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Subthalamic oscillatory activities at beta or higher frequency do not change after high-frequency DBS in Parkinson's disease

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Abstract

This study aimed to assess whether changes in the patterns of local field potential (LFP) oscillations of the subthalamic nucleus (STN) underlie to the clinical improvement within 60 s after turning off subthalamic DBS. We studied by spectral analysis the STN LFPs recorded in 13 nuclei from 7 patients with Parkinson's disease before and immediately after unilateral high-frequency (130 Hz) stimulation of the same nucleus, when the clinical benefit of DBS was unchanged. The results were compared with LFP data previously reported [A. Priori, G. Foffani, A. Pesenti, F. Tamma, A.M. Bianchi, M. Pellegrini et al., Rhythm-specific pharmacological modulation of subthalamic activity in Parkinson's disease. Exp. Neurol. 189 (2004) 369–379] – namely 13 STN from 9 parkinsonian patients recorded before and after levodopa administration – which were used as a control. Before DBS, in the 'off' clinical state after overnight withdrawal of dopaminergic therapy, the STN spectrum did not significantly differ from the control nuclei, showing prominent activity at beta frequencies (13–20 and 20–35 Hz). After DBS (10–15 min) of the STN, the recorded nuclei significantly differed from the control, failing to show significant changes either in the beta bands or at higher frequencies (60–90 and 250–350 Hz). The patterns of subthalamic LFP oscillations after DBS therefore differ from those after dopaminergic medication. These results suggest (1) that subthalamic LFP modulations are not the epiphenomenon of peripheral motor improvement and (2) that the transitory clinical efficacy maintained after discontinuation of subthalamic DBS is not associated with local modulation of LFP activity at beta or higher frequencies within the STN.

Keywords: Subthalamic nucleus STN; DBS; Local field potentials; LFPs; Basal ganglia; Human; Parkinson's disease

1. Introduction

Despite the remarkable clinical efficacy of high-frequency deep brain stimulation (DBS) for the management of advanced Parkinson's disease [36,42,43,66,67], its mechanisms of action are not completely understood [44,73]. Because the clinical effects induced by lesions and DBS of the same nucleus are similar [43], it was postulated that DBS acted mainly through local inhibition. Experimental data in vitro [9,45], in animals [7,8,10,68,70] and in humans [18,21,41,55,74,78] support the inhibitory hypothesis. Other studies, however, seem to contradict it, providing evidence of efferent excitation produced by DBS [1–6,17,28,33–35,46,58,60,76], consistent with classical electrophysiological observations [32]. A possible solution of the contradiction is the coexistence of local inhibition and efferent excitation [50,77], which can be explained by the differential excitability of neural elements [52,53,64]: DBS probably inhibits the cells' bodies while exciting their axons, hence reducing the cells' firing rate and increasing the efferent output at the same time [47]. Even though this view unifies apparently conflicting experimental results [30], it does not explain the still paradoxical clinical efficacy of DBS, which is likely due to "stimulation-induced modulation of pathological network activity" [48,49].

A common clinical observation offers an experimentally viable and conceptually intriguing opportunity to study the neurophysiolocal basis of DBS clinical efficacy: parkinsonian signs take minutes-to-hours to return after discontinuation of DBS [29,71]. Thus, immediately after turning the stimulator off there

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is a temporal window in which it is possible to investigate DBS-induced neurophysiological changes that are exclusively associated with DBS clinical efficacy but not with DBS per se. Somewhat surprisingly, all studies in human and non-human primates reported virtual absence of long-lasting neurophysiological changes at the single-neuron level after turning DBS off [6,10,18,21,33,50,74,78]. Conversely, long-lasting neurophysiological changes after turning DBS off were observed at the network level – namely in the frontal N30 component of somatosensory evoked potentials – in patients with Parkinson's disease [59]. These results support the above hypothesis that DBS clinical efficacy is related to "modulation of pathological network activity" [29,49]. However, the relative importance of locally induced changes versus efferent modifications induced far away from the site of stimulation remains unclear.

