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ORIGINAL ARTICLE

Long-term effects of pallidal and thalamic deep brain stimulation in myoclonus dystonia

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Abstract

Objective: Observational study to evaluate long-term effects of deep brain stimulation (DBS) of the globus pallidus internus (GPi) and the ventral intermediate thalamic nucleus (VIM) on patients with medically refractory myoclonus dystonia (MD).

Background: More recently, pallidal as well as thalamic DBS have been applied successfully in MD but long-term data are sparse.

Methods: We retrospectively analyzed a cohort of seven MD patients with either separate (n = 1, VIM) or combined GPi- DBS and VIM-DBS (n = 6). Myoclonus, dystonia and disability were rated at baseline (BL), short-term (ST-FU) and long-term follow-up (LT-FU) using the United Myoclonus Rating Scale, Burke–Fahn–Marsden Dystonia Rating Scale (BFMDRS) and Tsui rating scale, respectively. Quality of life (QoL) and mood were evaluated using the SF-36 and Beck Depression Inventory questionnaires, respectively.

Results: Patients reached a significant reduction of myoclonus at ST-FU (62% ± 7.3%; mean ± SE) and LT-FU (68% ± 3.4%). While overall motor BFMDRS changes were not significant at LT-FU, patients with GPi-DBS alone responded better and predominant cervical dystonia ameliorated significantly up to 54% ± 9.7% at long-term. Mean disability scores significantly improved by 44% ± 11.4% at ST-FU and 58% ± 14.8% at LT-FU. Mood and QoL remained unchanged between 5 and up to 20 years postoperatively. No serious long-lasting stimulation-related adverse events were observed.

Conclusions: We present a cohort of MD patients with very long follow-up of pallidal and/or thalamic DBS that supports the GPi as the favourable stimulation target in MD with safe and sustaining effects on motor symptoms (myoclonus>dystonia) and disability.

KEYWORDS
dystonia, myoclonus, pallidal DBS, thalamic DBS, long-term effects, DBS and quality of life

INTRODUCTION

Myoclonus dystonia (MD) is a rare inheritable movement disorder with clinical presentation of both myoclonic jerks and dystonic features of mainly the upper body.[1] Alcohol ingestion may ameliorate myoclonus and to a lesser degree also dystonia.[2,3] Co-existing psychiatric symptoms such as anxiety, obsessive–compulsive disorder (OCD) or depression can often be found in MD patients.[4] Inherited in an autosomal-dominant manner, MD is commonly but not exclusively caused by mutations in the epsilon-sarcoglycan gene (SGCE).[5] First symptoms occur in early childhood or adolescence.[3] Although the course of the disease is benign in most cases, myoclonus in particular

can be disabling with reduced quality of life (QoL).[6] The clinically heterogeneous phenotype as well as the reduced awareness of the disease often delays final diagnosis and leads to unnecessary investigations or inappropriate therapies.[7] Pharmacological treatment effects remain limited and are often associated with unacceptable side effects.[7] Deep brain stimulation (DBS) of the globus pallidus internus (GPi) is an effective treatment for medically refractory dystonia and reduces not only motor impairment but also disability.[7-9] DBS has progressively evolved into a widely available therapeutic strategy in generalized and segmental dystonia within the last two decades. More recently, pallidal as well as thalamic DBS has also been applied successfully in patients with MD.[10-16] Study results, so far, reported improvements in myoclonus and dystonia of between 60% and 90%.

The aim of this study was to report on the long-term motor and non-motor effects of GPi-DBS and/or ventral intermediate thalamic nucleus (VIM)-DBS in a cohort of MD patients at our centre after an observation period of up to 20 years.

METHODS

Patients

For the present study, seven MD patients (five women) with thalamic and/or pallidal deep brain stimulation operated on between 1997 and 2009 were available for long-term follow-up. Patients 1–6 had a SGCE mutation, while patient 7 was SGCE-negative but presented with typical MD phenotype. Patients had a mean disease duration of 44.4 ± 5.7 (range 23–63) years and a mean age of 50.9 ± 4.6 (range 37–69) years at surgery (for more details, see Table 1). Six patients were operated at the Charité, University Medicine Berlin, Germany. Patient 7 was implanted at the University Hospital Tübingen, Germany. Six patients (patients 2–7) received quadripolar stimulation (bilateral GPi- and VIM-electrodes). Patient 1 received bilateral VIM-electrodes only. Detailed diagnostic and exclusion criteria as well as the surgical procedure with short-term follow-up (ST-FU) have been reported previously.[13] Examination at long-term follow-up (LT-FU) presented here (mean 12 ± 1.7 years, range 7–20 years) included assessment of motor impairment, mood, QoL, stimulation parameters, side effects of stimulation as well as documentation of demographics, clinical history and medication intake. These data were compared with retrospective data from preoperative baseline (BL) and ST-FU (mean 10 ± 2.1 months, range 6–14 months)[13] including video documentation of each visit (for details see Table S1 and Table S2). LT-FU was performed using the same protocol as for BL-FU and ST-FU except for a systematic OFF-testing. The study was approved by the local ethics committee. All patients gave their written informed consent.

Assessment of motor function

Dystonia severity and disability were assessed using the Burke–Fahn–Marsden Dystonia Rating Scale (BFMDRS) and the Tsui rating scale in all patients.[17,18] Presence and intensity of myoclonus was rated by use of the Unified Myoclonus Rating Scale (UMRS).[19] The overall patient-related motor benefit was rated via the numeric rating score (NRS) from 0–100% (0 indicating no improvement, 100 indicating normal functioning).

Assessment of affective state and QoL

The individual effects of stimulation on health-related QoL and depressive symptoms were assessed using the SF-36[20] and the Beck Depression Inventory (BDI)[21] and compared with archival BL and the available ~5-year FU data in all but one patient.

Assessment of long-term safety

All reported device-related side effects and adverse events (AEs) as well as side effects of the stimulation were collected retrospectively from clinical neurological and neurosurgical records, and patients were additionally asked about chronic side effects or AEs at LT-FU. The exchange of the pulse generator due to battery depletion was not considered an AE within a typical lifespan of more than 2 years.

Statistical analysis

Statistical analysis of motor function, QoL data and comparison with baseline and ST-FU was done with Friedman Test and post hoc Wilcoxon test. A Spearman's correlation was done in order to investigate possible correlations between motor outcome and demographic factors such as age at onset, age at surgery, disease severity as well as changes in QoL and mood (SF-36 and BDI). All data are given as mean ± SE if not mentioned otherwise. A p value <0.05 was considered to be significant.

RESULTS

At LT-FU, patients 2 and 7 had activated bilateral VIM and GPi stimulation, patients 3–6 presented with pallidal stimulation and patient 1 had continued VIM-DBS (Table S2). All scores were obtained with stimulation at those targets.

Motor improvement

Improvement in myoclonus as assessed by UMRS total score reached 62.3% ± 7.3% (p = 0.004) at ST-FU and was similar at LT-FU with 68.0% ± 3.4% (p = 0.001). Figure 1 shows the mean UMRS total score at BL, ST-FU and LT-FU. All patients presented with mild dystonic features before surgery that were predominantly affecting the head/neck and upper extremities. DBS response on dystonic symptoms

TABLE 1 Individual demographic patient data

Patient	Sex	SGCE	Age at onset (years)	Age at surgery (years)	Disease duration before surgery (years)	Last follow-up (years)	DBS state at short-term follow-up	DBS state at last follow-up	Previous medical treatment trials	Medication at last follow-up	Device- and stimulation-related AEs until last follow-up
1	M	Positive (R102X)	6	60	54	20	VIM-ON	VIM-ON	Botulinum toxin Baclofen intrathecal Primidone Piracetam ß-Blocker	Diazepam	
2	F	Positive (EX5DEL)	14	37	23	13	VIM-ON and GPi-ON	VIM-ON and GPi-ON	Valproate ß-Blocker Clozapine	None	
3	F	Positive (n.a.)	1	60	59	11	GPi-ON	GPi-ON	Clonazepam Tiapride ß-Blocker	None	
4	F	Positive (C72 T)	6	69	63	7	VIM-ON and GPi-ON	GPi-ON	ß-Blocker	None	
5	M	Positive (R102X)	3	46	43	7	VIM-ON and GPi-ON	GPi-ON	Valproate Clonazepam Tetrazepam	None	
6	F	Positive (n.a.)	12	42	30	16	VIM-ON and GPi-ON	GPi-ON	Haloperidol Antiepileptic drugs Fluspirilene Diazepam Tetrabenazine ß-Blocker	Botulinum toxin	Wire lead revision due to scarring
7	F	Negative	3	42	39	11	VIM-ON and GPi-ON	VIM-ON and GPi-ON	Tiapride Biperiden Clonazepam Haloperidol ß-Blocker Valproate Levodopa Amantadine	Trihexyphenidyl (i.r.)	Dysarthria, gait disturbances
Mean (±SE)			6.4 ± 1.8	50.9 ± 4.6	44.4 ± 5.7	12 ± 1.8					

None of the patients had any structural brain abnormalities on individual magnetic resonance imaging. