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Unilateral deep brain stimulation surgery in Parkinson's disease improves ipsilateral symptoms regardless of laterality

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Abstract

Purpose—Researchers have consistently observed in right-handed individuals across normal and disease states that the ‘dominant’ left hemisphere has greater ipsilateral control of the left side than the right hemisphere has over the right. We sought to determine whether this ipsilateral influence of the dominant hemisphere reported in Parkinson’s disease extends to treatments such as deep brain stimulation (DBS) and whether it affects outcome. We hypothesised that among Parkinson right-handers, unilateral left DBS would provide greater ipsilateral motor improvement compared with the ipsilateral motor improvement experienced on the right side.

Scope—A total of 73 Parkinson patients who underwent unilateral DBS of the subthalamic nucleus (STN) or globus pallidus internus (GPi) participated. Left and right ‘composite scores’, were computed by separately adding all items on the left and right side from the motor section of the Unified Parkinson Disease Rating Scale. The change in the pre- and 4-month post-implantation score was the primary outcome measure. The mean motor scores improved by 4.96 ± 11.79 points ($p < 0.001$) post-surgery on the ipsilateral side of the DBS implantation. Regression analyses revealed that the side (left vs. right) and target (STN vs. GPi) did not significantly contribute in the effect of ipsilateral motor improvement ($p = 0.3557$).

Conclusion—While DBS on the ‘dominant’ left side failed to exert a greater ipsilateral influence compared with DBS on the non-dominant right side, significant ipsilateral motor

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Potential conflict of interest

Dr. Okun has received research grants from Medtronic fellowship training grants, has in the past received honoraria for DBS educational talks prior to 2010, but currently receives no support (since July 2009); and has potential royalty interest in the COMPRESS tool for DBS.

Dr. Foote has in the past received honoraria for DBS educational talks prior to 2010, but currently receives no support (since July 2009); and has potential royalty interest in the COMPRESS tool for DBS.

Dr. Oyama has received grant support for fellowship from Medtronic.

Dr. Fernandez is a patent co-owner of COMPRESS, a neurosurgical candidate selection tool; is a co-owner of DBS Solutions, Inc. that has a contractual agreement with Neurotrax to develop a software, COMPRESS.

improvements were observed after unilateral stimulation regardless of site of implantation and laterality.

Keywords

Unilateral DBS; STN; GPi; Parkinson's disease; UPDRS

1. Introduction

Parkinson's disease (PD) is a progressive neurodegenerative disorder characterised by cell death of both motor and non-motor pathways within the basal ganglia. The cardinal motor features of PD include bradykinesia, resting tremor, rigidity and gait/postural instability. Patients most often present with asymmetric symptoms, that is, disruptions within the left hemisphere and basal ganglia result in symptoms on the right side of the body, whereas dysfunctions within the right hemisphere result in symptoms on the left side of the body. The initial lateralisation of PD symptoms had been hypothesised to result from a more rapid depletion of neurotransmitters in one hemisphere [1–3]. With disease progression, the symptoms usually become evident on both sides of the body; however, the side of onset most often remains more affected [3]. PD has been viewed by many experts as a lateralised disorder with each hemisphere having designated motor and cognitive responsibilities. Thus, the side of symptom onset may carry differential effects on cognitive, visuospatial and perceptuo-motor functions [4–17]. Although some studies did not demonstrate a hemispheric difference on cognitive functioning [8,11] the majority of studies revealed some association with cognitive functions, especially those known to be located in a specific hemisphere [4,6,9,10,13,14].

The side of onset may also influence motor functioning due to the greater ipsilateral influence of the dominant left hemisphere compared with the right. Previously, we tested side of onset influence on 425 right-handed PD patients. In that retrospective, cross-sectional study, we found that patients with right-side symptom onset (RSO) possessed greater 'symmetry' of motor impairments than patients with left-side symptom onset (LSO). In other words, PD patients with RSO (i.e., presumably with greater dominant left-hemisphere damage) had greater detriments in their ipsilateral left hand than the group of PD patients with LSO (greater non-dominant right hemisphere involvement) [18]. More recently, we have also prospectively confirmed that the side of symptom onset affected upper-extremity motor functioning. Right-handed patients with an RSO had greater 'symmetry' in motor deficit observed during small- and large-object manipulation tasks than in those with an LSO. These findings further supported the hypothesis that there was greater ipsilateral control of both hand and finger movements of the left hemisphere.