The objective of this study was to investigate whether long-lasting changes of local network activity within the STN are responsible for the long-lasting clinical improvement maintained after discontinuation of subthalamic DBS. Local network activity within the STN was assessed by the analysis of local field potentials (LFPs), i.e. deep EEG activity, recorded through electrodes stereotactically implanted in the STN for DBS in patients with Parkinson's disease [11–13,22–24,26,40,57,63]. Previous studies have shown that STN LFPs are modulated by dopaminergic medication, which inhibits beta oscillations (13–35 Hz) [12] – more specifically in the low-beta range (13–20 Hz) [24,63] – and excites high-gamma oscillations (60–90 Hz) [12,16,23] and 300-Hz oscillations (250–350 Hz) [23,26]. To clarify whether similar network modulations could underlie the long-lasting clinical improvement of DBS, we studied by spectral analysis the STN LFPs recorded in 13 nuclei from 7 patients with Parkinson's disease before and immediately after unilateral high-frequency (130 Hz) stimulation of the same nucleus, when the clinical benefit of DBS was unchanged. The results were compared to LFP data previously reported [63] – namely 13 STN from 9 parkinsonian patients recorded before and after levodopa administration – which were used as a control.

2. Materials and methods

2.1. Patients

LFPs were post-operatively recorded before and after electrical stimulation (high-frequency DBS of the STN) in a sample of 13 STN from 7 patients with idiopathic Parkinson's disease (DBS group), and were contrasted with LFPs recorded before and after pharmacological stimulation (levodopa administration) in a previously reported sample of 13 STN from 9 patients (control group). Details about patients in the DBS group and in the control group can be found in Table 1. All procedures were performed after informed consent and with local ethical committee approval. All patients were treated with DBS only fulfilling specific inclusion criteria [39].

Table 1
Patients' details

	Gender	Age (years)	Disease history (years)	L-dopa equivalents (mg/day)		UPDRS III pre-surgery		Tremor (from UPDRS III) pre-surgery		UPDRS IV (A + B) pre-surgery	LFP recordings
				Pre-surgery	Post-surgery	Off	On	Off	On		
DBS group											
CE	f	55	9	1040	300	34.5	5.5	2	0	9	L–R
GI	f	52	13	900	150	68	21	2	0	5	L–R
PU	m	64	9	825	400	60	16.5	8	0	11	L–R
MA	m	55	12	1260	625	37.5	4	3	0	5	L–R
DM	m	38	3	3230	400	65.5	3	1	0	9	L–R
LG	m	66	10	975	400	30.5	12	0	0	7	R
DI	m	52	16	2400	300	66	18.5	1	0	9	L–R
Mean		54.6	10.3	1518.6	367.9	51.7	11.5	2.4	0.0	7.9	
S.D.		9.2	4.1	927.4	144.9	16.7	7.4	2.6	0.0	2.3	
Levodopa group (control)											
CO	f	54	14	1800	800	62	23.5	0	0	16	L
BE	f	69	14	1380	450	49	1	3	0	12	L–R
PA	f	55	20	1400	75	27	4.5	0	0	17	L–R
MA	m	59	11	1800	75	38.5	4	0	0	14	L–R
CM	m	44	9	1500	500	45.5	4	8	0	8	L
CR	m	48	11	1140	320	29	3.5	2	0	6	R
TO	f	69	12	1200	100	30.5	2.5	9.5	0	11	L–R
ZE	m	58	13	2800	400	39	2	2	1	12	L
SO	f	38	7	800	300	72.5	2	2	0	12	L
Mean		54.9	12.3	1535.6	335.6	43.7	5.2	2.9	0.1	12.0	
S.D.		10.5	3.7	569.3	237.9	15.5	7.0	3.5	0.3	3.5	

The columns represent the following variables: gender; age at time of surgery; years of disease history at time of surgery; therapy – expressed in levodopa equivalents – pre-surgery and 15–20 days post-surgery, at the end of the 'reglage'; UPDRS III pre-surgery 'off' and 'on' levodopa; sum of the five UPDRS scores related to rest tremor pre-surgery 'off' and 'on' levodopa; UPDRS IV (sum of parts A and B) pre-surgery; STN sides from which LFP data were recorded, either left (L), right (R) or both (L–R). The rows represent patients, separating the DBS group from the control group.