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Subthalamic deep brain stimulation for Parkinson's disease: Correlation between locations of oscillatory activity and optimal site of stimulation

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ABSTRACT

Subthalamic nucleus deep brain stimulation (STN DBS) is an effective surgical treatment for Parkinson's disease (PD). Recent studies demonstrated that pathological oscillations are seen largely within the dorsolateral portion of the STN, which is the same location that predicts optimal therapeutic benefit with DBS; however, the precise nature of the relationship between these two phenomena remains unclear. The purpose of this study was to explore localization of oscillatory activity in relation to the optimal contacts of DBS which results in the best motor improvement. We studied 23 PD patients who underwent electrode implantation into the STN for motor symptoms.

Microelectrode recordings were taken from the STN during surgery and neuronal activity was analyzed offline. Spectral characteristics were calculated. Clinical outcomes were evaluated pre- and post-STN DBS implantation using the Unified Parkinson's Disease Rating Scale (UPDRS III). The position of optimal electrode contacts was assessed by postoperative magnetic resonance imaging (MRI) and was compared to the location of oscillatory activity within the STN as well as its dorsal margin (where STN neuronal activity was first detected). Of the total 188 neurons obtained, 51 (27.1%) neurons showed significant oscillatory activity. Of those, 47 (92.2%) were localized in the dorsal portion of the STN. Furthermore, there was no significant difference between the averaged coordinates of the position of 40 optimal contacts and the coordinates of the dorsal margin of the STN. The data indicate that the positions of the best contacts correlate with the locations of the oscillatory neurons supporting the prediction that stimulation of the dorsolateral oscillatory region leads to an effective clinical outcome for STN DBS surgery.

1. Introduction

Subthalamic nucleus deep brain stimulation (STN DBS) is an effective surgical treatment for Parkinson's disease (PD). This therapeutic advance is not only based on an increased understanding of the pathophysiology of PD from studies of the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) monkey model of PD, but also on intraoperative neuronal recordings of patients with PD. These studies demonstrated changes in neuronal firing and excessive oscillations in the parkinsonian basal ganglia nuclei such as the STN and the globus pallidus internus, suggesting that altered neuronal activity may contribute to the pathophysiology of PD [1–7].

Neuronal recording from the human basal ganglia is possible because of the current surgical treatment for PD. During implantation of an STN DBS macroelectrode, a microelectrode recording of extracellular activity is performed to locate physiologically the STN. The local field potential (LFP) can also be extracted from the implanted macroelectrode within the STN [8]. These studies demonstrated that (a) oscillations in the STN in the tremor frequency band (4–6 Hz) were frequently consistent with the tremor in a particular limb [4]; and (b) the β frequency band may be particularly important in the development of bradykinesia [1,9]. In addition, oscillations in the tremor frequency and β frequency bands are preferentially expressed in the dorsolateral area of the STN [1,4–7]. Each of these frequencies in the dorsal region is consistent with activity over motor cortical areas, suggesting that this site might predict clinical outcome [10,11]. Moreover, it has been proposed that chronic stimulation of the STN improves parkinsonian symptoms by disrupting pathological oscillatory activity.

It is known that the sensorimotor region of the STN is primarily located dorsolaterally. Oscillatory activity is mainly distributed

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within the dorsolateral portion of the STN [6–8] where stimulation will likely produce optimal therapeutic benefit to patients undergoing STN DBS [6,7,12,13]. A significant correlation was seen between the outcome of STN DBS and length of the dorsolateral oscillatory region [6]. Moreover, there was also a correlation between oscillations of dorsal STN neurons and PD motor symptoms [7]. Although these findings indicate that interrupting oscillatory activities results in improved parkinsonian symptoms during DBS, the precise relationship between the best sites for these two phenomena remains unclear.

We investigated the relationship between the location of the oscillatory activity and the best electrode contacts of DBS. We recruited 23 PD patients who were undergoing electrode implantation into the STN. We measured the oscillatory activity and its location in the STN as well as the dorsal margin of the STN (where STN neuronal activity was first detected).