Herein, we sought to determine whether this ipsilateral motor influence of the dominant hemisphere seen in PD meaningfully affected treatment outcome. Currently, oral pharmacological therapies may not provide the best vehicles in predicting the laterality effects of Parkinsonism due to the bilateral and theoretically symmetric distribution of drugs throughout the central nervous system. Deep brain stimulation (DBS), however, when performed in a staged fashion, offers a unique opportunity to determine if the side of implantation would influence ipsilateral improvement. We hypothesised that among right-handers, PD patients with left DBS would have greater motor improvement in their ipsilateral left side compared with the patients with right DBS (on their ipsilateral right side). In addition, we sought to determine whether other factors influenced greater ipsilateral motor improvement from unilateral DBS. Specifically, we sought potential differences in ipsilateral motor improvement between two DBS sites (sub-thalamic nucleus (STN) vs.

globus pallidus internus (GPi)). All available studies to date have shown ipsilateral improvement with STN-DBS [22–25] and have not specifically examined GPi.

2. Methods

All right-handed PD patients who underwent unilateral DBS at the University of Florida Movement Disorders Center between 2002 and 2006, with a clear side of onset, were included. All data including demographic information and motor and functional rating scales on all patients seen at the UF Movement Disorders Center, during all their initial and follow-up visits, were entered in a central database upon the patient's consent. The collection and use of data in the database is Institutional Review Board (IRB) approved.

The Unified Parkinson Disease Rating Scale (UPDRS) motor subscale was performed in the OFF medication state (i.e., no medications for at least 12 h) prior to DBS and in the OFF medication state, but ON DBS 4 months post-surgery. Patients with dementia, autonomic dysfunction or previous neurologic disorders were excluded. DBS settings were adjusted clinically up to 4 months post DBS in an effort to optimise the treatment effect. Right and left DBS 'composite scores' were ascertained from the UPDRS motor subscale by adding up all the right-sided and all the left-sided items, respectively. The differences between the pre- and post-implantation states in each side were then calculated to determine improvement. A two-tailed *t*-test was used to determine demographic differences between left- and right-DBS groups. A paired *t*-test was used to compare the overall pre- versus post-DBS ipsilateral UPDRS motor scores. In addition, linear regression models were used to investigate effects of DBS side (left vs. right), DBS target (STN vs. GPi) and their interaction on ipsilateral and contralateral motor improvements.

3. Results

A total of 73 patients who underwent unilateral DBS were included. The cohort had a mean age of 59 years (SD = 8), disease duration of 147 months (SD = 62), and a pre-surgery UPDRS motor score in the OFF medication state of 42.6 (SD = 11.6). There were 54 males and 19 females. A total of 45 patients had left DBS and 28 underwent right DBS. As many as 47 patients were implanted in the STN and 26 had GPi-DBS (Table 1).

There were no differences between patients receiving left and right unilateral DBS regarding age, disease duration, gender, race and DBS targets. The mean ipsilateral UPDRS III motor scores improved following DBS by 4.96 points (SD = 11.79) (Tables 2 and 3). Improvements were observed across all motor parameters measured by the UPDRS including rigidity, bradykinesia and tremor (1.33; 1.59; and 2.04 point improvements, respectively; all with values of $p < 0.001$) (Table 2).

By contrast, the mean contralateral UPDRS motor scores improved after DBS by 9.6 points (SD = 5.6), (rigidity, bradykinesia and tremor; 2.48, 4.11 and 3.01 points, respectively; all values of $p < 0.001$) (Table 2). The mean contralateral motor improvement was 4.6 points greater than the ipsilateral improvement ($p < 0.001$). There was no difference in ipsilateral motor improvement between the left and right DBS implantation (5.38 vs. 4.29; $p = 0.335$). Further, target location of STN- and GPi-DBS did not influence the magnitude of ipsilateral improvement (4.49 vs. 5.81; $p = 0.251$, Table 2 and Fig. 1). Our regression analyses also suggested that the DBS side and target did not significantly differ in ipsilateral motor improvement; and there was no other significant predictor identified (Table 3).

