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ORIGINAL COMMUNICATION

Factors predicting protracted improvement after pallidal DBS for primary dystonia: the role of age and disease duration

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Abstract In many patients, optimal results after pallidal deep brain stimulation (DBS) for primary dystonia may appear over several months, possibly beyond 1 year after implant. In order to elucidate the factors predicting such protracted clinical effect, we retrospectively reviewed the clinical records of 44 patients with primary dystonia and bilateral pallidal DBS implants. Patients with fixed skeletal deformities, as well as those with a history of prior ablative procedures, were excluded. The Burke-Fahn-Marsden Dystonia Rating Scale (BFMDRS) scores at baseline, 1 and 3 years after DBS were used to evaluate clinical outcome. All subjects showed a significant improvement after DBS implants (mean BFMDRS improvement of 74.9% at 1 year and 82.6% at 3 years). Disease duration (DD, median 15 years, range 2–42) and age at surgery (AS, median 31 years, range 10–59) showed a significant negative correlation with DBS outcome at 1 and 3 years. A partition analysis, using DD and AS, clustered subjects into three groups: (1) younger subjects with shorter DD ($n = 19$, AS < 27, DD ≤ 17); (2) older subjects with shorter DD ($n = 8$, DD ≤ 17, AS ≥ 27); (3) older subjects with longer DD ($n = 17$, DD > 17, AS ≥ 27). Younger patients with short DD benefitted more and faster than older patients, who however continued to improve 10% on average 1 year after DBS implants. Our data suggest that subjects with short DD may expect to achieve a better general outcome than those with longer DD and that AS may influence the time necessary to achieve maximal clinical response.

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Abbreviations

DBS	Deep brain stimulation
GPi	Globus pallidus internus
BFMDRS	Burke-Fahn-Marsden Dystonia Rating Scale
AS	Age at surgery (in years)
DD	Disease duration (in years)
SS	Speech and swallowing
SY	Subjects with disease duration $\leq$17 years and age at surgery <27 years
SO	Subjects with disease duration $\leq$17 years and age at surgery $\geq$27 years
LO	Subjects with disease duration >17 years and age at surgery $\geq$27 years

Introduction

Dystonia is a neurological syndrome characterized by sustained, involuntary muscle contractions generating twisting and repetitive movements or abnormal postures [1]. Medical treatment for dystonia is limited by the poor efficacy and tolerability of available drugs [2]. Over the past decade, deep brain stimulation (DBS) of the globus pallidus internus (GPi) has emerged as a safe and effective treatment for patients with severe generalized primary dystonia, with positive results reported both at short-term [3, 4] and long-term follow-up [5, 6].

Outcome predictors for successful pallidal DBS in dystonia are poorly defined. We recently reported that younger age at surgery and shorter disease duration are associated with better outcomes 1 year after lead implant [7, 8]. However, improvement of dystonic symptoms slowly progress over many months in several patients, possibly beyond 1 year after implant. In this study, we investigated the magnitude of dystonia improvement beyond the first year of therapy and tested whether the clinical factors that are predictive of outcome at 1 year remain so in the longer term. In order to determine if these factors are significant in a wider clinical experience, we collected data from five established DBS centers in Europe and the United States.

Methods

Subjects

Data from the medical records of 44 patients with medically refractory multi-segmental or generalized primary dystonia who underwent stereotactic pallidal DBS surgery at five different movement disorders centers were collected. The participating centers were the Mount Sinai School of Medicine in New York (USA), Christian-Albrechts-University in Kiel (Germany), Charité University of Medicine in Berlin (Germany), University Hospital in Bern (Switzerland) and the University of California San Francisco in San Francisco (USA). Patients had been selected for DBS surgery based on a diagnosis of primary multi-segmental or generalized dystonia [1] with significant disability despite optimized medical management. All patients were implanted bilaterally. Patients with fixed skeletal deformities (radiologically documented), as well as those with secondary dystonia or history of prior central ablative procedures, were excluded from this analysis.

Thirty-six subjects had early-onset dystonia [1] and 23 tested positive for the DYT1 gene defect. Thirty-two patients were male and 12 female (M:F = 2.6:1); median age at symptoms onset was 15 years (range 4–50); median age at surgery was 31 years (range 10–59) and median disease duration was 15 years (range 2–42).

