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Research report

Effect of subthalamic stimulation on distal and proximal upper limb movements in Parkinson's disease

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ABSTRACT

Introduction: A different innervation pattern of proximal and distal muscles from the contra- and ipsilateral motor circuits raises the question as to whether bilateral, contra- and ipsilateral subthalamic stimulation may have different effects on the distal and proximal movements of the upper limb. To answer this question, we performed kinematic analyzes in patients with Parkinson's disease.
Methods: Twenty-eight Parkinsonian patients treated by bilateral subthalamic stimulation were examined with an age-matched control group of 28 healthy subjects. They performed 14 s of finger tapping, hand grasping and pronation-supination. The patient group performed these sessions in four conditions (BOTH ON, BOTH OFF, CONTRA ON, IPSI ON) after withdrawal of dopaminergic medication for 12 h and a fifth condition after taking medication (BOTH ON-MED ON). A motion sensor with a three-dimensional gyroscope was worn on the index finger. Speed, amplitude, rhythm and decrement of movements were calculated and compared across these conditions.
Results: Speed and amplitude of the more distal movements were improved similarly by contra- and bilateral stimulation. Bilateral stimulation was more effective than contralateral stimulation for the more proximal movements. Contra- and bilateral stimulation ameliorated the rhythm similarly in each movement task. Decrement of distal and proximal movements was not affected by the stimulation conditions.
Conclusion: This is the first study to show that the outcome of bi- and unilateral subthalamic stimulation on proximal and distal upper limb movements should be evaluated separately postulating the different somatotopic organization of subloops in the cortico-basal ganglia motor circuits.

1. Introduction

Bilateral stimulation of the subthalamic nucleus (STN) can effectively ameliorate bradykinesia, rigidity and tremor in appropriately selected patients with idiopathic Parkinson's disease (PD) (Limousin et al., 1998; Deuschl et al., 2006; Deli et al., 2015). However, the underlying mechanism of STN stimulation is not well understood. Bilateral stimulation provides more pronounced clinical recovery than unilateral stimulation (Bastian et al., 2003). According to previous clinical observations, 6–18 months after surgery improvement in Unified Parkinson's Disease Rating Scale

Abbreviations: BOTH OFF: bilateral stimulation is off; BOTH ON: bilateral stimulation is on; BOTH ON-MED ON: bilateral stimulation is on plus best medication effect; CAPSIT-PD: Core Assessment Program for Surgical Interventional Therapies for Parkinson's Disease; CONTRA ON: contralateral stimulation is on; FT: finger tapping; HG: hand grasping; IPSI ON: ipsilateral stimulation is on; PPN: pedunculopontine nucleus; PS: pronation-supination; STN: subthalamic nucleus; UPDRS: Unified Parkinson's Disease Rating Scale

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(UPDRS) Part III is 53.8–60% (Fahn et al., 1987), with 55.1–62.2% improvement in bradykinesia subscores (Limousin et al., 1998; Deuschl et al., 2006; Deli et al., 2015; Kumar et al., 1999). Axial motor scores (UPDRS III item 29–30) also decrease by 21–78% 3–18 months after surgery (Bejjani et al., 2000; Krack et al., 2003; Kumar et al., 1999; Limousin et al., 1998; Samii et al., 2007). Although unilateral subthalamic stimulation has a predominant clinical effect on the contralateral side, it affects the ipsilateral hemibody as well (improvement in UPDRS III total score: contralateral stimulation: 30.1–72.4%, ipsilateral stimulation: −1.2 to 20%) and moderately improves the axial symptoms (UPDRS III. item 29-30: 15–39% 3–18 months after surgery) (Kumar et al., 1999; Linazasoro et al., 2003; Germano et al., 2004; Chung et al., 2006; Samii et al., 2007; Slowinski et al., 2007).

Proximal muscles have bilateral, while distal muscles have primarily contralateral innervation from the cortico-basal ganglia motor circuits (Alexander and DeLong, 1986; Montgomery et al., 2013). This raises the question whether uni- and bilateral subthalamic stimulation can influence distal and proximal movements of the upper limb differently. Therefore, in the present study, we investigated the effects of bilateral, contra- and ipsilateral subthalamic stimulation on distal and proximal movements of the upper limbs. Motor outcome of unilateral stimulation was assessed by the Unified Parkinson's Disease Rating Scale part III (Fahn et al., 1987) in the aforementioned studies; however, in this study we used a three-dimensional motion capture device. Kinematic analyses of various types of upper limb movements have been reported in a few studies (Bastian et al., 2003; Wenzelburger et al., 2003; Timmermann et al., 2008; Tabbal et al., 2008) and have been shown to be more sensitive, more quantitative and more reliable than clinical scoring (Tabbal et al., 2008; Heldman et al., 2014). Our aim was to better understand the motor control and mechanism of STN stimulation. Our primary hypothesis was that distal movements are improved primarily by contralateral stimulation while bilateral stimulation is superior to contralateral stimulation for proximal movements. Our secondary hypothesis was that quantitative kinematic analysis might provide additional information about the mechanism of action of STN stimulation.

