

1 **The effectiveness of deep brain stimulation in dystonia: a patient-centered approach**

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32 **HIGHLIGHTS**

- 33 • Functional priorities in life of dystonia patients and their caregivers vary greatly
- 34 • The effect of DBS on functional priorities did not correlate with motor outcome
- 35 • Half of the motor ‘non-responder’ patients reported important changes in their
- 36 priorities
- 37 • The effect of DBS in dystonia should not be measured by motor outcome alone

38

39 **ABSTRACT**

40 **Background:** To systematically evaluate the effectiveness of deep brain stimulation of the
41 globus pallidus internus (GPi-DBS) in dystonia on pre-operatively set functional priorities in
42 daily living.

43 **Methods:** Fifteen pediatric and adult dystonia patients (8 male; median age 32y, range 8-65)
44 receiving GPi-DBS were recruited. All patients underwent a multidisciplinary evaluation
45 before and 1-year post DBS implantation. The Canadian Occupational Performance Measure
46 (COPM) first identified and then measured changes in functional priorities. The Burke-Fahn-
47 Marsden Dystonia Rating Scale (BFMDRS) was used to evaluate dystonia severity.

48 **Results:** Priorities in daily functioning substantially varied between patients but showed
49 significant improvements on performance and satisfaction after DBS. Clinically significant
50 COPM-score improvements were present in 7/8 motor responders, but also in 4/7 motor non-
51 responders.

52 **Discussion:** The use of a patient-oriented approach to measure GPi-DBS effectiveness in
53 dystonia provides an unique insight in patients' priorities and demonstrates that tangible
54 improvements can be achieved irrespective of motor response.

55

56 **INTRODUCTION**

57 Dystonia is a movement disorder characterized by sustained or intermittent muscle
58 contractions causing abnormal, often repetitive movements, abnormal posturing, or both.
59 Dystonia comprises a heterogeneous patient population due to a broad spectrum of
60 underlying acquired and inherited etiologies.[1]

61 Over the past decades, deep brain stimulation of the globus pallidus internus (GPi-DBS) has
62 emerged as a safe treatment option with a good response in non-lesional, mostly isolated
63 forms of dystonia and a more variable response in combined forms of dystonia that are due to
64 a static lesion or neurodegenerative process.[2] The application of this elective neurosurgical
65 procedure therefore frequently gives rise to discussion, especially in secondary dystonia
66 patients.

67 The effect of GPi-DBS has been predominantly measured with objective standardized
68 dystonia rating scales.² However, the variability of dystonic symptoms within days, or even
69 hours or minutes, makes it difficult to reliably capture overall dystonia severity in just one
70 evaluation. Furthermore, it is unclear how dystonia severity reflects disease burden and there
71 is only weak evidence that a reduction in symptoms in isolated forms of dystonia may
72 correlate with meaningful improvements in functioning.[3,4]

73 In line with the World Health Organization guidelines advocating patient-centered outcome
74 measures,[5] we aimed to systematically evaluate the effect of DBS in terms of
75 individualized functional priorities set by the patient and/or their caregivers.

76

77 **METHODS**

78 **Patients**

79 We prospectively included fifteen consecutive dystonia patients that received GPi-DBS
80 between January 2013 and July 2016. All patients were evaluated pre and 1-year post-

81 operatively screened by a multidisciplinary team. The local ethical committee classified the
82 study as care as usual.

83 **Outcome measures**

84 Priorities were identified by the Canadian Occupational Performance Measure (COPM). The
85 COPM is an individualized outcome measure to capture everyday problems that impact daily
86 functioning. Together with a trained occupational therapist, patients and/or caregivers
87 imaginary walked through a typical day in the patient's life to identify priorities that they
88 would like to see improved by GPi-DBS. For the three most important priorities performance
89 (1-10) and satisfaction (1-10) were rated. Change between pre- and postoperative ratings was
90 used for further analyses. At the 1-year follow-up, patients and/or their caregivers were
91 blinded for their pre-operative ratings. A difference of two or more points was considered
92 clinically significant.[6]

93 Dystonia severity was assessed with the motor subscale of the Burke-Fahn-Marsden dystonia
94 rating scale (BFMDRS). Videos were blinded for operative status and rated by experienced
95 clinicians (ALB, RB, KJP, MFC) who were blinded to treatment state. Mean total scores
96 were calculated. In order to be able to compare the results in all patients (generalized and
97 focal/segmental) the relative change in BFMDRS (% of improvement) was used for further
98 analyses. In addition, patients were subdivided into motor 'responders' (>20% change in
99 BFMDRS score) and 'non-responders' (<20% change in BFMDRS score).[7] For absolute
100 scores, see supplementary table 1.