Clinical evaluation and outcome measures

Each center retrospectively collected clinical records and standardized videotaped evaluations of all subjects included in the study, which was approved by the respective institutional review boards. All videos were blindly evaluated not by the treating physicians.

The severity of dystonia was evaluated using the Burke-Fahn-Marsden Dystonia Rating Scale (BFMDRS) [9]. BFMDRS scores at baseline, 1 and 3 years follow-up were collected. Post-operatively, patients were evaluated only while actively stimulated. Results were normalized by calculating the percentage BFMDRS change from baseline, according to the formula:

$$[(\text{Baseline BFMDRS score} - \text{Postoperative BFMDRS score})/\text{Baseline BFMDRS score}] \times 100$$

Changes in the BFMDRS percentage improvement between the 1- and 3-year follow-up examinations (Δ) were also calculated for every patient. Medication regimen and dosages were recorded at baseline and each follow-up visit, with particular attention to the following drug classes: dopaminergics, anticholinergics, antispasmodics and benzodiazepines. The reduction of daily medication was calculated averaging of the percentage reduction of each drug.

Neurosurgical procedure, active contacts location and DBS programming

All subjects included in this study underwent microelectrode-guided, frame-based stereotactic implantation of

DBS leads [model 3387 or model 3389 (2 patients), Medtronic], as extensively described in previous publications from the participating centers [4, 10–12]. Confirmation of electrode placement in the GPi was obtained in all patients with immediate post-implantation stereotactic MRI. In addition, each center was asked to calculate the coordinates of the active contacts, relative to the mid-commissural point (MCP) (x, mediolateral plane; y, anteroposterior plane; z, dorsoventral plane), according to previously described methodology [12].

Data on stimulation settings at 1 and 3 years follow-up were collected from each center, including active electrodes, configurations, voltage, pulse width and frequency. Stimulation strategies varied according to local methodology and expertise, with the common goal of maximizing clinical benefit and/or reducing adverse effects [13].

Statistical analysis

Results were analyzed on an intention-to-treat basis. Chi-Square was used to test demographic (e.g. gender) and clinical homogeneity (e.g. DYT1 status) among groups. The BFMDRS (total and sub-scores) percentage improvement at 1 and 3 years were compared by means of the Wilcoxon signed-rank test for matched pairs. A pair comprised data obtained in the same individual at different time points (i.e. year 3 vs. year 1). Analysis of variance (ANOVA) and Tukey's test were used to investigate BFMDRS total and sub-score differences between groups (e.g. early- vs. late-onset dystonia) and to compare each BFMDRS sub-score percentage improvement within the same year of follow-up.

In order to identify pre-operative predictors of improvement both at 1 and 3 years after implants, we used correlation multivariate (pairwise) analysis for quantitative variables (e.g. age at surgery [AS] and at onset of dystonia, disease duration [DD], and symptom severity at baseline) and the Wilcoxon for categorical variables (e.g. gender and DYT1 status). Clinical and demographic factors that proved predictive of percentage BFMDRS changes were then used in a partition analysis to identify cutoffs values and accordingly best split subjects into different groups. Clinical responses (i.e. changes in the BFMDRS scores at years 1 and 3) in these groups of patients were then compared by means of ANOVA and Tukey's test. This data-driven design allowed us to overcome the low number of patients and the interdependence of some of the variables (i.e. AS and DD) in order to make statistically and clinically relevant observations. P values <0.05 were considered to be statistically significant. Statistical analyses were performed with the JMP® statistical package, version 5.1 (SAS Institute, Inc.).

Results

Following surgery and device activation, every patient experienced an improvement in motor function, which was reflected in their BFMDRS motor and disability scores over time (Table 1). All BFMDRS sub-scores showed significant improvement at 1 year, with further gains at 3 years. Speech and swallowing (SS) improved less than other body regions at both end points (1- and 3-year follow-up, $p < 0.05$; Table 1).

Only three subjects showed a negative Δ, indicating a worsening of symptoms between years 1 and 3. One patient developed mild speech difficulty (BFMDRS sub-score of 1), which was not present at baseline. Two other patients showed mild worsening of axial (0.5 and 4.5 points, respectively) and limbs scores (4.5 and 7 points) from years 1 to 3. Five additional patients exhibited worse sub-scores at year 3 (3 axial, 1 limbs, and 1 facial and speech), but still showed a positive Δ and did not regress to their pre-surgical impairment scores (Table 1).

