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Pedunculopontine nucleus evoked potentials from subthalamic nucleus stimulation in Parkinson's disease

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ABSTRACT

The effects of subthalamic nucleus (STN) stimulation on the pedunculopontine nucleus area (PPNR) evoked activities were examined in two patients with Parkinson's disease. The patients had previously undergone bilateral STN deep brain stimulation (DBS) and subsequently received unilateral DBS electrodes in the PPNR. Evoked potentials were recorded from the local field potentials (LFP) from the PPNR with STN stimulation at different frequencies and bipolar contacts. Ipsilateral and contralateral short latency (<2 ms) PPNR responses were evoked from left but not from right STN stimulation. In both patients, STN stimulation evoked contralateral PPNR responses at medium latencies between 41 and 45 ms. Cortical evoked potentials to single pulse STN stimulation were observed at latencies between 18 and 27 ms. These results demonstrate a functional connection between the STN and the PPNR. It likely involves direct projections between the STN and PPNR or polysynaptic pathways with thalamic or cortical relays.

Olszewski and Baxter (1954) defined the nucleus tegmenti pedunculopontinus (PPN) in the human brainstem as a nucleus of "unknown connections" which occupies the ventrolateral part of the caudal mesencephalic tegmentum lateral to the superior cerebellar peduncle. In rodents, pedunculopontinus nucleus region (PPNR) connections have been studied using tracers and evoked-potentials (Garcia-Rill et al., 1987; Garcia-Rill and Skinner, 1987a,b; Rye et al., 1987; Spann and Grofova, 1989, 1991). There are differences between the connections described in rodents and those shown in primates using tracing studies (Lavoie and Parent, 1994a,b,c; Pahapill and Lozano, 2000). While both the rodent and primate PPNR have important connections with the subthalamic nucleus (STN), substantia nigra (SN), and globus pallidus (GP) (Lee et al., 2000), direct connections between the PPNR and motor cortex are present only in primates, and projections from the PPNR to the deep cerebellar nuclei or extending down the spinal cord have only been shown in rodents. A study using probabilistic diffusion tractography (PDT) (Muthusamy et al., 2007) suggested that PPNR connections in humans are similar to those in primates. A major limitation of diffusion tractography is that it cannot determine the direction of projections, or whether they are interrupted by synapses.

These different results illustrate the importance of verifying the existence of connections between PPNR and other nuclei and to study the nature of these connections in humans. With the emerging use of STN and PPNR DBS for treatment of movement disorders, it is of clinical importance to investigate the connectivity between STN and PPNR in humans. The effects of DBS are not limited to the targeted structure, but affect the distributed functional networks to which the target structure belongs. It has been suggested that some of the effects of STN DBS, particularly those related to gait and balance, are related to the connection from STN to PPNR (Chen and Lemon, 2004). Furthermore, establishing the topography of cortical and sub-cortical connections of the PPNR in the human brain may aid the accurate targeting of critical pathways in DBS.

The current study investigated the responses in PPNR from STN stimulation. We hypothesize that responses in the PPNR can be observed from STN stimulation, suggesting that there are mono- or poly-synaptic connections between the STN and PPNR.

Materials and methods

Patients

Two PD patients (1 man and 1 woman) who have had previous bilateral STN DBS subsequently received unilateral PPNR DBS (patient 1 right PPNR and patient 2 left PPNR). Details of the patients including the DBS clinical settings are presented in Table 1. The patients provided

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Table 1
Clinical details of patients studied.

Patient	Age (years)/ sex	Disease duration (years)	Preoperative medication (mg/day)	Predominant preoperative symptoms	mUPDRS		Therapeutic STN DBS settings	Therapeutic PPN DBS settings
					Off	On		
1	60/F	17	Levodopa 1000	Postural instability, falls, wearing off, off period dystonia, right arm tremor	43 36[a]	36.5 36	RSTN: 3.6 V, 185 Hz, 60 μs, 3 −/case + LSTN: 3.6 V, 185 Hz, 60 μs, 1 −,2 −/case +	RPPN: 3.5 V,70 Hz, 60 μs, 2 + 3 −
2	50/M	20	Levodopa 900 Pramipexole 7.5	Off freezing, off 50% of the day, motor fluctuations	25 19.5[a]	14 17	RSTN: 3.4 V, 185 Hz, 90 μs, 3 −/case + LSTN: 3 V, 185 Hz, 60 μs, 2 −,3 −/case +	LPPN: 3.6 V, 50 Hz, 60 μs, 2 + 3 −

Abbreviations: mUPDRS—motor section of the Unified Parkinson's Disease Rating Scale.
[a] On STN DBS.

written informed consent and the study was approved by the University Health Network Research Ethics Board.