101

102 **Data-analysis**

103 Data-analysis was performed using Statistical Package for the Social Sciences (SPSS, version
104 23.0). Due to the heterogeneity of the sample, medians and interquartile ranges (IQR) were
105 used. Differences between pre- and postoperative scores were compared with the Wilcoxon

106 Signed Ranked Test for total group and the responders and non-responder subgroups.
107 Correlations between the outcome measures were calculated with the Spearman's ρ .

108

109 **RESULTS**

110 Baseline characteristics, etiology and pharmacological treatment of all 15 patients (8 male;
111 median age 32y range 8-65; median disease duration 8y range 3-47) are shown in table 1.

112

113 **Individual priorities**

114 The 45 priorities (3 per patient) were categorized in self-care/activities of daily living (ADL)
115 (n=10); comfort in sitting and sleep (n=9); communication (n=7); social/leisure activities
116 (n=7); and mobility (n=12). Communication priorities involved the ability to use an electric
117 communication device, sign language or normal social interaction without interference of
118 dystonic posturing. Social activities included sports, interactive games or going out for
119 dinner. Mobility comprised walking, cycling, driving a car or the use of public transport.

120 For each patient, priorities comprised at least two categories. There was a very strong
121 correlation between performance and satisfaction scores ($\rho = 0.86$, $p < 0.0001$) and both scores
122 significantly improved after the application of DBS (Table 2). At patient level, a clinically
123 significant change in satisfaction in two or three individual priorities was reported in 73%
124 (11) of the patients. In 47% all three priorities were improved, in 27% two priorities were
125 improved, in 13% one priority was improved and in 13% none of the priorities was improved.

126

127 **Dystonia severity**

128 BFMDRS scores improved with a median change of 30% (pre 46.8 IQR 17.0-66.0 vs post
129 35.4 IQR 11.3-53.0; $p=0.027$). Eight patients (53%) were classified as responders with a
130 decrease in their BFMDRS of more than 20% and seven (47%) as non-responders.

131 The non-responders were two patients with cerebral palsy (case 8 and 14), one patient with a
132 mitochondrial disorder (case 1), one patient with DYT-THAP1 (case 6) and three patients
133 with segmental dystonia (case 3, 12 and 15).

134

135 **Priorities versus dystonia severity**

136 Change in dystonia severity did neither correlate with change in performance ($\rho = -0.15$,
137 $p=0.601$) nor satisfaction score ($\rho = 0.17$, $p=0.557$).

138 Seven of the eight responders reported a clinically significant improvement in performance
139 and satisfaction on at least two or three individual functional priorities. In the group of non-
140 responders, despite the lower motor response, clinical significant improvement in at least two
141 priorities was achieved in four of these patients for performance and three for satisfaction,
142 with a statistically significant change in COPM score (Case 6, 12, 14 and 15, $p=0.017$).

143

144 **DISCUSSION**

145 This prospective case series aimed to systematically evaluate the effectiveness of GPi-DBS
146 as measured with change in preoperatively set functional priorities. The priorities of the
147 patients and their caregivers lay within the domains of ADL, seating and sleep,
148 communication, social/leisure activities and mobility. A clinically significant motor response
149 coincided with improvements in functional priorities in 7/8 patients. Interestingly, half of the
150 motor ‘non-responder’ patients also showed a clinically significant change in two or three
151 priorities. Our findings are in line with a previous study in childhood dystonia showing that
152 DBS may lead to improvement of functional goals also in patients with only moderate to
153 ‘insignificant’ motor response.[8]

154 In contrast to the vast majority of efficacy studies primarily focusing on motor response, we
155 evaluated effect of GPi-DBS by looking at functional priorities. These priorities provide an

156 unique insight in what patients and their caregivers identify as most important aspects in
157 daily living. Given the heterogeneous nature of dystonia, it is not surprising that needs varied
158 greatly between patients. An additional advantage is that this method may facilitate
159 recognition of patients that might be unsuitable for the procedure due to goals that are
160 unrealistic or not likely to be achieved by GPi-DBS. One might argue that with a goal-
161 oriented approach changes are subjective to the patients' perception of improvement rather
162 than objective symptom reduction. In addition, a potential placebo effect cannot be excluded
163 in the absence of a control group. However, we agree with Kubu and colleagues that the main
164 goal of DBS is to improve quality of life as perceived by the patient more than by the
165 clinician, and that the effect of an elective neurosurgical option as DBS should be measured
166 accordingly.[9] In the future, it would be useful to objectify the patient centered outcome.
167 This can be done by transforming the patients' priorities into a treatment goal and pre-
168 operatively decide with the patient and caregivers when the goal is met, for instance by using
169 the goal attainment scale.