2. Methods

2.1. Patients

Twenty-three consecutive patients with PD (14 males, 9 females, age 58.2 ± 9.1) who underwent bilateral ($n = 17$) or unilateral ($n = 6$) implantation of electrodes for STN DBS were studied. All patients had the diagnosis of idiopathic PD based on medical history, physical and neurological examinations, response to levodopa or dopaminergic drugs, laboratory tests, and MRI scans to exclude other diseases. Mean duration of disease was 7.7 ± 3.3 years; mean dosage of L-dopa was 695.7 ± 354.8 (mg/day). All patients had obvious bradykinesia, rigidity and at least a mild tremor. They were assessed with the Unified Parkinson's Disease Rating Scale (UPDRS) [14], and Hoehn and Yahr staging [15] while off their medications. The mean UPDRS III (Motor) score was 35.6 ± 7.9 and the mean Hoehn and Yahr score was 2.8 ± 0.6 at time of surgery.

The study was approved by the Ethics Committee of Xuanwu Hospital, Capital Medical University, China according to the Declaration of Helsinki; written informed consent was obtained from all patients.

2.2. Surgical procedure and electrophysiology

Prior to surgery, patients were off all medications for at least 12 h. STN exploration was performed according to standard stereotactic surgery procedure [4,16,17] using the CRW frame (Radionics, Burlington, MA, USA). The frame coordinates of anterior (AC) and posterior (PC) commissures were measured by using sagittal magnetic resonance imaging (Siemens 1.5 T, Sonata, Germany). STN location was calculated based on the stereotactic atlas of Schaltenbrand & Wahren [18]. The coordinates for the target of the STN were: 12 mm lateral, 1 mm posterior, and 4 mm inferior to the midcommissural point. The anteroposterior angles were about 60° and lateromedial angles about 12° from horizontal. One microelectrode pass was usually used per patient to reduce the possibility of an intracranial hemorrhage. When the microelectrode did not hit the STN target a second microelectrode pass was made.

Microelectrode recording was performed to identify the borders of the STN and thus determine its maximal length. A tungsten microelectrode with tip size of 10–20 μm and resistances from 0.1 to 0.5 MΩ at 1000 Hz (AlphaOmega Engineering, Nazareth, Israel) was used. Localization of the STN was based on previous studies [4,16,17,19]. Briefly, when the electrode entered the dorsal border of the STN there was increased background and high-frequency activities with relatively irregular neuronal discharges as well as burst activity. As the electrodes were advanced past the ventral border of the STN, background noise gradually decreased until the substantia nigra pars reticulata was reached. This was identified by a higher frequency, which became more regular and had lower-amplitude discharges compared with the STN. The base of the STN was indicated by a reduced number of active neurons followed by electrical silence for 0.5–3 mm depending on laterality [4,19].

A channel of neuronal signals was amplified (×20,000–50,000), filtered (with bandpass of 200 Hz–10 kHz), and sampled at 50 kHz. Three channels of electromyograms (EMGs) were simultaneously recorded using surface electrodes from the extensor carpi radialis (ECR), flexor carpi radialis (FCR) and the tibialis anterior (TA) muscles on the contralateral side. EMG signals were amplified (×5000–10,000) and filtered (with bandpass of 100 Hz-1 kHz). All recordings were made with patients at rest using the Alpha Omega-Studio program (AlphaOmega Engineering, Nazareth, Israel).

After the dorsal and ventral margins were determined, the longest, most lateral segment of the STN was chosen to maximize the number of contacts within the STN as the ultimate DBS lead target [20]. A quadripolar electrode (model 3389; Medtronic, Inc., Minneapolis, MN, USA) was implanted instead of a microelectrode; efficacy and side effects were assessed using a Test Stimulator External Control (Mode 3625, Medtronic Inc., Minneapolis, MN, USA). The internal pulse generators (IPG) (Medtronic Inc. Minneapolis, MN, USA) were then implanted under general anesthesia on the day of surgery [20]. The post-operative MRI was obtained 3–5 days post-surgery to examine electrode position.

