

SHORT REPORT

The effect of subthalamic nucleus stimulation on kinaesthesia in Parkinson's disease

M Maschke, P J Tuite, K Pickett, T Wächter, J Konczak

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Background: Parkinson's disease is accompanied by deficits in passive motion and limb position sense.

Objective: To investigate whether deep brain stimulation of the subthalamic nucleus (STN-DBS) reverses these proprioceptive deficits.

Methods and results: A passive movement task was applied to nine patients with Parkinson's disease and bilateral chronic STN-DBS and to seven controls. Thresholds for 75% correct responses were 0.9° for controls, 2.5° for Parkinson's disease patients when stimulation was OFF, and 2.0° when stimulation was ON.

Conclusions: STN-DBS improves kinaesthetic deficits in Parkinson's disease, but does not lead to a full recovery of proprioceptive function.

Kinaesthesia is the conscious perception of limb and body position, orientation, and motion. Recent studies have shown that patients with Parkinson's disease have higher thresholds for detecting passive elbow movements, reflecting kinaesthetic deficits.^{1,2} Patients with Parkinson's disease show altered proprioception related EEG potentials during passive movements, which probably reflect changes in the cortical processing of kinaesthetic signals.³ Dopaminergic drugs appear to enhance this deficit.⁴ In contrast, we found no effect of levodopa on kinaesthesia.² Deep brain stimulation of the subthalamic nucleus (STN-DBS) improves motor deficits in Parkinson's disease⁵ but it may worsen cognitive functions such as working memory.⁶ However, the effects of STN-DBS on kinaesthesia are unknown. We therefore sought to determine how STN-DBS affects the perception of limb position.

METHODS

Subjects

Participants were nine patients with Parkinson's disease who had STN-DBS installed (mean (SD) age, 60.3 (8.7) years, range 44 to 71; four female, five male) and seven age matched healthy controls with no neurological or general medical limitations (61.0 (9.1) years, range 45 to 72; four female, three male). The patients were recruited from the movement disorders outpatient clinic at the University of Minnesota and were diagnosed as having idiopathic Parkinson's disease. At the time of testing, they all had normal values on the mini-mental state examination (MMSE) (table 1). Preoperative neuropsychological testing—including tests for concentration, attention, and executive functions (WAIS-III digit span, Wisconsin card sorting test III) and additional tests for verbal memory (CVLT), visual-spatial performance (WASI matrix reasoning), and visual memory (WMS-III faces 1 and 2)—revealed mild impaired concentration and executive function in one patient (subject 2; table 1). Two patients had mild to moderate dyskinesias (subjects 1 and 9; table 1) and four had a mild to moderate rest tremor (subjects 1, 6, 7, 8; table 1). Neurological examination did not reveal signs or symptoms of peripheral nerve disorders. All patients were tested on drug

treatment—that is, they were told to take their antiparkinsonian drugs in their usual dose and time schedule.

All patients and healthy subjects gave their informed consent to participate in the study. The study was approved by the institutional review board of the University of Minnesota.

Testing apparatus and procedure

The experimental setup is presented in detail elsewhere.² Briefly, the subject's forearm was moved passively (~0.5°/s) while resting on a splint. A torque motor was mechanically connected to the splint, moving it at a constant speed to cause forearm flexion or extension. For each condition (ON or OFF stimulation), 40 flexion and 40 extension movements were recorded with elbow joint angular displacements of 0.2°, 0.6°, 1°, 2°, 3°, 4°, 5°, 6°, 7°, and 8°. Angular displacements and their directions were pseudorandomly presented, every displacement being made twice in both directions. Both arms were tested in each subject. The right arm was tested first.

To account for order effects, a subset of the Parkinson's disease group (n = 5) was tested in the ON stimulation state first, while the remaining patients were first examined during the OFF stimulation state (n = 4). Between the conditions, patients had a 30 minute break to adjust to the change in stimulation (ON→OFF or OFF→ON).