4. Discussion

We previously reported that PD patients who were more dominant hemisphere affected had greater ipsilateral motor deficits when compared with PD patients whose symptoms started on their non-dominant side [18]. This is the first study examining the ipsilateral motor effects on both side and surgical target within a PD DBS cohort. We report significant improvement in ipsilateral motor function following unilateral DBS regardless of the target site (GPi or STN) or hemisphere (left-dominant or right-non-dominant). Importantly, the 'ipsilateral' motor score improvement was observed in all motor features as measured by the UPDRS, including rigidity, bradykinesia and tremor. The principal finding of our study was that the side of implantation did not seem to influence the magnitude of ipsilateral motor improvements. Previously, greater ipsilateral control was observed in left hemisphere-dominant patients.

Schrag et al. in a meta-analysis reported that a five-point improvement in the motor subscore of the UPDRS indicated a clinically relevant result [19]. We observed a 4.96 point mean ipsilateral and 9.6 point contralateral motor score improvement following unilateral DBS. Therefore, if the Schrag criteria [19] are applied to our cohort, one may argue that clinically meaningful ipsilateral motor improvements can occur following unilateral DBS. This information may be useful for patients and clinicians attempting to make important treatment decisions. Currently, a subject of considerable debate in the neurosurgical community is whether unilateral DBS should be considered a therapeutic option especially in a selective subset of PD patients [20]. The benefits, risks and patient selection of unilateral versus bilateral DBS must be carefully considered and systematic careful analyses should be the subject of future studies.

The ipsilateral effects following DBS have been reported in several retrospective series [21–25]. Collectively, these studies confirm that while ipsilateral improvements exist, they are generally smaller than those observed contralaterally. However, it should be noted that previous comparative effects between unilateral and bilateral DBS were retrospective and that patient selection failed to consider ipsilateral motor function as a part of the assessment [22–25]. Further, the majority of literature has focussed on unilateral STN-DBS exclusively [22–25]. In our study, interestingly, the improvement in ipsilateral motor scores from STN- and GPi-DBS did not differ. Thus, our study confirms the findings of previous reports that the ipsilateral STN or GPi benefits, while smaller than those observed contralaterally, may have clinical relevance.

Our study was not without limitations. To determine the ipsilateral effects of the dominant left hemisphere, we included only right-handed patients. In addition, we had more STN than GPi patients in our cohort. The decision for brain target was biased by many factors, such as cognition, dyskinesia and perceived need for medication reduction. As an example, patients with mild cognitive deficits, significant dyskinesias or those with perceived greater risks for behavioural dyscontrol may have been likely to receive GPi-DBS, whereas patients with a bigger need for medication reduction would have been more likely to receive STN-DBS. Although there were more males in our study, there was no gender effect. In addition, it remains to be studied whether the magnitude of ipsilateral effects seen in our cohort of PD patients with unilateral DBS would be greater or lesser with bilateral DBS. However, we chose this cohort of unilateral DBS patients to simplify interpretations and minimise confounders.

Despite these limitations, we believe the relatively large sample size and the standardised data collection offer important insights into both ipsilateral and dominant hemisphere effects. To our knowledge, our study incorporates the largest prospectively acquired sample

to examine the ipsilateral effects of DBS. Our study suggests that clinically meaningful ipsilateral motor improvement exists after unilateral DBS but the side and target location do not provide additional influence on this phenomenon. The knowledge of a significant, but lesser improvement in ipsilateral (compared with contralateral) motor function may contribute to the surgical decision-making process and we believe neurologist and neurosurgeons should be aware of their occurrence and potential impact.

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Fig. 1. Change in Ipsilateral UPDRS scores expressed as mean over 4 months. These lines intersect indicating no measurable difference between side or site of implantation.

Table 1

Comparison of demographic and clinical factors between patients receiving unilateral left versus right DBS.

