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Short communication

Bradykinesia induced by frequency-specific pallidal stimulation in patients with cervical and segmental dystonia

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ABSTRACT

Introduction: Pallidal deep brain stimulation (DBS) is an effective treatment for patients with primary dystonia leading to a substantial reduction of symptom severity. However, stimulation induced side effects such as bradykinesia have also been reported recently. The influence of stimulation parameters on such side effects have not yet been systemically assessed in these patients.
Methods: Here we tested the effect of stimulation frequency and duration of stimulation period on hand motor function in 22 patients with primary cervical and segmental dystonia using an unimanual tapping task. Patients performed the task at 4 different stimulation frequencies (0 Hz = OFF stimulation, 20, 50 and ≥130 Hz = high frequency stimulation) after either an SHORT (5 min, N = 16) or a LONG (60 min, N = 6) stimulation period (i.e. changing of DBS-frequency). The change of overall mobility under HFS compared to the preoperative state was assessed with a 5-point Likert-scale. Tapping performance was analysed using a repeated measures ANOVA with the main factor 'FREQUENCY'. Tapping performance at HFS and changes in general mobility were correlated using Spearman's Rho.
Results: We found a frequency specific modulation of hand motor function: HFS led to deterioration and 20 Hz stimulation to improvement of tapping rate. The effects were predominant in the 'LONG' group suggesting a significant contribution of stimulation duration.
Conclusions: This is important to consider during DBS-programming and evaluation of potential side effects. Furthermore, the impairment in hand motor function under HFS was mirrored by the patients' observation of a deterioration of general mobility.

1. Introduction

Over the recent years deep brain stimulation (DBS) of the internal segment of the *Globus pallidus* (GPi) has been established as an effective treatment for primary dystonia including generalized, segmental and focal dystonia [1]. Parameter setting for DBS in patients with dystonia is, however, more challenging and requires more time and effort as compared to other indications for DBS such as Parkinson's disease (PD) and essential tremor because DBS-induced clinical effects often occur only after days to weeks or months [2]. Thus, a top-down approach has been suggested meaning that high amplitudes of DBS just below the threshold for immediate side effects (such as capsular effects, phosphenes or dysarthria) are used during initial programming. Similar to the delayed clinical effect seen in patients with primary dystonia that may reflect changes in plasticity [3], also stimulation-induced deleterious effects may build up over time in those patients. This limitation becomes more evident in patients with focal (e.g. cervical) dystonia that are successfully treated with DBS but at the same time develop stimulation induced bradykinesia as recent studies have reported [e.g.4]. In these patients reduction of stimulation amplitude improved bradykinesia but worsened dystonic

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symptoms. Moreover, bradykinesia was not responsive to levodopa treatment. The time course of these adverse effects as well as frequency-specific effects of stimulation were, however, not systematically assessed in these studies. Here, we tested the effect of stimulation frequency and duration of stimulation period on hand motor function in patients with cervical and segmental dystonia. Importantly, all patients had preserved normal hand motor function prior to DBS.

2. Methods and material

2.1. Patients and surgery

We examined 22 consecutive patients (aged 53 ± 9.4) with idiopathic cervical or segmental dystonia who had undergone electrode implantation (Model 3389, Medtronic, Minneapolis, MA) either at Charité – Universitätsmedizin Berlin (N = 17) or Universitätsmedizin Mannheim – University of Heidelberg (N = 5) for therapeutic pallidal DBS. Detailed patient demographics and individual DBS parameters are given in Table 1. The stereotactic coordinates at the tip of electrode 0 were 17.4–22 mm lateral from the midline, 2–4 mm in front of the midcommissural point, and 2–4 mm below the midcommissural point. Adjustments were made according to individual anatomic conditions. Correct electrode placement was confirmed in all patients via post-operative MRI (Berlin) or CT scan (Mannheim). In all patients GPi DBS was efficacious leading to a mean improvement in the TWSTRS severity subscale by 49.3% ± 27.1 (n = 20 patients, 2 missing). During regular visits of either inpatient or outpatient care for routine follow up for assessment of the DBS system and for clinical evaluation patients participated in the study after written informed consent. The study was approved by the local ethics committees and was conducted in accordance with the declaration of Helsinki. The mean time between implantation of DBS electrodes in the GPi and participation in the study was 23.7 ± 26.2 months (range 2.4–89.0). Only patients with stable (i.e. unchanged parameters for ≥8 weeks) DBS settings leading to clinical improvement (reflected by the reduction in TWSTRS severity scale) were included in the study. Prior to the experiment patients were queried to define how their overall mobility in daily living has changed under pallidal DBS therapy (i.e. before electrode implantation vs. the current state) on a 5-point Likert scale (−1 = improvement; 0 = no change; 1 = mild, 2 = moderate, 3 = severe deterioration).