Each trial was signalled to the subject by a tactile cue on the subject's shoulder two to five seconds before the start of the movement. The end of each trial was announced by a second tactile cue on the left forearm. After each passive movement, subjects had to judge and express verbally whether the forearm was moved "towards" or "away" from their body or if they "could not tell." There were no time limitations for subjects to respond. Incorrect responses and "could not tell" responses were both scored as an incorrect response. Subjects wore goggles to exclude all visual input, and headphones with "pink noise" masked all auditory cues during testing. The total testing time was around 80 minutes.

Statistical analysis

The percentage of correct responses per angular displacement was calculated for each of the three groups (Parkinson's disease patients ON stimulation; Parkinson's disease patients OFF stimulation; controls). Group differences in the percentage of correct responses were determined using separate Kruskal–Wallis tests for each displacement. The performance data for both arms of the Parkinson's disease patients were entered in this analysis. Differences in percentages of correct responses between ON and OFF stimulation states were tested by separate Mann–Whitney U tests for each displacement. Both tests were corrected for multiple comparisons. A curve fitting procedure (Box Lucas exponential fit) was also

Abbreviations: CVLT, California verbal learning test; MMSE, mini-mental state examination; STN-DBS, deep brain stimulation of the subthalamic nucleus; WAIS, Wechsler adult intelligence scale; WASI, Wechsler abbreviated scale of intelligence; WMS, Wechsler memory scale

Table 1 Patient characteristics

Pt	Sex	Age (y)	Disease duration (y)	STN-DBS duration (m)	UPDRS III off dopa*	UPDRS III DBS on	UPDRS III DBS off	Associated symptoms†	Kinaesthesia results‡	MMSE	L-dopa equiv dose (mg)	Dopaminergic medication§
1	M	44	13	36	62	16	27	DYS, RT	ON +25%	30/30	1850	L-dopa, pergolide
2	M	70	12	12	53	28	32		ON +13%	28/30	1400	L-dopa, pramipexole
3	F	68	11	11	22	18	28		ON +50%	28/30	900	L-dopa, pramipexole, selegiline
4	M	56	21	12	48	22	25		ON +25%	28/30	1200	L-dopa, ropinirole, amantadine
5	M	57	9	12	29	18	27		+/-0%	30/30	650	L-dopa, pramipexole
6	F	66	22	4	57	46	65	RT	OFF +25%	29/30	1300	L-dopa, amantadine
7	F	71	14	15	70	14	32	RT	ON +25%	30/30	2000	L-dopa, pergolide
8	F	51	23	20	70	30	54	RT	+/-0%	29/30	617	L-dopa, amantadine, pramipexole
9	M	60	10	11	43	35	44	DYS	ON +13%	29/30	367	L-dopa, ropinirole, amantadine

*Assessed preoperatively.

†Dyskinesias (DYS), dystonia (DYSTO), rest tremor (RT).

‡Correct responses during 2° angular displacement better during ON or OFF stimulation. §100 mg standard levodopa = 125 mg sustained release levodopa, 1.5 mg pramipexole, 6 mg ropinirole, 10 mg bromocriptine, or 1 mg pergolide.

DBS, deep brain stimulation; m, months; MMSE, mini-mental state examination; Pt, patient; y, years.

carried out to determine the threshold for 75% correct responses. The model equation was as follows:

$$y = a(1 - e^{-bx})$$

where y = number of correct responses (%), x = displacement (degrees), a, b = coefficients, and e = Euler's number (2.718). Probability (p) values of <0.05 were assumed to be significant.

RESULTS

We found no differences in the percentage of correct responses between passive forearm extension and flexion movements ($p > 0.2$). Thus we collapsed these two datasets and report all results for the combined flexion/extension movements.

