Pallidal Stimulation for Cervical Dystonia Does Not Correct Abnormal Temporal Discrimination

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ABSTRACT

Background: We investigated whether clinical improvement observed after deep brain stimulation (DBS) of the globus pallidus internus (GPi) in cervical dystonia (CD) is paralleled by the normalisation of temporal discrimination thresholds (TDTs), a marker of abnormal sensory processing in CD.

Methods: TDT was tested in 11 patients with CD after they received DBS and was compared with TDT scores from 24 patients with CD and a group of 61 controls.

Results: A clear clinical response to GPi-DBS was demonstrated (total Toronto Western Spasmodic Torticollis Rating Scale scores fell from 50 to 18; $P < 0.001$). In contrast, TDT remained abnormal in the CD-DBS group ($P < 0.001$) and was not significantly different from the abnormal TDT range observed in CD.

Conclusions: Underlying sensory abnormalities in temporal discrimination observed in dystonia do not seem to be corrected by successful GPi-DBS. This adds further data to the ongoing debate regarding which pathophysiological abnormalities observed in dystonia are likely to be causal in the genesis of the disease rather than epiphenomena observed secondary to abnormal motor activity. © 2013 International Parkinson and Movement Disorder Society

Key Words: cervical dystonia; deep brain stimulation; temporal discrimination threshold

The role of the sensory system in the pathophysiology of dystonia has been debated ever since the observation that the "geste antagoniste" could clearly influence dystonic contractions. Experimentally across the domains of psychophysics, neurophysiology, and imaging, subtle abnormalities in sensory processing and sensorimotor integration have been demonstrated in both generalised and focal dystonia.[1] The most consistent of these is an abnormal temporal discrimination threshold (TDT).[2] The TDT is defined as the shortest time interval at which two stimuli can be determined to be separate. In a recent series of patients, an abnormal TDT score was remarkably sensitive and specific to the presence of cervical dystonia (CD) compared with age-matched healthy controls (97% and 100%, respectively).[2]

Treatment of primary dystonia with deep brain stimulation (DBS) of the globus pallidus internus (GPi) is an established treatment for generalised dystonia and more recently has been used to treat medically refractory CD. The mechanisms of benefit of DBS are incompletely understood. Some insight has been derived from neurophysiological studies in primary dystonia, which have shown that GPi-DBS is associated with normalisation of intracortical inhibition and associative plasticity.[3] The effects of GPi-DBS on sensory processing deficits observed in dystonia are unknown.

In this study we used the excellent sensitivity and specificity of the TDT to evaluate whether clinical improvements in CD after GPi-DBS are paralleled by normalisation of TDT, a marker of abnormal sensory processing.

Patients and Methods

Eleven patients who had primary CD treated with GPi-DBS (CD-DBS) were recruited from the National Hospital for Neurology and Neurosurgery, London. Bilateral GPi-DBS was performed according to previously published procedures.[4] Patients were scored preoperatively and postoperatively (at the date of TDT testing) by the same neurologist using the Toronto Western Spasmodic Torticollis Rating Scale

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(TWSTRS). TDT was tested at a mean of 26 months after surgery, allowing time for optimisation of DBS, and all were tested at least three months after their most recent change in stimulation settings. An additional 24 patients who had focal CD and 61 control participants were recruited at St. Vincent's University Hospital, Dublin (some of these have been published in a separate series[5]). Written informed consent was obtained from all participants, and the study was approved by the local ethics committees.

The TDT was tested in an identical manner at both centres using the same standardised protocol (see supplementary materials). The mean visual, tactile, and combined TDT results (in ms) were converted to Example z scores (z score = [actual TDT − age-related control mean TDT] / age-related control standard deviation). z scores > 2.5 were considered abnormal.

The SPSS statistical software package (SPSS, Inc., Chicago, IL) was used for statistical analyses. Paired t tests were used to assess changes in TWSTRS scores (Bonferroni correction for three subscore comparisons: $\alpha = 0.017$). z scores for the different groups (control, CD, and CD-DBS) were compared using one-way analysis of variance. z scores satisfied the Kolmogorov-Smirnov test for normality, but homogeneity of variance assumption was broken (Levene's test: $p < 0.05$), and Welch's F was used. Covariance between the z score and response to DBS (estimated as the percentage reduction in total TWSTRS score) was assessed by Pearson's correlation coefficient (two-tailed).

Results

Characteristics of patients in the CD-DBS group are provided in Table 1. There was a clear clinical response to GPi-DBS demonstrated by a fall in the total TWSTRS score from 50 to 18 ($P < 0.001$). In addition, scores for the severity (23 to 9.1; $P < 0.001$) and disability (19 to 6.1; $P < 0.001$) components of the TWSTRS were reduced. The pain subscore was not significantly reduced (7.4 to 2.9; $P = 0.021$). No consistent change in sensory geste scores was observed.