Among demographic features, only age at surgery negatively correlated with clinical outcome both at 1 ($r^2 = 0.28$; $p < 0.001$) and 3 years of stimulation ($r^2 = 0.18$; $p < 0.01$). Among clinical variables, only disease duration negatively correlated with clinical outcome at both time points ($r^2 = 0.3$ and 0.26, respectively; $p < 0.001$). No other significant correlations were found. Among BFMDRS sub-scores, the strongest correlation was seen between SS improvement and disease duration (1-year: $r^2 = 0.42$, $p < 0.001$; 3 years: $r^2 = 0.64$, $p < 0.001$). BFMDRS sub-score correlations with age at surgery and disease duration are detailed in Table 2.

The partition analysis cutoffs that best split our cohort in terms of outcomes were age at surgery of 27 years and disease duration of 17 years (Table 3A). Based on these cutoffs, subjects were clustered into three groups (Table 3B). Group SY ($n = 17$) included subjects with DD shorter than 17 years and AS less than 27 years; group SO ($n = 8$) was characterized by DD shorter than 17 years and AS greater than 27 years; group LO ($n = 19$) included patients with DD longer than 17 years and AS greater than 27 years. None of the patients included in this study had long DD and young AS. Subjects in the SY group consistently showed better outcomes than those in the SO group [mean BFMDRS change difference of 10% ($p < 0.05$) at 1 year and 3% (n.s.) at 3 years] and LO group [mean BFMDRS change difference of 25% ($p < 0.01$) at 1 year and 16% ($p < 0.05$) at 3 years (Fig. 1)]. The SY group did not exhibit significant changes between years 1 and 3 (mean $\Delta = 2.8\% \pm 5$SD). However, both SO and LO groups showed significant increments of clinical benefit over that time period [mean $\Delta = 9.3\% \pm 10$ (SO) and

Table 1 Clinical features at baseline and at 1 and 3 years post-DBS

	N	Score baseline	Score at 1 year	Improvement (%) at 1 year	Score at 3 years	Improvement (%) at 3 years	Δ
BFMDRS	44	45.1 ± 22 (10–81.5)	10.5 ± 10.2 (0–55.5)	74.9 ±18 (40–100)	7.6 ± 7.6 (0–31.5)	82.6 ± 13.3 (57.1–100)	7.7 ± 9.9 (−14–35)
Speech and swallowing	25[a]	3.9 ± 3 (1–12)	1.8 ± 2 (0–6)	50.7 ± 43.9* (0–100)	1.8 ± 2 (0–6)	61.7 ± 39.4* (0–100)	11 ± 29.4 (−33.3–100)
Face	22	5 ± 4.2 (1–14)	1.2 ± 1.7 (0–6.5)	70.2 ± 35.4 (0–100)	0.7 ± 1.2 (0–4.5)	86.9 ± 19.8 (33.3–100)	16.7 ± 37.1 (−33.3–100)
Axial	41	14 ± 6.8 (3–24)	3.4 ± 3.9 (0–15)	78 ± 19.4 (37.5–100)	2.3 ± 2.6 (0–10)	84.3 ± 14.6 (54.5–100)	6.3 ± 15.1 (−25–41.7)
Limbs	43	27.8 ± 17.4 (2–64)	5.7 ± 7 (0–39)	76.9 ± 22.9 (0–100)	4.1 ± 5.4 (0–22)	84.6 ± 17.9 (50–100)	7.6 ± 15.1 (−35.3–66.7)
Disability	44	10.4 ± 5.4 (3–23)	2.7 ± 2.2 (0–9)	69 ± 21.2 (30–100)	2.2 ± 1.8 (0–6)	76.1 ± 20.9 (0–100)	7 ± 25 (−44.4–86.7)

Speech and swallowing symptoms improved significantly less than other body regions at both end points (* $p < 0.05$). For all body sites, we found a similar additional improvement from 1 year to 3 years of stimulation (Δ = % improvement at 3 years − % improvement at 1 year). Data are reported as mean ± SD (range)

The total score for the movement subscale of the Burke-Fahn-Marsden Dystonia Rating Scale (BFMDRS), which can range from 0 to 120, is the sum of individual scores of nine body regions and represents the severity of motor disability related to dystonia. The total disability score can range from 0 to 30 and is the sum of individual ratings for seven activities: speech, handwriting, and the degree of dependence with respect to hygiene, dressing and feeding, swallowing and walking. A high score indicates worse disability

[a] Subjects showing speech and swallowing dystonic symptoms were 25 at baseline, 26 at 1-year and 3-year follow-up

12 ± 10.8 (LO), $p < 0.05$; Fig. 1c]. The magnitude of Δ correlated with age at surgery ($r^2 = 0.16$, $p < 0.01$) but not with duration of disease ($r^2 = 0.08$, n.s.) or other clinical or demographic features.

In comparison to DYT1 negative subjects ($n = 21$), DYT1 positive subjects ($n = 23$) were, on average, younger at symptomatic onset (9 ± 4 years vs. 22 ± 15 years, $p < 0.001$) and at surgery (21 ± 12 years vs. 42 ± 13 years, $p < 0.001$); consequently, DYT1 positive subjects also had a shorter average DD at the time of DBS surgery (12 ± 10 years vs. 20 ± 11 years, $p < 0.05$). There were no other significant differences in the demographic or baseline clinical characteristics in these two groups, with the exception of a higher prevalence of SS involvement in DYT1 negative subjects (15/20 vs. 10/23; $p < 0.05$). DYT1 positive patients exhibited a greater BFMDRS percentage improvement both 1 year (81.6 ± 16.6 vs. 67.5 ± 16.7, $p < 0.01$), and 3 years (87.6 ± 11.7 vs. 77 ± 13, $p < 0.01$) after surgery. However, the statistical significance was lost when comparison was weighted for DD and AS. Indeed, DYT1 negative and positive subjects were unevenly distributed among the partition analysis groups (SY: 2 DYT− vs. 15 DYT+; SO: 7 vs. 1; LO: 12 vs. 7; $p < 0.001$).

Subjects with late-onset dystonia exhibited an improvement comparable to early-onset patients at both time points when adjusted for AS or DD (1-year follow-up: 64.2 ± 62.1 vs. 68.3 ± 71.7; 3-year follow-up: 76 ± 50.8 vs. 77.7 ± 51.5; p = n.s.).

Stimulation settings were stable from year 1 to year 3. A monopolar configuration was predominant both at year 1 (79/88 leads; 47 single, 30 double, 2 triple) and year 3 (79/88 leads; 37 single, 38 double, 4 triple); the remaining electrodes were set in a bipolar configuration (7 simple bipolar and 2 tripolar at 1 year; 7 simple bipolar, 1 tripolar and 1 quadripolar at 3 years). At year 1, the mean stimulation amplitude was 3 V (±0.8), the mean pulse width was 184.3 ms (±83) and the mean frequency was 113.7 Hz (±45). At year 3, the mean stimulation amplitude was 3 V (±0.7), the mean pulse width was 181 ms (±79) and mean frequency was 115.7 Hz (±47). No difference was found in the mean stimulation amplitude among the partition analysis sub-groups (i.e. SY, SO and LO); pulse width was significantly lower in SO subjects at 1-year follow-up; SY subjects had significantly lower frequencies of stimulation both at 1 and 3 years after surgery (Table 3C). When weighted for different DBS settings, improvement differences among cohorts proved to be statistically independent.

The active contacts location relative to the MCP is listed in Table 3D. We found no significant difference between the mean active contact locations among the three partition analysis subgroups. Both mean active contacts location and

Table 2 Correlation matrix result for BFMDRS total and sub-scores percentage improvements with age at surgery and disease duration

	Age at surgery		Disease duration	
	1-year	3-year	1-year	3-year
BFMDRS ($n = 44$)	0.28 (<0.001)	0.18 (<0.01)	0.3 (<0.001)	0.26 (<0.001)
Speech and swallowing ($n = 25$)	0.2 (<0.05)	n.s.	0.42 (<0.001)	0.64 (<0.001)
Face ($n = 22$)	0.2 (<0.05)	n.s.	0.25 (0.01)	n.s.
Axial ($n = 41$)	0.25 (<0.001)	n.s.	0.12 (<0.05)	n.s.
Limbs ($n = 43$)	n.s.	n.s.	0.23 (<0.01)	0.23 (<0.001)

Data are reported as r^2 (p value)

stimulation settings did not correlate with BFMDRS percentage improvement at 1 and 3 years after surgery.

Thirty-two subjects (72%) were taking one or more medications before surgery. One year after surgery, the average percentage reduction of daily medication was 52.1% (±40.2) with eight patients (18%) able to completely discontinue medications. Three years after surgery the average medication reduction was 80% (±30) and 16 subjects (36%) had discontinued all medications. No demographic or baseline clinical features predicted medication reduction or their discontinuation.

Three patients (6.8%) experienced three adverse events (AEs) during the study period, yielding a complication rate of 3.4% (3/88 electrode-years) or 0.01 events/year of stimulation. Adverse events included two device infections each of which was treated by removing the infected device components and re-implanting following an appropriate course of intravenous antibiotics. One patient suffered extension cable fractures, which required surgical replacement. There were no intracerebral hemorrhages and no adverse neurological events.

Discussion

This multicenter, retrospective analysis confirms that medically refractory primary dystonia is highly responsive to pallidal DBS and suggests that the maximal response may take more than 1 year to develop, particularly in older patients.

The improvement in BFMDRS scores described in this study is higher than reported by others [4, 5, 14]. This may due to (1) the much shorter disease duration of our population and (2) the exclusion of subjects known to benefit less from DBS due to non-neurological causes (e.g. skeletal deformities) [8].

Inclusion criteria may possibly account for the low AEs rate described in this study [15] as we excluded subjects that interrupted the stimulation because of AEs and did not reached a 3-year follow-up thereafter.

Patients older than 27 years at the time of DBS surgery showed an additional 10% average improvement between years 1 and 3 of stimulation. This added benefit was not explained by changes in stimulation parameters and medication intake, which actually decreased in the same interval. However, we cannot exclude that significantly lower stimulation frequency in the SY group might have had a positive effect on the rate and extent of improvement as compared to the older groups. Results were not correlated with active electrode location, as previously suggested by other groups not involved in the present analysis [16].

Finally, this study confirms and extends previous findings indicating that younger age and shorter symptom duration at the time of surgery predict better clinical outcomes. Younger patients with shorter disease duration fare best after pallidal DBS. Older patients appear to take longer to reach maximal response than younger subjects with comparable disease duration. The novel finding of this multicenter, long-term analysis is that age and disease duration appear to play complementary roles in predicting clinical outcomes in patients with primary dystonia undergoing GPi–DBS. As previously described by independent studies [8, 17], disease duration is inversely correlated with the magnitude of the response to DBS as measured by the percent change in the BFMDRS motor score. At the same time, we also found that age at surgery directly correlated with continued BFMDRS improvements (Δ) between years 1- and 3-year of follow-up, suggesting that older dystonia patients (independent of their duration of disease) may require more time to achieve their maximal response to pallidal stimulation. A similar trend toward continued improvement of BFMDRS scores beyond 6 months of stimulation was described in adult patients with tardive dystonia and disease duration shorter than 15 years [18].

The predictive roles of disease duration and age are of great interest in light of current models of DBS mechanism of action, which propose that the therapeutic effects of stimulation are mediated by a gradual brain reorganization or plasticity [11, 19–22]. The severity of aberrant function in dystonia may be correlated with disease duration, making complete resolution of symptoms by DBS more difficult the more longstanding the aberrancy. In contrast, age at surgery may not necessarily relate to the evolution of the disease. However, age may affect brain plasticity in and

Table 3 Partition analysis results (A), clinical and demographic features (B), stimulation settings (C), and location (D) of active contacts of subgroups of patients

A	Age at surgery		Disease duration	
Partition analysis for 1-year % improvement				
Cut-off value (*n* of patients)	<27 years ($n = 17$)	≥27 years ($n = 27$)	≤17 years ($n = 26$)	>17 years ($n = 18$)
BFMDRS % imp.	87.2 ± 11.1	67.1 ± 17.2	83.1 ± 13	63.0 ± 17.8
Partition analysis for 3-year % improvement				
Cut-off value (*n* of patients)	<27 years ($n = 17$)	≥27 years ($n = 27$)	≤17 years ($n = 26$)	>17 years ($n = 18$)
BFMDRS % imp.	89.4 ± 12	78.2 ± 12.3	87.8 ± 11	74.8 ± 12.6

B

Group	N	Age at surgery	Disease duration	BFMDRS % imp. 1-year	BFMDRS % imp. 3-year	Δ
SY	17	13.5 ± 3.3*	5.2 ± 2.4*	87.2 ± 11.1*	90 ± 12	2.8 ± 5*
SO	8	43.6 ± 13.8	10 ± 3.7	77.7 ± 11.6	87 ± 7.1	9.3 ± 10
LO	19	42 ± 10	27 ± 8	62.7 ± 17.4	74.5 ± 12.3*	12 ± 10.8

C

Group	DBS settings					
	1-year follow-up			3-year follow-up		
	Hz	PW	V	Hz	PW	V
SY	89.4 ± 42.2*	221.6 ± 87.1	2.9 ± 0.6	93.9 ± 41*	206.3 ± 73	2.9 ± 0.6
SO	118.8 ± 31.2	120 ± 58*	3.1 ± 0.6	140.6 ± 36.9	140.6 ± 58.7	3.3 ± 0.8
LO	125.6 ± 39.2	178.6 ± 93.5	3.2 ± 0.7	121.6 ± 46.4	180.3 ± 88.7	3.0 ± 0.9

D

Group	Location of active contacts relative to the midcommissural point					
	1-year follow-up			3-year follow-up		
	x	*y*	*z*	*x*	*y*	*z*
SY	19.8 ± 1.1	2.4 ± 1.2	−2 ± 2.3	19.5 ± 1.2	2.7 ± 1.7	−2.7 ± 1.9
SO	20.2 ± 1.8	4 ± 1.8	−2.9 ± 2.1	20.3 ± 1.9	4.3 ± 1.3	−3.3 ± 2
LO	20.1 ± 1.2	2.5 ± 1.3	−2.4 ± 1.5	21.6 ± 3	3.0 ± 1.4	−1.7 ± 1.7

Clusters: SY: disease duration ≤17 years and age at surgery <27 years; SO: disease duration ≤17 years and age at surgery ≥27 years; LO: disease duration >17 years and age at surgery ≥27 years

x, mediolateral coordinate of the active contacts relative to midcommissural point (MCP); *y*, anteroposterior coordinate of the active contacts relative to MCP; *z*, dorsoventral coordinate of the active contacts relative to MCP

* $p < 0.05$

of itself, thereby determining the capacity of the brain to adapt in response to DBS. Indeed, age at surgery, but not disease duration correlates with Δ, and subjects with short disease duration but older age at surgery (SO group) reached a clinical improvement comparable to younger patients after a longer time on stimulation. Improvement in older subjects with longer duration of disease (LO group) remained significantly lower even after 3 years of stimulation, further supporting the strong basic influence of disease duration on clinical outcome after DBS.

Functional imaging studies in normal humans show age related changes during the execution of various motor tasks. Older subjects activate the same cortical regions as their younger counterparts, but to a greater extent, or they activate additional brain regions [23–27]. These age-related differences become more pronounced with increasingly complex motor tasks and usually include activation of additional brain regions involved in higher-order aspects of motor control, such as increased processing of somatosensory information [27]. Interestingly, sensory-motor

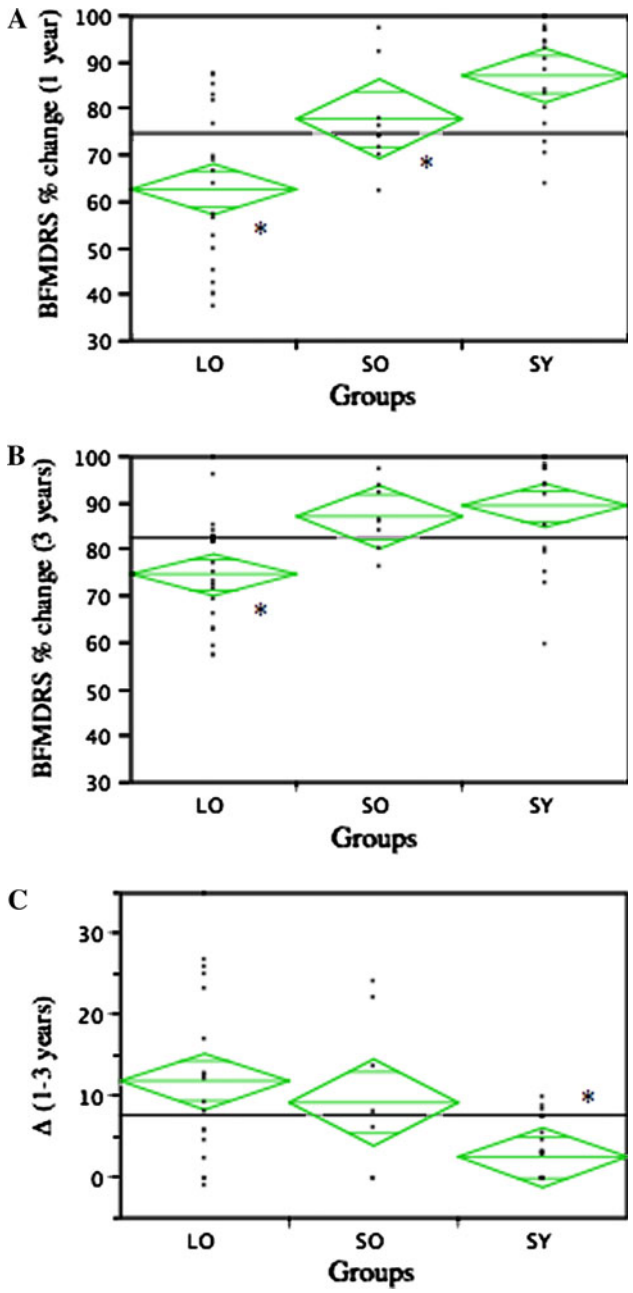

Fig. 1 Differential outcomes in age and disease duration clusters. Younger patients with short disease duration (SY) showed better outcome both 1 (**a**) and 3 years after surgery (**b**), without a significant change between the two observations. Subjects with older age at surgery showed a significant additional outcome improvement between year 1 and 3 follow-up (**c**). *SY* disease duration ≤17 years and age at surgery <27 years, *SO* disease duration ≤17 years and age at surgery ≥27 years, *LO* disease duration >17 years and age at surgery ≥27 years. $*p < 0.05$

integration plays a crucial part in the pathophysiology of dystonia [28]. Other age-related changes in synaptic function that may affect plasticity include reduced synaptic strength and the inability to maintain synaptic potentiation [29–31]. In animal models, high-frequency stimulation generates long-term potentiation (LTP) and effects long-term changes in the efficiency of synaptic transmission, phenomena which have been postulated to underlie the clinical effects of DBS [32]. The decay rate for LTP is accelerated during aging [33], impacting the brain's capacity to maintain synaptic enhancement. This implies that aging animals lack specific cellular mechanisms (e.g. protein synthesis), which mediate LTP persistence [34, 35]. Aging animals also lose the capacity to maintain synaptic enhancement in response to low frequency stimulation (1–3 Hz) [36]. It is currently unclear whether these experimental observations could be extended to pallidal stimulation in humans.

Age at disease onset did not play a role in determining DBS outcomes. In fact, the response to pallidal DBS was similar in patients with late- and early-onset dystonia when results were weighted for age at surgery and disease duration. Similarly, disease severity did not correlate with clinical outcome at either 1 or 3 years of follow-up.

DYT1-positive status was associated with greater improvement both at 1 and 3 years, in line with a recent metaregression study of DBS outcomes in dystonia [15]. However, our data suggest that DYT1 status may not be an independent outcome predictor. As previously observed [8], the superior DBS outcomes in DYT1-positive subjects appears to be correlated with their younger age and short disease duration at the time of surgery. In addition, DYT1-positive subjects consistently have a low burden of SS symptoms, which are less responsive to pallidal DBS. These clinical features may confer to DYT1-positive subjects the observed DBS outcome advantage.

In conclusion, we confirm that patients with primary, medically refractory dystonia are excellent candidates for pallidal DBS. Patients with short disease duration may expect to achieve a better general outcome than those with longer disease duration. Age at the time DBS surgery is performed appears to influence the time necessary to achieve maximal clinical response.

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Conflict of interest None.

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