170 The heterogeneous patient sample may be seen as a limitation, both in terms of age as well as
171 etiology. On the other hand, it can be seen as an advantage for the generalizability of the
172 study. We did not correct for changes in medication, which could account for some of the
173 perceived improvements. We realize that our conclusions are based on a small case series
174 with a possibly limited power, but hope these results serve as a pilot study to trigger future
175 studies focusing on the effectiveness of GPi-DBS in dystonia. First to assess to what extent a
176 good motor outcome corresponds with the perceived outcome on the patient's priorities. This
177 may not always be the case, as 1/8 motor responders did not reach a significant improvement
178 on his priorities, and might provide clarity in the repeatedly reported discrepancy between
179 motor outcome and patient reported outcome. A systematical use of patient centered

180 outcomes might shine a new light on the current opinion that GPi-DBS is more effective in
181 isolated than in combined forms of dystonia.

182 In conclusion, the effect of GPi-DBS should be measured not by motor symptom reduction
183 alone, as clinically significant improvements on individual predefined priorities can be
184 achieved irrespective of motor response. In addition, a goal- or patient-oriented approach
185 provides unique insights in the priorities in daily living of dystonia patients and their
186 caregivers. This may not only be of added value for DBS candidates, but also for patients
187 across the entire dystonia population.

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233 **Table 1: Patient characteristics and pharmacological treatment**

Pt	Gender / age (yr)	Body distribution	Isolated or combined	Etiology	Pre-operative medical treatment	Post-operative medical treatment
1	M/8	Generalized	Combined (spasticity)	Mitochondrial disorder	Gabapentin 100mg; intrathecal baclofen 3ug/hr	Unchanged
2	M/8	Generalized	Isolated	Idiopathic	THP 20mg	No
3	M/18	Segmental	Isolated	Idiopathic	THP 24mg; BTX	THP 24mg
4	F/22	Generalized	Isolated	ACTB mutation	THP 16mg; tramadol 50mg	THP 12mg; clonazepam 1.5mg; clozapine 18.75; BTX
5	F/32	Segmental	Isolated	Idiopathic	Ibuprofen; BTX	No
6	M/9	Generalized	Isolated	DYT-THAP1	THP 21mg; baclofen 12.5mg	THP 11mg
7	M/22	Segmental	Isolated	TTPA	Vitamin E	Unchanged
8	M/47	Generalized	Combined (spasticity)	Cerebral palsy	Antidepressants	Unchanged
9	M/53	Segmental	Isolated	Idiopathic	Clonazepam 0.5mg; BTX	BTX
10	F/65	Segmental	Combined (parkinsonism)	Idiopathic	Pramipexole; L-dopa; Diazepam 5mg; BTX	Pramipexole; L-Dopa
11	F/48	Generalized	Isolated	ACTB mutation	THP 12mg; clozapine 12.5mg; oxazepam 10mg; diclofenac; BTX antidepressant	THP 12mg; clozapine 12.5mg; antidepressant
12	F/63	Segmental	Isolated	Idiopathic	Clonazepam 2.5mg	Clonazepam 0.5mg
13	M/62	Segmental	Isolated	Idiopathic	BTX	Clonazepam 1.0mg; BTX
14	F/8	Generalized	Combined (spasticity)	Cerebral palsy	THP 1.5mg; baclofen 12mg; gabapentin 600mg; clonazepam 0.5mg	Unchanged
15	F/63	Segmental	Isolated	Idiopathic	No	No

234
 235 ACTB: beta-actin gene; BTX: botulinum toxin injections; THP: trihexiphenidyl; TTPA α -
 236 tocopherol transfer protein – vitamin E.

237

238 **Table 2: Pre- and postoperative COPM scores for all functional priorities and per**
 239 **subcategory**

	COPM-Performance			COPM-Satisfaction		
	Baseline	1 year	Improved priorities†	Baseline	1 year	Improved priorities†
All priorities	3.0 (1.0-4.0)	7.0 (5.0-8.0)	32/45*	2.0 (1.0-3.5)	7.0 (4.0-8.5)	31/45*
- sitting and sleep	3.0 (2.0-4.0)	7.0 (5.5-8.0)	8/9	2.0 (1.5-3.5)	7.0 (3.5-9.0)	5/9
- self-care/ADL	1.5 (1.0-4.3)	6.0 (2.5-7.3)	6/10	1.5 (1.0-3.0)	6.5 (2.5-7.3)	7/10
- communication	4.0 (3.0-4.0)	8.0 (6.0-10.0)	5/7	3.0 (1.0-4.0)	9.0 (7.0-9.0)	6/7
- social/leisure	3.0 (1.0-4.0)	7.0 (3.0-7.0)	4/7	3.0 (1.0-4.0)	6.0 (1.0-7.0)	4/7
- transfer	2.5 (1.3-4.8)	6.5 (5.3-7.0)	9/12	2.0 (1.0-3.8)	6.5 (5.3-8.8)	9/12

240
 241 ADL activities of daily living; †Change or 2 point or more between baseline and 1-year post-
 242 operative score *p<0.0001

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