Mean TDT data and z scores are summarised in Table 2. The combined TDT for the control group was 24.5 ms for those aged < 50 years and 31.1 ms for those aged ≥ 50 years. In the CD group, the combined TDT was 68.1 ms; and, in the CD-DBS group, the combined TDT was 58.3 ms. In both the CD group (2 patients) and the CD-DBS group (3 patients), some patients could not complete the tactile part of the test because of erratic reporting of the four response choices. For these patients, the mean of the visual TDT scores was used. There was no significant difference in mean age between the CD and CD-DBS groups.

TABLE 1. Clinical characteristics of the patients with cervical dystonia that underwent surgery and their clinical response to deep brain stimulation

Patient	Sex	Age, (y)	Age at onset, (y)	Disease duration, (y)[b]	Duration of BTX (with good effect), (y)	Time since GPi-DBS at TDT, (m)	Sensory geste score[c]		TWSTRS score[a]							
									Severity		Disability		Pain		Total	
							Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
1	W	68	45	22	15 (4)	24	2	2	24	10	22	13	7	5	53	28
2	W	61	51	8	4 (2)	26	1	2	23	11	22	7	6	0	61	18
3	W	70	50	20	20 (18)	22	1	1	19	6	14	5	2	4	35	15
4	W	63	41	20	17 (15)	39	1	0	25	7	18	3	6	2	49	12
5	M	58	50	6	5 (4)	32	1	1	20	16	11	10	4	8	35	34
6	M	38	31	6	2 (0)	15	1	0	33	2	25	1	17	0	75	4
7	W	56	39	17	15 (13)	14	1	1	14	8	21	10	13	1	38	19
8	M	59	37	22	10 (8)	9	2	1	26	15	12	6	3	0	41	21
9	M	59	40	17	7 (6)	26	1	1	20	8	18	3	10	6	48	13
10	M	40	28	28	18 (18)	61	1	1	25	4	25	1	6	0	56	5
11	W	42	37	15	13 (11)	13	1	1	25	13	21	8	8	7	54	28
Mean	—	56	41	16	12 (9.2)	26	1.2	1.0	23	9.1	19	6.1	7.4	2.9	50	18
SD	—	11	7.6	7.2	6.2 (6.5)	15	2.9	0.6	4.9	4.4	5.0	3.9	4.5	3.0	12.2	9.4

[a]TWSTRS scores are subdivided into severity (range, 0–30, with higher scores indicating greater impairment), disability (range, 0–30), and pain (range, 0–40).
[b]Both disease duration and duration of botulinum toxin therapy (BTX) were measured at the time of surgery and given in years (y).
[c]For the sensory geste score, 0 indicates complete relief by sensory trick; 1, partial relief by sensory trick; 2, no relief offered by sensory trick.
TWSTRS, Toronto Western Spasmodic Torticollis Rating Scale; W, woman; M, male; Pre, preoperative; Post, postoperative; SD, standard deviation.

TABLE 2. Temporal discrimination threshold values and *z* scores for the control and patient groups

Study group/TDT task	No.	TDT: Mean ± SD, (ms)	*z* score, mean	*z* score range	Abnormal *z* score: No. (%)
Controls: Age < 50 y					
Visual	39	24.5 ± 9.0	0	−1.6 to 1.9	0 (0)
Tactile	39	24.9 ± 10.4	0	−1.6 to 3.4	1 (3)
Combined	39	24.5 ± 9.0	0	−1.4 to 2.3	0 (0)
Controls: Age ≥ 50 y					
Visual	22	31.1 ± 9.7	0	−1.6 to 3.3	1 (5)
Tactile	22	32.0 ± 11.8	0	−2.0 to 1.7	0 (0)
Combined	22	31.1 ± 5.7	0	−1.5 to 2.9	1 (5)
CD: Mean age, 57 y					
Visual	24	65.7 ± 18.0	3.3	0.75 to 7.2	17 (71)
Tactile	22	70.5 ± 23.4	5.49	1.0 to 14.7	18 (81)
Combined	24	68.1 ± 18.2	4.45	0.96 to 8.2	18 (75)
CD-DBS: Mean age, 56 y					
Visual	11	61.1 ± 13.5	2.9	1.3 to 5.5	6 (55)
Tactile	8	51.7 ± 27.8	3.3	1.4 to 6.0	4 (50)
Combined	11	58.3 ± 11.0	3.3	1.9 to 5.4	9 (82)

Abnormal TDTs (*z* scores > 2.5) were observed in 1 of 61 (2%) control participants and in 18 of 24 patients (75%) in the CD group; thus, the sensitivity of the TDT test was 75%, and the specificity was 99.5%. In the CD-DBS group, 82% of patients had an abnormal TDT. There was a significant effect of group (control, CD, CD-DBS) on *z* scores ($F[2,93] = 84.3$; $P < 0.001$). Post hoc analysis indicated that this effect was caused by differences between the control group and the patient groups (CD and CD-DBS groups: $P < 0.001$ for both comparisons) (Fig. 1). There was no correlation between response to DBS and TDT *z* score ($R^2 = 0.17$; $P = 0.71$).

