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Functional neuronal activity and connectivity within the subthalamic nucleus in Parkinson's disease

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HIGHLIGHTS

- Significantly different firing behavior of single units has been demonstrated in the sensorimotor part of the STN compared to the remaining part in PD patients.
- This includes increased mean firing rate, more bursty behavior of neurons and increased interneuronal coherences in the beta band.
- Postoperative evaluation of target stimulation areas in the investigated PD patients with DBS shows a significant preference for the sensorimotor part of the STN.

ABSTRACT

Objective: Characterization of the functional neuronal activity and connectivity within the subthalamic nucleus (STN) in patients with Parkinson's disease (PD).
Methods: Single units were extracted from micro-electrode recording (MER) of 18 PD patients who underwent STN deep brain stimulation (DBS) surgery. The firing rate and pattern of simultaneously recorded spike trains and their coherence were analyzed. To provide a precise functional assignment of position to the observed activities, for each patient we mapped its classified multichannel STN MERs to a generic atlas representation with a sensorimotor part and a remaining part.
Results: Within the sensorimotor part we found significantly higher mean firing rate ($P < 0.05$) and significantly more burst-like activity ($P < 0.05$) than within the remaining part. The proportion of significant coherence in the beta band (13–30 Hz) is significantly higher in the sensorimotor part of the STN than elsewhere ($P = 0.015$).
Conclusions: The STN sensorimotor part distinguishes itself from the remaining part with respect to beta coherence, firing rate and burst-like activity and postoperatively was found as the preferred target area.
Significance: Our firing behavior analysis may help to discriminate the STN sensorimotor part for the placement of the DBS electrode.

1. Introduction

Parkinson's disease (PD) is a progressive neurodegenerative disorder primarily associated with motor symptoms including muscle rigidity, tremor of the limbs at rest, slowness and impaired scaling of voluntary movement (bradykinesia), loss of voluntary movements (akinesia) and postural instability (Jankovic, 2008). The underlying pathology in PD mainly consists of a loss of dopaminergic neurons in the substantia nigra pars compacta. These neurons project to the striatum and hence their degeneration leads to a loss of dopamine in the main input structure of the basal ganglia. This depletion changes neuronal firing rates in basal ganglia nuclei, increasing firing rates in the striatum, the globus pallidus pars interna and the subthalamic nucleus (STN) and a slightly decreased

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discharge in the globus pallidus pars externa (Heida et al., 2008). On the other hand, the type of discharge pattern, i.e., the interneuronal synchronization of basal ganglia neurons, is thought to be as important as the rate of discharge in the execution of smooth movements (Bergman et al., 1998; Bergman and Deuschl, 2002; Boraud et al., 2002; Hammond et al., 2007). In PD patients several alterations in the discharge pattern and interneuronal synchronization have been observed in neurons of the basal ganglia, including a tendency of neurons to discharge in bursts, an increased synchronization of discharge rate between neighboring neurons, and rhythmic and oscillatory behavior (Levy et al., 2000; Brown, 2003, 2007; Kühn et al., 2004; Gatev et al., 2006).

State of art models are inferring synchronously oscillating activity in one or several nuclei of the basal ganglia as being strongly related to PD motor symptoms, with the STN playing a pivotal role (Hammond et al., 2007; Jenkinson and Brown, 2011). Furthermore, it is recognized that the STN is subdivided in functionally segregated areas, including the sensorimotor, associative and limbic area (Parent and Hazrati, 1995; Hamani et al., 2004; Benarroch, 2008). It is also hypothesized that symptom-specific topography within STN is determined by distinct neuronal oscillatory activity, with beta-frequency oscillations (13–30 Hz) correlating to bradykinesia and rigidity (Kühn et al., 2006, 2009; Weinberger et al., 2006; Ray et al., 2008). Theta-frequency oscillations in the basal ganglia (3–8 Hz) have been associated with both Parkinsonian tremor and essential tremor (Levy et al., 2000; Steigerwald et al., 2008; Contarino et al., 2012).

Deep brain stimulation (DBS) is an established therapy to reduce PD motor symptoms, when medication does no longer produce satisfying results (Hamani et al., 2006; Benabid et al., 2009). The STN is a commonly used target of DBS for PD. During the stereotactic surgery, to verify and refine the position of the DBS target, often microelectrode recording (MER) is performed with up to five parallel tracks. Spiking activity and noise levels are visually inspected and interpreted real-time during surgery, but the obtained MER signals can also be analyzed more extensively and quantitatively off-line.

A way to obtain more knowledge about the functional anatomical network structure within the STN is to study the coherence between firing behavior of the STN neurons. Coherence between neuronal firing patterns is a quantitative measure to characterize neuron's synchronous activity which is a consequence of neuronal interconnections. In the current study we analyzed local coherence from the MER signal, i.e., the coherence between single units lying within the capture area of the micro-electrode (distance <150 μm). Also the global coherence was analyzed, i.e., the coherence between units that are identified on different micro-electrodes (distance >2 mm).

As a result of this analysis the spatial distribution of coherences within the STN across different frequency bands was obtained and we were able to relate coherent activity and connectivity in the different frequency bands to the sensorimotor part and the limbic associative part of the STN. In addition, we investigated the firing rate and discharge pattern of individual cells within the different areas of the STN. If the obtained information about neuronal activity is distinct for the two STN regions, it might be used to refine further the electrode implantation for DBS in the sensorimotor part.

2. Methods

Data of STN spiking activity obtained during DBS surgery in PD patients as part of the routine procedure was retrospectively retrieved. The position of each recording in each patient was mapped onto a generic STN. We generated spike trains from single units using spike sorting from the recorded activity. If a recording contained activity of reliably identified multiple units, the firing rate and discharge pattern of each unit were analyzed as well the interneuronal correlation of their activity. The Medical Ethical Committee of the Academic Medical Center in Amsterdam was officially consulted and denied the need for an approval for this study.

2.1. Patients

Micro-electrode recordings (MER) from PD patients who underwent stereotactic surgery from January 2008 until April 2011 for implantation of stimulating electrode in the STN were considered. In total MER data from 18 PD patients, with at least two simultaneously recorded single units, were used. MERs of 11 patients were bilateral. Demographic data and clinical information were retrospectively collected from the patient files (Table 1). The presence of tremor was preoperatively evaluated by a neurologist or Parkinson nurse specialized in movement disorders.

2.2. Surgical and micro-electrode recording procedure

The procedure for STN-DBS was a one-stage bilateral stereotactic approach, using MER to delineate the borders of the STN. Frame-based three-dimensional MRI reconstructions were used for STN targeting and trajectory planning. For this purpose the Leksell stereotactic frame and Leksell Surgiplan software (Elekta Instruments AB, Stockholm, Sweden) were used. On T1 MRI scans the position of the anterior commissure (AC) and posterior commissure (PC) were marked by the neurosurgeon and standard STN coordinates were obtained 12 mm lateral, 2 mm posterior and 4 mm below the midcommissural point (MCP). Adjustments were then made according to individual anatomy as visible on axial and coronal T2 MRI sequences, providing the stereotactic cartesian (x, y, z) coordinates of the STN target point. The trajectories of the micro-electrodes, that were attached to the frame and placed in a microdrive, were expressed in the stereotactic space by the arc and ring angle relative to the frame and by the STN target point. The microdrive depth zero of the central electrode corresponded to the MRI based STN target point. The paths were defined using the following criteria: anterior angulation to intercommissural line of 15–20°, lateral angulation from midline 20–30°, entry on top of a gyrus and avoiding sulci, cortical surface veins, and lateral ventricles. Under local anesthesia a 12 mm diameter burr-hole in the skull was made centered on the stereotactically identified entry point. All patients were awake during the entire recording session and without any sedatives. Surgery was performed following overnight withdrawal of anti-Parkinson medication.

Extracellular single/multi-unit micro-recordings were performed from small polyamide-coated tungsten micro-electrodes (FHC micro-electrode 291; impedance 1.1 ± 0.4 MΩ measured at 220 Hz, at the beginning of each recording session) with 20 μm exposure, mounted on a sliding cannula. Three to five steel cannulas and micro-electrodes (Table 1) were used and were placed in a so-called Ben's gun, with a central cannula directed to the planned STN coordinates and four parallel cannulas equally spaced around the central position with a center-to-center distance of 2.0 mm (anterior, posterior, lateral and medial cannulas). Starting 6–8 mm above the MRI-calculated STN target, the micro-electrodes were advanced simultaneously in 0.5-mm-steps by a manual microdrive. Advancing was stopped when electrical activity typical of substantia nigra cells was recognizable in at least one of the electrodes or when a significant decrease of electrical activity was present in all recordings. Clinical testing was performed at several sites by an experienced movement disorders neurologist. The permanent quadripolar DBS electrode (Model 3389) was implanted at the site with the best therapeutic window, i.e., best effect on motor symptoms and higher threshold for side-effects. The final position of all