Postoperatively, the contact with the best effect and least significant adverse effect was chosen for chronic stimulation [13]. All patients were awake and conscious throughout the procedure, to insure their cooperation with the neurosurgeon.

2.3. Data analysis

Single units were first identified visually to detect neuronal waveform and shape [17,19]. Action potentials were confirmed to arise from a single neuron by amplitude and waveform criteria including examining whether the shape of the action potential was constant for at least 15–20 s. Then, neuronal discharges were converted into Spike2 (Cambridge Electronic Design, UK) using the spike-sorting function for further discrimination. Only periods during which there were no voluntary movements or artifacts were analyzed and spikes having a signal-to-noise ratio greater than 2:1 were used. Rectified raw signals, spike trains, and EMG data were imported into MATLAB 7 (The MathWorks, Natick, MA, USA) for further analysis. The interspike interval (ISI) and mean spontaneous firing rate (MSFR) were measured. The ISI histogram was constructed. For spectral analysis, all spike trains and EMG signals were full wave corrected, down sampled, and then imported into MATLAB 7 (The MathWorks, Natick, MA, USA) and MATLAB sigTOOL (version 0.96) for further analysis.

Oscillatory characteristics were evaluated using the power spectrum density (PSD) of the spike trains with the Welch method. Its parameters included a Hanning window of a length equal to the number of samples in 2 s, and a 50% overlap between windows that yielded a frequency resolution of 0.5 Hz. Significant oscillation frequencies were determined when those exceeded a threshold of 5 SD above the mean power in the 30–70 Hz band [3]. The main oscillation frequency was defined as the frequency with the maximal power of all the frequencies which exceeded the threshold.

Coherence analysis was used to study the extent of the relationship between neuronal oscillatory activity with TFB and related EMG activity. The coherence function is the cross spectral density of the two traces normalized by their autospectrums. Therefore, coherence values range between 0 and 1, indicating no relationship and a perfect linear phase relationship. Perfect coherence in a certain frequency requires both signals to have a constant phase relation throughout the entire recording duration. The frequency resolution was 0.5 Hz, using the same parameters as for the PSD calculation [21]. A coherence of >0.42 at a given frequency indicated that the two signals were likely ($p < 0.05$) to be related linearly at that oscillatory frequency [22].

2.4. Postoperative MRI and position of electrode

As suggested in a previously published report, postoperative MPRAGE MRI (magnetization-prepared rapid acquisition gradient sequence) was used 3–7 days after the surgery to measure electrode position [16]. The exact position of each contact was not visible in the postoperative MRI due to artifacts. The coordinates of each contact were calculated according to the most reliable distal tip of the electrode [16]. Since both contacts and corresponding artifacts have the same center, the distance from the distal tip of artifacts to the center of each contact (distal to proximal: contact 0, contact 1, contact 2, and contact 3) was 2.15 mm, 4.15 mm, 6.15 mm, and 8.15 mm. Moreover, the anteroposterior angle of the electrode and the anteroposterior and vertical coordinates of the distal tip were calculated on the sagittal planes. The lateromedial angle of the electrode and the lateral coordinate of the distal tip were obtained on the coronal planes. When all information, including position of the tip, trajectory angle, and distance from the distal tip to the center of each contact was obtained, the coordinates of each contact could be deduced relative to the mid-commissural point.

2.5. Position of the dorsal and ventral margins and dorsal half of the STN

The length of the STN was determined by microelectrode recordings. In the postoperative MRI, the coordinates of the dorsal margin of STN were obtained by calculating the vertical plane of the implantation trajectory (related to the target) corresponding to the most proximal point at which the typical discharge pattern of the STN neurons was located. In contrast, the ventral margin of STN was obtained by calculating the most distal point at which the typical discharge patterns of the STN completely disappeared. The dorsal half of the STN was defined as the midpoint between the dorsal and ventral margins of the STN [16].

2.6. Assessment of clinical outcome and definition of the best contact

All patients were assessed pre- and post-operatively using the UPDRS III [14] in the "off" and "on" medicated states, and were followed for at least 12 months after DBS implantation.