changes that were identified with the change point analysis. The red arrows specify changes after which a significant increase or decrease in firing rate relatively to the 100-ms preceding stimulation was found. These periods are also indicated with shaded areas in which "I" denotes a period of inhibition, while "E" represents a period of excitation. When 2 periods of inhibition occurred after each other, a change is indicated with a dashed line. No results at −1.5 mm on the medial and central electrode are shown, as no neurons were measured on these locations. MCS, motor cortex stimulation; PSTH, peristimulus time histogram; STN, subthalamic nucleus. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

STN no responses were observed except for the medial electrode at 2.5 mm from target (Fig. 1). Responses varied between different depths and between different locations in the anterior-posterior and mediolateral plane within the STN.

A focal seizure was seen in the first 2 patients; therefore Diphantoine was given preoperatively in the 3 following patients with approval of the Medical Ethical Committee. No seizures were present in patients 3 and 4. Unfortunately, the fifth patient also had a focal seizure. In all patients, the seizure started in the contralateral hand area corresponding with the cortical stimulation side, with repetitive twitching. The seizure did not occur during stimulation, but with a latency period of more than 1 hour. The seizure could be controlled by acute application of additional intravenous (i.v.) antiepileptic drugs. The antiepileptics were stopped before discharge from the hospital. In the follow-up, no recurrent seizures occurred.

Discussion

The goal of this study was to provide insight in the cortically-evoked responses of the human STN and evaluate the safety of this approach. We observed significant excitations and inhibitions as a response to MCS. Responses varied between different depths and between different locations in the anterior-posterior and

mediolateral plane within the STN. These responses can be used to identify the motor area of the STN. Selective DBS of the motor part of the STN has the potential to prevent unwanted behavioral side effects.

Studies in rats and primates showed typical triphasic responses, consisting of an initial excitation, a subsequent inhibition, and a second excitation.[19,22–24] In contrast to intracortical stimulation electrodes in animal studies, we used flat stimulation electrodes placed on the cortical surface. It is likely that the difference in methodology is responsible for the lack of clear triphasic responses in human studies.[25] On the other hand, a contraction of the contralateral hand musculature was observed after each cortical stimulus, which indirectly proved that a significant number of pyramidal neurons in the hand area of the motor cortex (MC) were excited. A new finding is that in all electrode trajectories at different ventrodorsal locations an ''intermediate'' excitation (starting from ~63–79 ms) was present in the period of the long-lasting inhibition. The most reasonable explanation for this third excitation is a sensory response of the STN to the muscular contraction induced by the MCS.[26]

We believed that the burden of the affective and cognitive side effects outweighed the risks of the MCS procedure (additional burr hole, cortical stimulation). An important limitation of subdural MCS in our study is the occurrence of partial seizures. The risk of a seizure is related to the applied current and current density. In our stimulation protocol (settings: bipolar, monophasic, 0.2 ms, 15 mA, 1.1 Hz), the current density was $\pm 72\ \mu C/cm^2$, which might have been too high and thereby causing seizures. A second important consideration is the application of charge-balanced stimulation, which is achieved by biphasic instead of monophasic stimulation. Seizures also occur in other intraoperative procedures during which the cortex is stimulated repetitively (incidence of 1.2%).[27] Interestingly, subdural MCS has been applied with a similar stimulation protocol without inducing epileptic seizures.[14] The main difference between the stimulation protocols is that Nishibayashi et al.[14] applied a lower number of stimuli and the electrode contact size was larger. To prevent seizures the current density should be lowered, so that MCS-evoked responses can be safely used during DBS surgery. ■

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