Variable	Label	Overall	DBS Side		p-value
			Left (<i>n</i> = 45)	Right (<i>n</i> = 28)	
Age (years)		59 ± 8	58 ± 9	59 ± 8	0.783
Disease Duration (months)		147(62)	144(67)	151(55)	0.647
Gender	Female (<i>n</i> = 19)	26.02%	22.22%	32.14%	0.348
	Male (<i>n</i> = 54)	73.97%	77.77%	67.85%	
Race	Hispanic (<i>n</i> = 7)	9.589%	6.666%	14.28%	0.282
	White (<i>n</i> = 66)	90.41%	93.33%	85.71%	
	GPI (<i>n</i> = 26)	35.61%	35.55%	35.71%	
DBS Site	STN (<i>n</i> = 47)	64.38%	64.44%	64.28%	0.989

DBS- Deep Brain Stimulation, STN- Subthalamic Nucleus, GPI- Globus Pallidus Interna.

Table 2
Mean and Standard Deviation of UPDRS scores at baseline and changes 4 months post DBS. Mean (SD).

Variable	Label	DBS Side		p-value
		Left (n = 45)	Right (n = 28)	
UPDRS III	Baseline	42.6(11.57)	42.69(13.33)	0.936
	4 month post DBS	20.92(9.34)	21.11(8.64)	0.824
	Change	21.68(11.79)	21.58(11.98)	0.922
Ipsilateral UPDRS motor	Baseline	13.23(5.36)	13.96(6.1)	0.145
	4 month post DBS	8.27(3.78)	8.58(3.89)	0.387
	Change	4.96 (4.67)	5.38(5.01)	0.335
Contralateral UPDRS motor	Baseline	15.51(5.04)	15.02(5.04)	0.301
	4 month post DBS	5.9(3.45)	5.73(3.06)	0.595
	Change	9.6(5.6)	9.29(5.3)	0.547
Ipsilateral Rigidity	Baseline	3.34(1.65)	3.36(1.72)	0.932
	4 month post DBS	2.01(1.43)	1.91(1.46)	0.441
	Change	1.33(1.5)	1.44(1.57)	0.407
Contralateral Rigidity	Baseline	3.73(1.53)	3.64(1.6)	0.567
	4 month post DBS	1.25(1.26)	1.22(1.24)	0.835
	Change	2.48(1.48)	2.42(1.51)	0.679
Ipsilateral Tremor	Baseline	2.51(2.15)	2.84(2.41)	0.089
	4 month post DBS	0.92(1.36)	1.02(1.56)	0.410
	Change	1.59(1.86)	1.82(2.07)	0.177
Contralateral Tremor	Baseline	3.48(2.42)	3.38(2.49)	0.652
	4 month post DBS	0.47(0.85)	0.33(0.74)	0.092
	Change	3.01(2.39)	3.04(2.48)	0.890
Ipsilateral Bradykinesia	Baseline	7.38(2.99)	7.76(3.41)	0.179
	4 month post DBS	5.34(2.73)	5.64(2.4)	0.234
	Change	2.04(3.04)	2.11(3.09)	0.805
Contralateral Bradykinesia	Baseline	8.3(2.62)	8(2.65)	0.216
	4 month post DBS	4.19(2.62)	4.18(2.39)	0.954
	Change	4.11(3.4)	3.82(3.08)	0.364

DBS- Deep Brain Stimulation, UPDRS- Unified Parkinson Disease Rating Scale.

Table 3

Results from regression analyses for ipsilateral and contralateral motor improvement.

Dependent	Parameter	Estimate	Standard Error	p-Value
Ipsilateral UPDRS motor Change	Intercept	3.19	1.09	0.005
	Age	-0.08	0.07	0.248
	Duration	0.02	0.01	0.079
	Site = GPi	2.96	1.84	0.112
	Side = Left	2.08	1.42	0.146
	Site*Side (GPi Left)	-2.68	2.38	0.265
Contralateral UPDRS motor Change	Intercept	9.83	1.32	<0.001
	Age	-0.12	0.08	0.163
	Duration	0.01	0.01	0.56
	Site = GPi	0.8	2.21	0.72
	Side = Left	0.6	1.71	0.727
	Site*Side (GPi Left)	-3.76	2.87	0.195

The values in bold are of statistical significance.