Stimulation and recording

The studies were performed 2 days after the implantation of quadripolar PPNR DBS electrodes (Medtronic 3387) with 1.5-mm between the contacts that were numbered 0 to 3 from ventral to dorsal. The STN DBS stimulator not being studied was turned off. Both patients took their regular dopaminergic medications and were comfortably seated in a chair throughout the study that lasted about 60 min. Monopolar LFPs from the PPNR DBS electrodes and scalp EEG at Fp1, Fz, Cz, C3, C4, CP3, and CP4 according to the International 10–20 system were recorded with linked ear reference using a SynAmps Amplifier (Neuroscan, NC USA) with gain of 2500 and sampling rate of 10 kHz. STN stimulation was carried out with the Kinetra implanted pulse generators (IPG) (Medtronic Inc.). Because monopolar stimulation produced large and prolonged stimulus artifacts, STN was stimulated using bipolar configurations at 3 Hz, 5 Hz and 10 Hz at a pulse width of 60 μs or 90 μs. The bipolar stimulating configurations were: 0 − 1+, 0 + 1−, 1 − 2+, 1 + 2−, 2 − 3+, 2 + 3−. Not all bipolar configurations and stimulation frequencies were tested in each patient due to time limitations. For each stimulating frequency, the recording time was adjusted to obtain at least 1000 epochs for averaging. The STN bipolar derivations and stimulation parameters used during this study are shown in Table 2.

During the recordings, surface electromyography (EMG) was recorded from the contralateral abductor pollicis brevis (APB). The EMG signal was amplified through an Intronix amplifier (Model 2024F, Intronix Technologies Corporation, Canada) with a gain of 1000 and band pass filter 20 to 200 Hz.

Details regarding the location of the PPNR electrodes were previously described (Tsang et al., 2010; in figure e-1, location 3b refers to the location of PPNR contact for patient 1 and location 4b refers to that for patient 2). For both patients, contact 2 was located in the vicinity of the pedunculopontine nucleus, pars diffusa (PPTgD). For the electrode location in STN, post-operative MRI revealed that for patient 1, contact 2 was located in the RSTN and contact 1 was located in the LSTN. For patient 2, contact 1 was located in the RSTN and LSTN.

Data analysis

The LFP recordings were DC corrected and transformed to epochs, with the stimulus artifact at the beginning of each epoch. The length of the epoch varied between 100 and 333 μs depending on the stimulation frequency. The monopolar PPNR recordings were transformed into bipolar montages between adjacent contacts (0–1, 1–2, 2–3) and then time averaged. We analyzed the amplitudes and latencies of the responses evoked in the cortex and PPNR following STN stimulation. All the amplitudes were calculated as peak-to-peak (p–p). For waveforms with phase reversal, the amplitude of the reversal was measured from the peak preceding the phase reversal. If the phase reversal was polyphasic, we measured the latency and the amplitude of the first major peak of the complex. For the monopolar cortical evoked potentials, we calculated the peak to peak amplitude of the first positive deflection from the preceding negative peak.

To reduce the stimulus artifacts and detect short latency evoked responses in the PPNR, we added the recorded sweeps obtained with bipolar STN stimulation of opposite polarity (e.g. STN 0 − 1+ and STN 0 + 1− were added). The rationale for this was that with stimulation of opposite polarity, evoked responses would not change polarity while the artifacts would reverse polarity (Walker et al., 2012). Thus, by addition the artifacts of opposite polarity will cancel each other out.

Data analysis was performed using Scan 4.5 (Neuroscan, NC USA) and Origin 8 (OriginLab Corporation). No statistical methods were used in the data analysis.

Results

The recordings from patient 1 are presented in Fig. 1 and from patient 2 in Fig. 2.

Table 2
STN bipolar stimulation configurations and parameters used.

Patient 1 (RPPN)				Patient 2 (LPPN)			
RSTN		LSTN		LSTN		RSTN	
Contact	Stimulation parameters	Contact	Stimulation parameters	Contact	Stimulation parameters	Contact	Stimulation parameters
3 − 2+	5 Hz, 10.5 V, 60 μs	2 − 3+	5 Hz, 10.5 V, 60 μs	2 − 3+	5 Hz, 10.5 V, 60 μs	3 − 2+	5 Hz, 10.5 V, 90 μs
3 − 2+	10 Hz, 10.5 V, 60 μs	3 − 2+	5 Hz, 10.5 V, 60 μs	2 − 3+	10 Hz, 10.5 V, 60 μs	3 − 2+	10 Hz, 10.5 V, 90 μs
3 − 2+	3 Hz, 10.5 V, 60 μs	2 − 1+	5 Hz, 10.5 V, 60 μs	2 − 3+	3 Hz, 10.5 V, 60 μs	3 − 2+	3 Hz, 10.5 V, 90 μs
2 − 3+	5 Hz, 10.5 V, 60 μs	2 − 1+	10 Hz, 10.5 V, 60 μs	3 − 2+	5 Hz, 10.5 V, 60 μs	2 − 3+	5 Hz, 10.5 V, 90 μs
1 − 2+	5 Hz, 10.5 V, 60 μs	2 − 1+	3 Hz, 10.5 V, 60 μs	1 − 2+	5 Hz, 9.5 V, 60 μs	1 − 2+	5 Hz, 5 V, 90 μs
0 − 1+	5 Hz, 10.5 V, 60 μs	1 − 2+	5 Hz, 10.5 V, 60 μs	2 − 1+	5 Hz,10.5 V, 60 μs	0 − 1+	5 Hz, 4.5 V, 90 μs
		0 − 1+	5 Hz, 10.5 V, 60 μs	0 − 1+	5 Hz, 6.5 V, 60 μs		
		1 − 0+	5 Hz, 10.5 V, 60 μs	1 − 0+	5 Hz, 10.5 V, 60 μs		