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Causes of failure of pallidal deep brain stimulation in cases with pre-operative diagnosis of isolated dystonia

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ABSTRACT

Introduction: Pallidal deep brain stimulation (GPi-DBS) is an effective therapy for isolated dystonia, but 10–20% of patients show improvement below 25–30%. We here investigated causes of insufficient response to GPi-DBS in isolated dystonia in a cross-sectional study.
Methods: Patients with isolated dystonia at time of surgery, and <30% improvement on the Burke-Fahn-Marsden dystonia-rating-scale (BFMDRS) after ≥6 months of continuous GPi-DBS were videotaped ON and OFF stimulation, and history, preoperative videos, brain MRI, medical records, stimulation settings, stimulation system integrity, lead location, and genetic information were obtained and reviewed by an expert panel.
Results: 22 patients from 11 centres were included (8 men, 14 women; 9 generalized, 9 segmental, 3 focal, 1 bibrachial dystonia; mean (range): age 48.7 (25–72) years, disease duration 22.0 (2–40) years, DBS duration 45.5 (6–131) months). Mean BFMDRS-score was 31.7 (4–93) preoperatively and 32.3 (5–101) postoperatively. Half of the patients (n = 11) had poor lead positioning alone or in combination with other problems (combined with: other disease n = 6, functional dystonia n = 1, other problems n = 2). Other problems were disease other than isolated inherited or idiopathic dystonia (n = 5), fixed deformities (n = 2), functional dystonia (n = 3), and other causes (n = 1). Excluding patients with poor lead location from further analysis, non-isolated dystonia accounted for 45.5%, functional dystonia for

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27.3%, and fixed deformities for 18.2%. In patients with true isolated dystonia, lead location was the most frequent problem.
Conclusion: After exclusion of lead placement and stimulation programming issues, non-isolated dystonia, functional dystonia and fixed deformities account for the majority of GPi-DBS failures in dystonia.

1. Introduction

Bilateral pallidal deep brain stimulation (GPi-DBS) is a safe and effective therapy for generalized, segmental [1,2] and focal [3] isolated (genetic or idiopathic, non-neurodegenerative) dystonia (henceforth referred to as isolated dystonia). Improvements are maintained long-term [4–7], although secondary worsening is sometimes observed [5]. In combined inherited neurodegenerative or acquired dystonias, DBS outcome is less impressive and more variable [8–10].

Given the cost, possibly severe complications of the DBS procedure, and high patient expectations, a reliable outcome prediction would be desirable. Individual prediction is difficult, but some factors such as disease duration [11–13], patient age [14], severity of dystonia [12], the presence of fixed musculoskeletal deformities [11,13] (henceforth referred to as 'fixed deformities'), GPi volume [15], lead location [16] and etiology of dystonia [8–10,12,15,17,18], can help in estimating benefits. Particular symptoms, such as orofacial dystonia, respond less [1,2]. 10–20% of patients with isolated (previously 'primary') dystonia show insufficient benefit (motor improvement <25–30% [1,2,6] for unknown reasons.

In a previous study addressing causes of DBS failure in movement disorders, comprising one patient with dystonia [19], stimulation-system related issues were the most frequent cause (>50%) [19]. There are no studies on DBS-nonresponders in isolated dystonia, yet understanding the causes of insufficient outcome could help manage these patients, and could affect patient selection and counselling for GPi-DBS.

Thus, we assessed a cohort of patients diagnosed with isolated dystonia at the time of surgery, and insufficient response to GPi-DBS. We hypothesized that insufficient therapeutic response could be due to one or more of the following causes: disease other than isolated inherited or idiopathic dystonia, functional comorbidity or disease, fixed deformities, stimulation-related problems (device malfunction, lead misplacement, inadequate programming), or other causes.

2. Materials and methods

2.1. Patient selection

We asked all centers of the *German DBS Study Group* to refer all patients diagnosed with isolated idiopathic or genetic non-neurodegenerative, non-acquired dystonia at the time of surgery, and insufficient response to GPi-DBS (defined as <30% improvement on the Burke-Fahn-Marsden Dystonia Rating Scale [20] motor score (BFMDRS-M) postoperatively vs. preoperatively) after at least 6 months of continuous GPi-DBS for inclusion in this study. Patients could be referred regardless of whether therapeutic failure was primary (i.e. patients had never shown any response) or secondary (loss of response after initial improvement). The study was approved by the University Hospital of Cologne Ethics Committee (study number 10–092), and was carried out in accordance with the Declaration of Helsinki. The study is registered with the German Registry for Clinical Studies (Study number DRKS00003105).

2.2. Procedure

After referral and informed written consent, all patients were seen at least once at the Department of Neurology of the University Hospital of Cologne for follow-up to acquire ON and OFF videography, postoperative high-resolution computed tomography scan of the brain, stimulator check-up, side effect testing, stimulator adjustments, and cognitive testing. In addition, the four primary nonresponders (<25% improvement) from the German multicentre trial on GPi-DBS for general and segmental isolated dystonia [2] were also included. Of these, one was seen in Cologne, the others had follow-up visits at their local center.

2.3. Patient history and clinical information

Patients' history (including birth and childhood development, age and site of onset of dystonia, course of dystonia over time, other (non-dystonic neurological) symptoms, psychiatric and family history, genetics if available) was obtained through asking the patient and by reviewing medical records supplied by the patient and the cooperating center.

2.4. Lead location

A postoperative high-resolution computed tomography brain scan was obtained in all patients to determine the localization of the lead and of the active contacts used for stimulation as described previously [21]. Briefly, postoperative CCT scans and preoperative brain MR (or CT) imaging were imported into a planning software (STP 3.0 and STVX, Stryker Leibinger, Freiburg, Germany) and merged. Coordinates of the active lead contacts were read out and transformed into standard space. The GPi target region was judged based on previous studies relating quality of clinical outcome to target coordinates [22–24] (standard coordinate range related to good outcomes: x = 17.5 to 22.4, y = +1.2 to +8, z = −5.3 to +3.1 mm). Unless individual brain MRI anatomy clearly indicated good placement, if individual active contacts were outside the above range, the lead was classified as suboptimally placed, and if all active contacts were outside the above range, the lead was considered misplaced. Cases with unilateral suboptimally placed leads were not considered to be causative for GPi-DBS failure.

2.5. Stimulation system integrity

Patients underwent a check-up of battery function, therapeutic and individual lead impedances (for both active and inactive contacts to exclude short circuits or disconnection), and current stimulation settings. All lead contacts were tested individually for side effects, and effects and side effect thresholds and profiles were documented.

2.6. Brain MRI assessment

Preoperative brain MRI images were obtained and assessed by an independent senior neuroradiologist (T.L.) blinded to the outcome for the presence of any abnormalities such as atrophy, vascular or other lesions, or signal intensity alterations in the basal ganglia etc. MRIs were classified as (1) normal, (2) pathological (specifying pathology) and (3) not assessable (if available MRI quality and data did not allow for a conclusive assessment). If original imaging data were unavailable, external preoperative brain MRI findings were reported (n = 1).

2.7. Clinical phenotyping, expert panel assessment and case classification

Patients were videotaped according to a standardized video protocol in stimulation ON and after ≥14-h OFF. Preoperative videos were obtained from the centers where patients were operated (two patients with missing preoperative video). All videos were rated by K.A.M.P. using BFMDRS-M [20]. In patients with pure cervical dystonia (n = 3), the Toronto Western Spasmodic Torticollis Rating Scale severity scale (TWSTRS-S) was also rated. The preoperative BFMDRS-M was used if a video was unavailable (n = 2). A thorough, videotaped neurological examination was also carried out with particular emphasis on other neurological signs and presence of fixed dystonia.

After all of the above data were collated, a panel of dystonia experts (A.A.K., E.M., J.K·K., J.V., K.B. and L.T.) clinically assessed all cases from the preoperative videos, and postoperative videos taken as part of the study. Raters were blinded to lead positioning information. The panel (1) assessed and classified the hyperkinetic symptoms present, (2) documented additional movement disorders signs or other neurological signs (e.g. ataxia, spasticity, hypotonia, tremor), (3) assessed the presence of visible fixed deformities, (4) assessed signs of functional disease (i.e. inconsistencies over time, symptoms incongruent with classic dystonia, functional gait disorder, excessive slowness, improvement with distraction, entrainment, improvement with suggestion). Functional dystonia was categorized into possible, probable, clinically established and documented functional dystonia according to the criteria proposed by Williams and coworkers [25]. Each case was then further discussed based on clinical phenotype, history and available findings.

Finally, the individual cases were assigned to one or more of following five categories: stimulation-related problems, evidence of neurodegenerative or acquired dystonia, or combined dystonia, evidence of functional comorbidity or disease, presence of significant fixed deformities, or additional other problems. Assignment to more than one category was possible.

3. Results

3.1. Patient characteristics

24 patients from 11 centres (Cologne n = 6, Hannover n = 5, Hannover/Mannheim n = 2, Berlin n = 2, Düsseldorf n = 2, Rostock n = 2, Hamm n = 1, Heidelberg n = 1, Innsbruck n = 1, Kiel/Würzburg n = 1, Wiesbaden n = 1) were enrolled in the study. Subsequently, two patients were excluded because they showed a therapeutic response of >30% BFMDRS improvement in the video ratings (BFMDRS-M preoperative/postoperative ON: patient 7: 10/2 points; patient 19: 9/4 points). Thus, 22 patients were included in the final cohort (8 men, 14 women; 9 generalized, 9 segmental, 3 focal, 1 bibrachial dystonia). Individual patient characteristics are given in Table 1.

3.2. Assessment of lead location and integrity of stimulation system

No problems with battery function were encountered in the current cohort. Individual and mean coordinates of all contacts active at follow-up are visualized in Fig. 1, individual coordinates are listed in Supplementary Table 1. Ten leads in nine patients were judged to be misplaced, nine leads in seven patients were placed suboptimally, five patients had bilateral lead location problems. One patient (patient 2) had a lead malfunction with very high therapeutic impedances (Kinetra generator, >4000 Ω) in one of the optimally placed contacts. Stimulation settings are summarized in Supplementary Table 2.

3.3. Clinical phenotyping, case reviews and expert panel assessment

A summary of relevant history, clinical and diagnostic findings and stimulation system information is given in Table 2. Details on additional clinical findings are also provided in Supplementary Table 3. Based on these data, patients were assigned to one or more categories for therapeutic failure (Table 2). The most frequent problems were poor lead location (n = 11, 50.0%, bilateral in n = 5, unilateral in n = 6), or disease other than isolated inherited or idiopathic dystonia (n = 11, 50.0%). Further problems were fixed deformities (n = 2, 9.1%), functional dystonia or comorbidity (n = 4, 18.2%; documented n = 1, clinically established n = 2, probable n = 1), and other causes (n = 3, 13.6%; non-representative preoperative or postoperative video (n = 2), in one case due to excessive benzodiazepine use, rating scale-associated problems (n = 1)). A combination of poor lead location and other problems was found in 9 cases (combination with other disease n = 6, 27.3%, functional dystonia n = 1, 4.6%, other problems n = 2, 9.1%).

If patients with poor lead location were excluded from further analysis (n = 11 remaining), non-isolated dystonia accounted for 45.5%, functional dystonia for 27.3%, fixed deformities for 18.2%, and other problems for 9.1% of cases. Likewise, excluding patients with non-isolated dystonia or functional dystonia (i.e. other diagnoses, n = 7 remaining), lead location problems occurred in 57.1%, other problems occurred in 42.9%, and fixed deformities occurred in 28.6% of cases. Patient 23 (DYT1-positive) who had bilateral electrode misplacement received a bilateral re-implantation to GPi, patient 1 received additional ventrolateral thalamic stimulation for her head and trunk tremor, both with good therapeutic outcome (patient 23: BFMDRS-M before repositioning 23 points, after repositioning 6 points; patient 1: BFMDRS-M before thalamic stimulation 6 points, after thalamic stimulation 3 points, Fahn-Tolosa-Marin tremor rating scale [26] (item head/neck tremor while seated or walking) before thalamic stimulation 3 points, after thalamic stimulation 1 point). The locations of active contacts for the repositioned GPi leads in patient 23 were x = −21.1, y = 2.9, and z = −1.9 on the left and x = 21.6, y = 2.8, and z = −2.9 on the right. Patient 11 declined re-surgery because of worries about the risks of a new intervention after wound healing problems after the first procedure. The final classification is visualized in Supplementary Fig. 1. Based on the findings, we suggest a clinical assessment algorithm for patients with GPi-DBS and insufficient therapeutic response which is given in Fig. 2.

4. Discussion

In this cohort of dystonia patients with GPi-DBS and insufficient therapeutic response, the most frequent reasons for lack of response were poor lead location (alone or in combination with other problems), or disease other than isolated inherited or idiopathic dystonia. Further reasons were fixed deformities, functional dystonia or comorbidity and mixed other causes. In patients with

Table 1
Patient characteristics.

Pat. no.	Age (y)	Gender	Age at onset (y)	Disease duration (y)	Type of dystonia	Genetics	Site of onset	Dur. of GPi-DBS at follow-up (m)	BFMDRS-M/TWSTRS-S[b]					Medication eliciting dystonia
									preop	ON	OFF	% change ON vs. preop	% change ON vs. OFF	
1	59	f	31	28	focal		neck (pain)	47	6[a]	5 (13)[b]	6 (13)[b]	16.7	16.7	
2	37	m	9	28	generalized	DYT 1 neg DYT 6 pos. (atypical, previously unknown: Ex03 c.388_389 del TC(het.))	loss of voice followed by writer's cramp	89	60	57	63	5.0	9.5	
3	66	f	47	19	segmental		neck (twisting)	29	11	9	10	18.2	10.0	metoclopramide
4	72	f	47	25	segmental		neck (twisting)	34	10	8	10	20.0	20.0	
5	32	f	23	9	generalized	DYT 11 neg.	cramping of right hand	61	39	34.5	44	11.5	21.6	
6[a]	59	m	37	22	segmental		neck (twisting)	80	18	14.5	15	19.4	3.3	
7	58	f	44	14	segmental		neck (twisting)	29	10	2	5.5	80.0	63.6	
8	29	f	9	20	generalized	DYT 1 neg.	legs (delayed walking)	127	73.5	80	87	−8.8	8.0	
9	66	f	59	7	segmental		blepharospasm	27	22	16	20.5	27.3	22.0	olanzapine (after onset)
10	55	m	47	8	segmental		neck (twisting, pain)	10	5	8	11	−60.0	27.3	
11	62	f	22	40	generalized		neck (twisting) and orofacial during pregnancy	9	34	38	44	−11.8	13.6	
12	51	m	11	40	bibrachial	DYT 1 pos. (class. Mutation)	right hand	33	24	20	24.5	16.7	18.4	
13	46	f	29	17	focal		neck (twisting)	17	6	6 (9)[b]	6 (11)[b]	0.0	0.0	amitriptyline
14	68	f	55	13	segmental		blepharospasm	22	8	7	8.5	12.5	17.6	fluspirilene
15	33	f	3	30	generalized	DYT 1 neg.	legs (gait problems)	131	106[a]	101	108.5	4.7	6.9	
16	42	m	9	33	generalized	DYT 1 pos.	right foot	39	62	62	72	0.0	13.9	
17	60	m	58	2	segmental		neck (retrocollis)	20	10	11.5	14	−15.0	17.9	
18	50	f	43	7	focal	DYT 1 neg.	neck (laterocollis)	14	4	7 (12)[b]	8 (12)[b]	−75.0	12.5	flupentixol, opipramol. doxepin, metoclopramide
19	65	f	40	25	segmental		neck and shoulder (twisting, pain)	23	9	4	5	55.6	20.0	
20	43	f	3	40	segmental		legs (gait problems), trunk hypotonia	27	33.5	27.5	32	17.9	14.1	
21	25	f	6	19	generalized	DYT 1 neg.	right leg dystonia	60	93	94	n.a.	−1.1	n.a.	
22	25	f	3	22	generalized	n.a. (brother DYT 1 and DYT 6 neg.)	torsion movement of right shoulder	60	84.5	66.5	n.a.	21.3	n.a.	
23	44	m	17	27	generalized	DYT 1 positive	restlessness of head	6	21	25	n.a.	−19.0	n.a.	
24	47	m	20	27	segmental	DYT 1 neg. DYT 6 pos.	neck (rotation deficit to the left)	60	15	12	n.a.	20.0	n.a.	
Mean[c] +/− StD	48.7 ± 14.1	14 f, 8 m	26.7 ± 19.0	22.0 ± 10.9	9 generalized, 9 segmental, 3 focal, 1 bibrachial	3 DYT 1 positive, 2 DYT 6 positive		45.5 ± 34.6	33.9 ± 31.6	32.3 ± 30.5	32.4 ± 31.1	0.9 ± 25.8	14.1 ± 7.0	5 with possible tardive origin

Excluded patients are shown in grey. StD: standard deviation, MD: movement disorders, m: months, y: years.
[a] Preoperative clinical score (preoperative video not available).
[b] TWSTRS Torticollis Severity Scale (TWSTRS-S) in parentheses in cases with focal cervical dystonia (out of 25 points: effect of sensory trick, range of motion and time were not rated).
[c] Without two excluded patients.

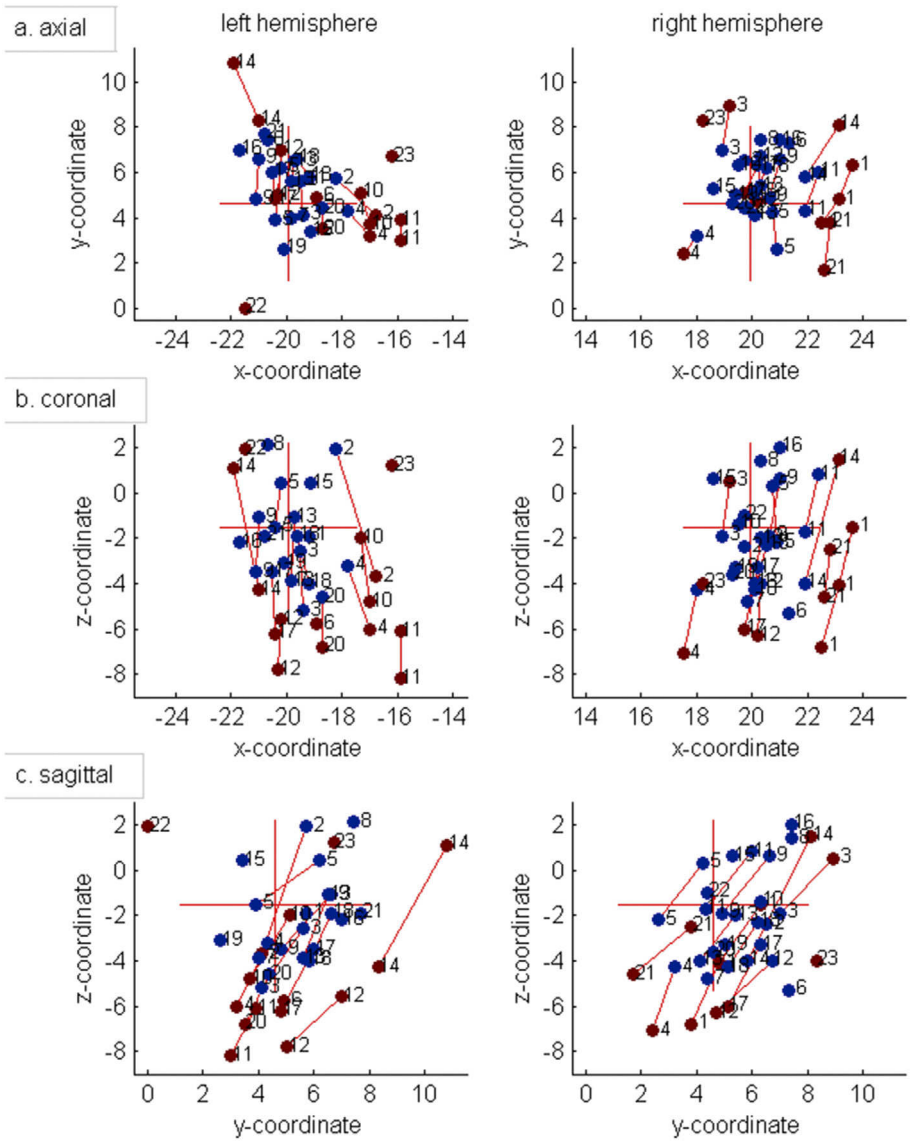

Fig. 1. Rendering of active DBS lead contacts.
Individual active contacts in axial (A), coronal (B) and sagittal (C) planes (see Table 2 for coordinates). Numbers refer to patients, red crosshairs indicate the optimal range based on Tisch et al. [23] and Starr et al. [22] Red dots indicate location outside this range. If more than one contact was active, they are connected.

adequate lead location, non-isolated dystonia accounted for the majority of GPI-DBS failures. In patients with isolated inherited or idiopathic dystonia, poor lead location was the most frequent cause of GPi-DBS failure.

Comparing our findings to previous studies, we found eleven patients (50%) with lead positioning problems, compared to 46% reported previously in patients with various movement disorders [19]. Lead repositioning in two previous small case series achieved mixed results [27,28]. Thus, the numbers are comparable and highlight the importance of postoperative evaluation of lead positioning, since adequate lead positioning is equally important for clinical outcome in both isolated and combined (e.g. neurodegenerative) dystonias.

Interestingly, about half of the cases in the current cohort, or even as many as 68% of cases when including the patients with functional dystonia, were deemed to have a diagnosis other than isolated dystonia, compared to only 12% in DBS failure in a cohort of various movement disorder patients by Okun et al. [19]. The previous study comprised 75% Parkinson's disease patients and one dystonia patient, whereas we investigated dystonia patients only. The diagnosis of isolated idiopathic dystonia often relies on clinical presentation and exclusion of other underlying disorders. Many conditions can cause dystonia, initially without additional neurological signs, and further symptoms may become apparent only later during the course of the disease. Thus, it can be difficult to establish definite isolated idiopathic dystonia, and a definite diagnosis can only be ascertained in subgroups of patients, e.g. via genetic testing.

In our cohort, there were two patients with dystonia accompanied by other symptoms (tics and essential tremor with head tremor). While their dystonia responded to GPi-DBS, the tics and tremor did not improve. These patients present a particular diagnostic and therapeutic challenge: tics can resemble dystonic movements, and tremor, particularly head tremor, can accompany isolated dystonia (and frequently responds well to GPi-DBS). Dystonia was present and improved in both our cases, but therapeutic

Table 2
Summary of findings and classification.

PAT NO.	EVIDENCE OF FUNCTIONAL DISEASE	OTHER HYPERKINETIC SYMPTOMS	EVIDENCE OF OTHER DISEASE			FIXED DEFORMITIES	PROBLEM WITH STIMULATION SYSTEM INTEGRITY			CAUSE OF FAILURE	COMMENTS
			Other neurological symptoms	Brain MRI findings	Other findings		Electrode position left	Electrode position right	Other system integrity problem		
1		tremor	lateralized bradykinesia, slowness turning, ataxia (broad based gait, gait deviation)	basal ganglia calcifications (confirmed on CT scan)				misplaced		electrode positioning, other disease	M. Fahr significant improvement of tremor after additional thalamic DBS (BFMDRS-M before/after: 6/3 points; Fahn-Tolosa-Marin Tremor Scale neck item: 3/1 points)
2			dominant bulbar symptoms, anarthria		highly path. dopamine transporter imaging, not previously described mutation in exon 3 of DYT6 gene		suboptimal		contact damaged (contact 2)	electrode malfunction, other disease	poss. neurodegen.
3				FLAIR hyperintensities		neck (limited passive mobility, inccomplete resolution under general anaesthesia)		suboptimal		fixed deformities	
4							suboptimal	suboptimal		electrode positioning, other cause**	other cause: rating scale not sensitive to tremor
5		myoclonus, excessive startle	gait clumsy, not much rolling of feet, bilaterally positive palmomental reflex		serum and CSF glutamic acid decarboxylase (GAD)-antibodies, motor polyneuropathy of legs, polyglandular syndrome					other disease	combined, possibly acquired dystonia
6*		postural hand tremor (l>r), head tremor, mild bilateral intention tremor					misplaced			other disease	dystonia plus essential tremor (tremor remaining)
8		tremor, myoclonus	bradykinesia, hypotonia of trunk, cognitive impairment/retardation, delayed motor milestones, childhood epilepsy	marked brain atrophy with maximum frontally, otherwise normal, no basal ganglia pathology						other disease	neurodegen. disease
9	functional gait disorder, some entrainment, excessive slowness, better when unobserved, almost complete relief 2 mins after L-Dopa administration			slight brain atrophy, otherwise normal	3 x 2/1000 acanthocytes in blood smear					functional dystonia	documented functional
10		minimal intention tremor of right hand					misplaced			electrode positioning, other cause**	other cause: baseline video not representative of baseline due to uncontrolled benzodiazpine consumption
11							misplaced			electrode positioning	
12			urinary retention requiring permanent catheter, arms atactic, intention tremor of hands, paresis	multiple T2 hyperintense white matter lesions bilaterally	CSF oligoclonal bands type II, mild dopaminergic deficit on dopamine transporter imaging		misplaced	suboptimal		electrode positioning, other disease	additional multiple sclerosis or other cervical myelon pathology
13	dystonia inconsistent over time. incongruent with classical dystonia (age of onset, shoulder drop on side of dystonia)									functional dystonia	probable functional
14	dystonia inconsistent over time (no blepharospasm while driving, recurrence immediately afterwards), less when concentrating or when moving/attending to other body part, development of tics after						misplaced	suboptimal		electrode positioning, functional dystonia	clinically established functional

	acquaintance with Tourette patient										
15		high frequency myoclonus	severe bradykinesia, severe bulbar symptoms, neck and trunk hypotonia, unusual facial physique	T2 hyperintense putaminal lesions bilaterally	path. dopamine transporter imaging, decreased perfusion of basal ganglia on perfusion scintigram				other disease	neurodegen. disease
16						extensive (hips, knees, feet and ankles, spinal)			fixed deformities	Legs and trunk: BFMDRS ON 48 points, BFMDRS OFF 48 points Rest of body: BFMDRS ON 14 points, BFMDRS OFF 24 points
17		tics*			mild bilateral putaminal dopaminergic deficit on dopamine transporter imaging		suboptimal	suboptimal	electrode positioning, other disease	combined dystonia: dystonia and tics (tics remaining)
18	excessive slowness when attending to movement, functional gait disorder, functional paresis, shoulder drop on side of torticollis, complete relief with distraction				mild bilateral putaminal dopaminergic deficit on dopamine transporter imaging				functional dystonia	clinically established functional
20		tremor	broad based atactic gait		increased alpha fetoprotein, ATM gene mut. (c.8147T>C, p.V2716A het., c8578_8580delTCT, p.S2860del. het.)		suboptimal		other disease	atypical Louis Bar syndrome
21			severe bulbar involvement, broad based unsteady gait					misplaced	electrode positioning, other disease	neurodegen. or acquired
22			truncal hypotonia, pathological laughter				misplaced		electrode positioning, other disease	neurodegen. or acquired
23							misplaced	misplaced	electrode positioning	significant improvement after electrode repositioning (BFMDRS-M before/after: 23/6 points)
24									other cause**	other cause: postoperativelvideo does not reflect postoperative patient status (patient is clinically better upon re-examination)

*tics in childhood.

**note that “other causes” includes patients which are formally nonresponders (according to scales or video), but are clinically improved upon re-examination.

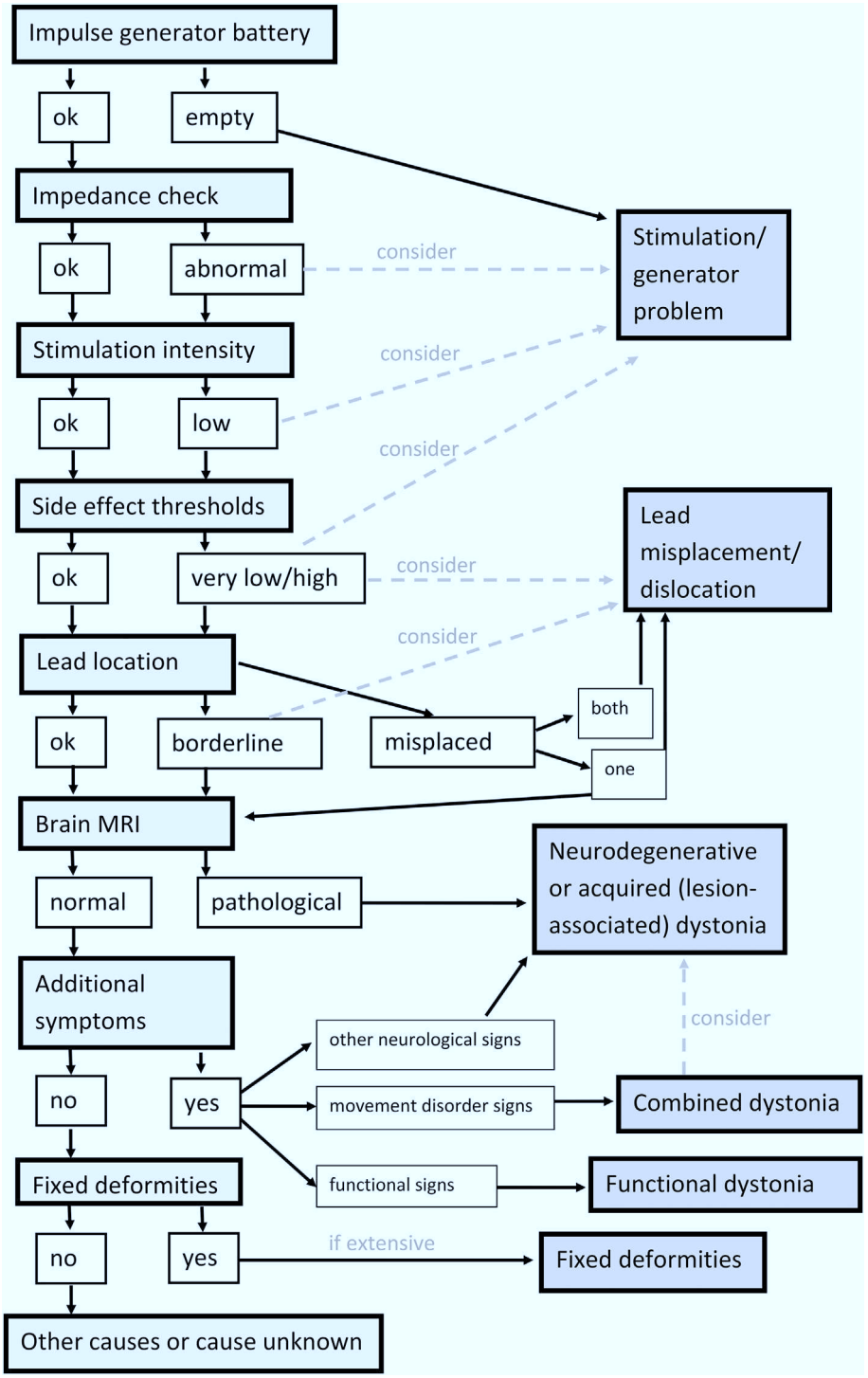

Fig. 2. Assessment algorithm for patients with dystonia and insufficient GPi-DBS outcome.
Flowchart illustrating the suggested therapeutic algorithm for assessing patients with insufficient response to GPi-DBS.

outcome was unsatisfactory due to remaining other symptoms. Thus, preoperative recognition of possible pseudodystonias is important, but therapeutic decision making and patient counselling are difficult nevertheless.

Of note also is the percentage of functional disease (18.2% of the total cohort, 27.3% if excluding cases with poor lead location), which was not encountered in the study by Okun et al. [19]. Formally, functional dystonia can be classified as 'other disease'. However, like idiopathic dystonia, functional dystonia is a purely clinical diagnosis and can be difficult to diagnose because of the fluctuating nature of dystonia. Thus, particular attention should be paid to functional signs or inconsistencies in dystonic symptoms in the assessment of dystonia patients for GPi-DBS.

Stimulation programming was very heterogeneous in the current cohort. While some open label studies have compared different parameters [7], prospective randomized controlled

studies demonstrating clear advantages of some settings over others are lacking and there is little consensus regarding optimal stimulation settings. Larger GPi stimulation volumes were shown to be associated with better outcomes [15], and additional GPi leads improved outcome in secondary loss of therapeutic effect [29].

There are some limitations to the study. Firstly, the study was of a retrospective and cross-sectional nature. With a frequency of therapeutic failure of approximately 15% [1,2], about 150 patients would be necessary for a similarly sized nonresponder cohort in a prospective study design, which would be very difficult and costly. However, the four non-responders we included (pats. 21–24) from the randomized prospective controlled German trial [2] were representative of the remaining cohort. Is a control group necessary to demonstrate that combined dystonia is associated with reduced GPi-DBS motor outcome? An ample body of literature shows that GPi-DBS motor outcomes in dystonia aetiologies associated with combined dystonias [8–10,17] are poorer than those for isolated dystonias, such as DYT 1 dystonia or idiopathic dystonia [1,2]. While the non-responder rates in isolated dystonias are typically at 15–20%, the non-responder rates in the combined dystonias are frequently much higher, up to above 50% [8], and outcomes are significantly poorer [17]. Thus, patients with combined dystonia are more likely to be non-responders than patients with isolated dystonia.

Secondly, there was considerable heterogeneity in terms of the severity of disease, as well as the heterogeneity arising from retrospective data analysis. To minimize heterogeneity in the assessment of lead location and brain MRI findings, these were both assessed by an independent expert. Furthermore, a panel of dystonia experts assessed the clinical phenotype based on pre- and postoperative videos as well as a videotaped neurological exam, patients' history and other available diagnostic data. Thus, heterogeneity arising from different clinicians initially assessing patients locally was minimized as far as possible.

Furthermore, follow-up time was below 12 months in three of the patients at the time of assessment (6, 9 and 10 months, respectively; mean follow-up time 45.5 months). This time may be too short to evaluate the full benefit of GPi-DBS on dystonia since patients can improve further from 3 to 12 months postoperatively [1]. Still, the majority of patients improve most within the first 3–6 months postoperatively and this follow-up time has been used in previous studies of GPi-DBS in dystonia [2]. All of the patients with follow-up below 12 months had phasic dystonia, which frequently responds quickly to GPi-DBS. One of the patients (patient 23) who received a repositioning of his electrodes significantly benefited from this repositioning within 3 months. Thus, longer follow-up time is unlikely to fundamentally change the outcome of this study.

Finally, lead placement, which is critical for successful DBS therapy, was assessed by comparing individual lead locations to a coordinate range derived from previous studies investigating DBS lead positioning in GPi-DBS [22–24], taking into account individual anatomy. Interestingly, the coordinate ranges reported in these studies [22–24] are wide and differ between studies, emphasizing the variability in individual GPi anatomy and its role in assessment of DBS lead position. Furthermore, large stimulation volumes can probably compensate for minor deviations from optimal target and may explain the large range found in previous studies.

Based on our findings, we propose an assessment algorithm summarized in Fig. 1. A dystonia patient with insufficient response to GPi-DBS should first receive a check-up of the stimulation system (stimulation settings, battery, therapeutic impedances). Next, lead misplacement should be excluded. After problems with system integrity, lead placement and programming issues have been excluded, the clinical phenotype should be reviewed for signs of neurodegenerative or acquired dystonia. Hyperkinetic symptoms need to be carefully assessed to exclude pseudodystonias (e.g. tics). Functional dystonia should be considered also. Extensive fixed musculoskeletal deformities limit functional outcomes.

As for preoperative clinical practice and patient counselling, the study underlines the relevance of careful clinical phenotyping, with particular attention to presence of additional neurological and functional symptoms, fixed deformities and pseudodystonias. Moreover, knowledge of underlying mutations can be of help: For example, outcome appears more variable in DYT6 patients with sometimes delayed responses [18]. Furthermore, even though they are formally “nonresponders”, some of the patients with combined inherited or acquired dystonia benefit subjectively and objectively without improvement on clinical motor scales [30,31], highlighting the limitations of these scales and the importance of patient-centered assessments such as quality of life. However, counselling about variable and more limited improvements is important to manage patient expectations appropriately.

In summary, dystonia patients with insufficient response to GPi-DBS should receive a thorough checkup of stimulation system integrity, lead placement and DBS programming. Neurological signs other than dystonia or pathological brain MRI point towards disease other than isolated (idiopathic or genetic) dystonia. During preoperative DBS assessment of dystonia patients, particular attention should be paid to additional neurological and functional signs and symptoms, and a definitive diagnosis should be sought as often as possible.

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Appendix A. Supplementary data

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