Discussion

We identified abnormalities in TDT that are present despite the efficacy of surgery. Thus, GPi-DBS does not seem to improve dystonic motor activity by correcting abnormalities in sensory processing, at least as measured by the TDT. In healthy individuals, a variety of experimental methods have demonstrated the involvement of a distributed network in the performance of the TDT task, including input and output nuclei of the basal ganglia, the cerebellum, and multiple cortical regions.[6,7] Alterations in this network that must underlie the abnormal TDT performance in dystonia do not seem vulnerable to modulation by GPi-DBS.

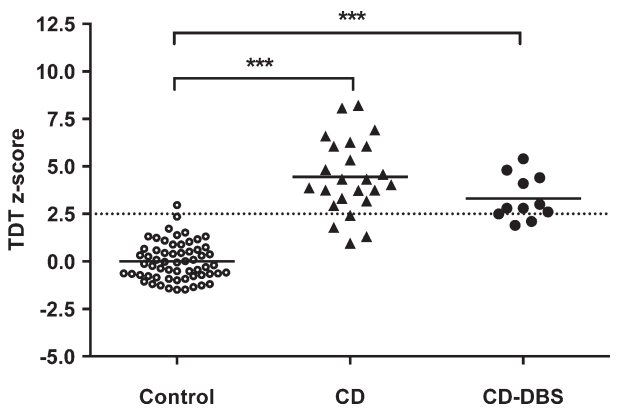

FIG. 1. Temporal discrimination threshold (TDT) *z* scores are illustrated for control and patient groups. The dotted line at a score of 2.5 demonstrates the cut-off for an abnormal TDT.

Electrophysiological data in patients with primary dystonia implanted with GPi-DBS demonstrate that markers of inhibition improve toward normality in parallel with clinical improvement, and response to plasticity protocols is immediately reduced by GPi-DBS.[3] Similarly, botulinum toxin may change plasticity responses in CD.[8] However, GPi-DBS in this study and botulinum toxin in a previous study did not appear to change TDT in dystonic patients.[9] One explanation is that GPi-DBS and botulinum toxin work on downstream components of the dystonic network and that upstream pathophysiological processes, which also presumably disturb temporal sensory processing, are not corrected.

TDT does indeed seem to fulfill the criteria of an endophenotype in dystonia, ie, a measurement that reflects disease susceptibility and is not altered by clinical disease severity. It is in this context that TDT has been explored in families of patients with apparently sporadic CD, in which abnormal TDT values occur in approximately 50% of unaffected first-degree relatives.[5] Lateral head turning can effect temporal processing, but our findings are against the hypothesis that neck rotation itself underpins the abnormal TDT.[10] We have also demonstrated an excellent

clinical response to GPi-DBS surgery, which adds a further case series to the growing literature outlining the role of GPi-DBS in medically refractory CD.

It would be interesting to study patients before and after DBS; however, psychophysical tests like the TDT could be confounded by different influences on decision-making parameters at retest. Studying patients ON and OFF DBS stimulation could be attempted; however, in contrast to patients with Parkinson's disease, there is often a delay in return of symptoms among patients with dystonia when the stimulator has been turned off.[11] We believe that the between-subject design in the current study to has significant merits and that the high specificity and sensitivity of TDT abnormalities in CD support our comparison.

These results suggest that underlying sensory abnormalities in temporal discrimination observed in dystonia are not corrected by successful GPi surgery, adding further data to the ongoing debate about which pathophysiological abnormalities observed in dystonia are likely to be causal in the genesis of the disease rather than epiphenomena observed secondary to abnormal motor activity. ■

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Subthalamus Deep Brain Stimulation for Primary Dystonia Patients: A Long-Term Follow-up Study

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ABSTRACT

Background: Deep brain stimulation has generated sustained improvement in motor function for patients with dystonia, but the long-term impact of subthalamic nucleus stimulation on dystonia has not been elucidated.

Methods: Patients with primary dystonia underwent bilateral subthalamic nucleus stimulation and were evaluated with the Burke–Fahn–Marsden dystonia rating scale and the Medical Outcomes Study 36-item Short-Form General Health Survey at baseline and 1 month, 1 year, and 3 to 10 years postoperatively.

Results: Improvements in motor function according to the Burke–Fahn–Marsden dystonia rating scale at 1 month, 1 year, and 3 to 10 years of stimulation were 55%, 77%, and 79%, respectively. The quality of life improved after 1 month of stimulation ($P < 0.001$), progressed within 1 year ($P < 0.001$), and then remained stable. Disease duration was negatively correlated with an improvement in motor function.

Conclusions: Our results demonstrate that the subthalamus is an alternative to the globus pallidus internus as a target for deep brain stimulation to treat primary dystonia. © 2013 International Parkinson and Movement Disorder Society

Key Words: primary dystonia; subthalamic nucleus; deep brain stimulation; Burke–Fahn–Marsden dystonia rating scale; Medical Outcomes Study 36-item Short-Form General Health Survey

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