All groups had difficulty in detecting very small displacements of 0.2° . Control subjects showed a rapid improvement in percentages of correct responses with increasing angular displacement. A 1.0° displacement was detected in 78% of trials and a 2° displacement in over 91% of trials by the control subjects (fig 1; table 2). In contrast, the patients with Parkinson's disease were clearly impaired in the correct detection of movement direction. During ON stimulation they showed correct responses in 74% for 2° displacements. Deficits worsened when the DBS device was OFF, with correct detection of 2° displacements in only 60% of trials.

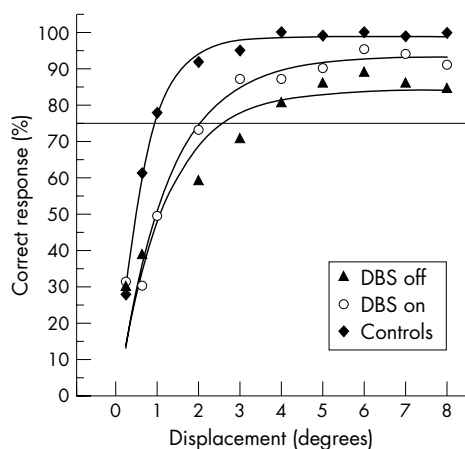


Figure 1 Comparison of percentages of correct responses per displacement between groups. Patients with Parkinson's disease had higher percentages of incorrect responses than control subjects. However, patients appeared less impaired during ON stimulation.

The differences between all three groups were statistically significant for all displacements with the exception for 0.2° displacements (all p values <0.05). The difference between the ON and OFF stimulation states in the Parkinson group was significant for 2° and 3° displacements ($p < 0.05$). At these displacements six patients had a greater number of correct responses during the ON stimulation state, two showed no difference, and only one had a greater percentage of correct responses during OFF stimulation (table 1). Thresholds for 75% correct responses underlined these results. Controls had a 75% threshold of 0.9° . Parkinson's disease patients were not normal, but improved during the ON stimulation state (2.0°) compared with the 75% threshold obtained during the OFF stimulation state (2.5°).

DISCUSSION

Previous studies suggested that movement difficulties such as bradykinesia in Parkinson's disease are related in part to a decrease in proprioceptive function or to impaired sensorimotor integration.⁷ Thus therapy that could alleviate kinaesthetic deficits would be an important adjunct to the treatment of these patients. The results of the present study suggest that STN-DBS has the ability to improve kinaesthesia in Parkinson's disease.

What is the neurophysiological basis for our finding of an improved limb position sense during DBS stimulation? It is known that neuronal activity elicited by passive movements

Table 2 Percentages of correct responses per group and displacement

Displacement	Correct response (%)			p Value*
	Controls	PD patients		
		ON	OFF	
0.2°	28 (25)	32 (25)	30 (27)	0.9
0.6°	62 (31)	31 (20)	39 (30)	<0.001
1°	78 (31)	50 (29)	50 (31)	<0.001
2°	92 (14)	74 (17)	60 (30)	<0.001
3°	95 (6)	88 (14)	71 (27)	<0.001
4°	100 (0)	88 (17)	81 (25)	<0.001
5°	99 (5)	90 (10)	86 (16)	0.006
6°	100 (0)	96 (9)	89 (13)	0.003
7°	99 (4)	94 (7)	86 (19)	0.003
8°	100 (0)	92 (11)	85 (21)	0.001
Total	85 (29)	73 (29)	67 (31)	0.0004

Values are mean (SD).

*Kruskal-Wallis test.

ON/OFF, on or off stimulation; PD, Parkinson's disease.

and somatosensory evoked potentials can be recorded within the STN.^{8,9} Thus a role of the STN in analysing proprioceptive signals is plausible. As STN stimulation alters the proprioceptive inputs that reach the nucleus from the somatosensory cortex,¹⁰ it is not unlikely that it reduces the noise of the signals processed in the STN and their basal ganglia targets. Given that many of these cerebro-basal ganglia connections are reciprocal, altered STN output will ultimately affect processing in the somatosensory cortex, where a reduced noise level could then facilitate the perception of limb position. Moreover, the findings of the present study are in line with previous reports of improved sensorimotor integration during STN-DBS.^{11,12} However, one needs to recognise that several other factors could also have influenced our experimental outcome.

First, STN-DBS might have improved cognitive dysfunction in our study population, leading to improved kinaesthesia. This scenario is somewhat unlikely as no patient had substantial cognitive deficits on neuropsychological testing, either preoperatively or postoperatively. On the other hand, recent studies suggest that STN stimulation impairs cognitive function in Parkinson's disease,^{6,13} and therefore one would expect that kinaesthetic deficits would have been greater in the ON stimulation state if cognitive dysfunction was the main cause of these deficits. However, on a cautionary note, one needs to realise that the MMSE alone is a poor tool to detect *subtle* cognitive deficits, and extensive neuropsychological testing was only available preoperatively and not postoperatively at the time of this study. Moreover, in contrast to the reports mentioned above,^{6,13} recent studies suggest a mild increase in psychomotor speed and working memory in patients with Parkinson's disease who have STN-DBS.¹⁴ Thus we cannot completely rule out the possibility that STN-DBS implantation induced cognitive improvements that enhanced the patients' perceptual performance.

Second, one could argue that the alleviation of kinaesthetic deficits during ON stimulation was simply an order effect. Our study design was nearly balanced (five patients were tested first ON, four patients first OFF), yet we found no evidence that the order of the treatments had a significant impact. The patients who were first tested OFF did not perform better than those first tested ON. It could also be argued that, although we considered possible order effects, patients were not randomised into groups. This might have resulted in differences in dopaminergic drug treatment between the patient groups. Dopaminergic treatment is known to influence the results of kinaesthetic testing, though the exact nature of this influence is controversial.^{2,4} However, levodopa equivalent doses did not differ significantly between patients first tested OFF and those first tested ON ($p = 0.33$). Thus the results cannot be solely explained by differences in dopaminergic drug treatment.

Third, one may speculate that tremor as well as dyskinesias might have an impact on kinaesthesia, and that these symptoms were less pronounced during the ON condition. In our study, five patients had rest tremor ($n = 4$) or dyskinesias ($n = 2$). However, three of the remaining four patients without visible rest tremor or dyskinesia during examination showed significant improvement in kinaesthesia on DBS. Thus the cessation of a rest tremor alone cannot account for the improvement in limb position sense.

Finally, the pause between changes of condition might have been too short. A recently published study found that 30 minutes appeared to be sufficient to reach a steady state after change from OFF to ON but might not be enough from ON to OFF.¹⁵ However, our results in those patients who were tested first in the OFF state were not different from those who were tested first in the ON state, strongly arguing against an influence of break duration on our perceptual results.

Conclusions

Our study underlines the role of the basal ganglia in kinaesthesia and shows that kinaesthetic function may be improved by STN-DBS in Parkinson's disease. We found no clear evidence that these improvements in limb perception reflected enhanced cognitive function. It also needs to be stated that, although STN-DBS may have a positive effect on kinaesthesia, our data show that it does not fully restore limb position sense in Parkinson's disease.

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Authors' affiliations

M Maschke, K Pickett, J Konczak, Sensorimotor Control Laboratory, Division of Kinesiology, University of Minnesota, Minneapolis, Minnesota, USA

M Maschke, Department of Neurology, University Duisburg-Essen, Essen, Germany

P J Tuite, T Wächter, J Konczak, Department of Neurology, University of Minnesota

T Wächter, Brain Sciences Center, Minneapolis VAMC, University of Minnesota

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Correspondence to: Dr Matthias Maschke, Department of Neurology, University Duisburg-Essen, Hufelandstr. 55, 45122 Essen, Germany; matthias.maschke@uni-essen.de

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