2. Results

Twenty-eight Parkinsonian patients implanted with bilateral STN-DBS and a healthy control group performed 14 s of UPDRS-directed repetitive finger tapping (FT), hand grasping (HG) and pronation-supination (PS) as quickly as possible (Fahn et al., 1987). Both hands were tested separately. The patient group repeated these sessions in four experimental DBS conditions (BOTH ON, BOTH OFF, CONTRA ON, IPSI ON) in counterbalanced order after withdrawal of dopaminergic medication for 12 h. A fifth and final condition (BOTH ON-MED ON) was then evaluated during a period of maximal clinical benefit after administration of a levodopa dose 1.5 times higher than the patient's usual morning dose (Krack et al., 2003). A one-hour time interval was maintained as a resting period between data acquisitions in the different conditions. A Kinesia (Great Lakes NeuroTechnologies Inc., Cleveland, OH) motion sensor captured kinematic parameters of the upper limb movement in each condition (Giuffrida et al., 2009; Heldman et al., 2011; Espay et al., 2011; Heldman et al., 2014). Speed, amplitude, rhythm (coefficient of variation), and the decrement of speed and amplitude were calculated. All of the aforementioned parameters were represented as their ratio (hereafter relative values) to the mean values of the right hand in the control group. Relative speed, amplitude, rhythm, and the decrement of speed and amplitude were compared with ANOVA for repeated measures, separately for the three tasks. Within group factors included: CONDITION (BOTH ON, BOTH OFF, CONTRA ON, IPSI ON, BOTH ON-MED ON) and HAND (more affected, less affected).

We confirmed the anatomical locations of the stimulating contacts in our patient group. In 54 out of the 56 hemispheres, the active contact was located within or on the border of the dorsolateral STN (Table 1). For the remaining two hemispheres, active contacts were located dorsal to the border of the STN.

Values of relative speed, amplitude and rhythm related to the more and less affected hand are presented in Fig. 1. ANOVA results and significant results of the post hoc comparisons are summarized in Table 2. Differences of relative speed, amplitude and the rhythm between the more and less affected hand were not different across the five conditions. HAND factor was not significant ($p \geq 0.05$) in the three tasks. The differential effects of bilateral and contralateral stimulation in the three tasks are presented in Fig. 2.

2.1. Speed

CONDITION effect was significant when analyzing the relative speed values in all three tasks (Table 2). Relative speed was significantly higher in the BOTH ON condition than it was in BOTH OFF and IPSI ON conditions, but was similar to BOTH ON-MED ON condition (FT: $p=0.99$; HG: $p=0.99$; PS: $p=0.85$). Relative speed

Table 1
Preoperative clinical data of the patients, details of the postoperative therapy.

Disease duration (years, mean ± SD)		13.2 ± 5.07		
Time after operation (years, mean ± SD)		2.1 ± 1.28		
Levodopa equivalent dose (mg/day)	Before operation	820.6 ± 318.0		
	At the time of assessment	294.4 ± 174.43		
Preoperative scores	UPDRS III (max: 108)	46.9 ± 16.51		
	UPDRS IV (max: 23)	7.9 ± 3.56		
	Hoehn-Yahr scale (worst stage: 5)	3.2 ± 0.70		
DBS Programming parameters (L/R)	Configuration	Monopolar: 22/23 contacts Bipolar: 6/5 contacts		
	Impulse width (us)	60us: 16/16 contacts 90us: 12/12 contacts		
	Amplitude (V)	2.78 ± 0.72/ 2.78 ± 0.77		
	Frequency (Hz)	130.2 ± 6.73/ 130.2 ± 6.73		
Test dose of levodopa for the study (mg)		113.4 ± 61.91		
Active contact location (L/R)	Direct visualization	Inside the dorsolateral STN: 25/24	On the dorsal border of STN: 2/3	Dorsal to the border of STN: 1/1
	Distances from the middle commissural point (mm; mean ± SD)	X: −11.6 ± 1.49/12.6 ± 1.4	Y: −1.8 ± 1.8/−1.5 ± 1.57	Z: −3.5 ± 1.79/−3.88 ± 1.9

-values: X-left; Y-posterior; Z-caudal; L: left hemisphere, R: right hemisphere.