2.2. Paradigm

Patients performed an unimanual tapping task. They were instructed to tap a joystick-button with the index finger as often as possible for a period of 30 s. Trials were performed with each hand separately for each frequency condition that included i) therapeutic (chronically used) high frequency (HFS, ≥130 Hz), ii) 20 Hz, iii) 50 Hz and iv) OFF stimulation. Conditions were performed in a randomized order in each patient who was not aware of the current frequency. The task was initiated 5 min (N = 16, 'SHORT' group) or 60 min (N = 6, 'LONG' group) after the frequency had been changed,,i.e the stimulation period was either 5 min or 60 min for each stimulation frequency. There were no group differences regarding age, disease duration or symptom severity (all $p > 0.1$, unpaired t-tests). Tapping performance was sampled online with an analogue-to-digital converter (1401 power mk-II, Cambridge Electronic Design, CED, Cambridge, UK) at 1 kHz and stored for offline analysis. As a reference group, eight healthy subjects (aged 52 ± 8.8) without history of neurological or psychiatric disorder or current prescription for CNS effective medication performed the paradigm.

2.3. Analysis

A repeated measures ANOVA with the main factor 'FREQUENCY' (4 levels: OFF, 20 Hz, 50 Hz, HFS) was calculated for each group.

Table 1
Demographic and clinical patient data.

#	Sex	Centre	Group	Diagnosis	t after OP	Age	TWSTRS		Improvement	Amplitude (V)		DBS contact		PW (μs)		Freq (Hz)
							Severity	Severity								
					Months	Years	Pre OP	Post OP	%	Right	Left	Right	Left	Right	Left	Both
1	f	Berlin	Short	CD	2.63	61	21	6	71.4	2.8	2.8	−1	−5	120	120	180
2	m	Berlin	Short	SD (Meige)	10.70	63	20	7	65.0	3.8	4	−1	−5	90	90	130
3	f	Berlin	Short	CD	19.40	66	21	13	38.1	4	4	−2; −3	−6;−7	90	90	165
4	f	Berlin	Short	CD	16.1	58	26	10	61.5	3	2	−1	−5	90	90	180
5	m	Berlin	Short	CD	9.4	46	23	21	8.7	4	4	−2	−6	120	120	180
6	f	Berlin	Short	CD	29.4	68	23	16	30.4	4	4	0	−4	90	90	130
7	f	Berlin	Short	CD	4.6	49	22	2	90.9	2.6	3	−2	−6	90	90	130
8	m	Berlin	Short	CD	8.3	57	23	17	26.1	5.5	5.5	−3	−7	90	90	130
9	m	Berlin	Short	CD	3.1	54	22	13	40.9	2.05	2.05	−1	−7	90	90	130
10	f	Mannheim	Short	CD	21.1	51	26	16	38.5	3.8	3.8	−1;−2	−5;−6	210	210	130
11	m	Mannheim	Short	CD	89.0	46	24	11	54.2	2.8	3	−2	−5; +6	210	210	130
12	m	Mannheim	Short	CD	10.0	47	23	16	30.4	4.8	4.8	−1; +2	−5; +6	210	210	130
13	m	Mannheim	Short	CD	13.0	51	27	21	22.2	4.9	4.9	−1; +2	−5; +6	210	210	130
14	m	Mannheim	Short	CD	17.0	50	22	8	63.6	2.6	2.6	−2; +3	−6; +7	210	210	130
15	m	Berlin	Short	CD	27.4	43	20	11	45.0	5	7	−2	+5;−6	120	120	130
16	f	Berlin	Long	SD	2.4	49	25	12	52.0	2.5	2.5	−0;−1	−4;−5	90	90	180
17	m	Berlin	Long	SD	12.0	55	22	16	27.3	1	4	−0; +1; +2	−4;−5;−6	60	60	210
18	m	Berlin	Long	CD	11.8	46	19	12	36.8	3.8	2	−1	−5	60	60	130
19	m	Berlin	Long	CD	78.4	68	16	n.a.	n.a.	4.1	3.8	−1	−5	60	90	210
20	f	Berlin	Long	CD	3.2	63	n.a.	n.a.	n.a.	2.4	3.5	−0	−4	90	90	130
21	m	Berlin	Long	CD	67.2	30	22	3	86.4	3.2	2.4	−3	−6	120	120	180
22	m	Berlin	Long	CD	65.4	46	24	1	95.8	2.5	2.5	−1	−5	90	90	130
mean					23.71	53.05	22.43	11.60	49.27	3.42	3.55	mono = 18	mono = 17	118.64	120.00	150.23
SD					26.15	9.33	5.39	6.47	27.09	1.10	1.25	bi = 4	bi = 5	53.57	52.37	28.89

Centre = neurosurgical centre where patients were operated; Group = LONG or SHORT stimulation period; CD = cervical dystonia; SD = segmental dystonia; time of the experiment after DBS operation in months; TWSTRS = Toronto Western Spasmodic Torticollis Rating Scale Severity Subscale; DBS contact: 0 most caudal, 3 most dorsal; Polarity: + = cathode, - = anode, IPG case is used as cathode if not otherwise specified; PW = pulse width in μs; Freq = stimulation frequency in Hertz for chronic (i.e. therapeutic stimulation).

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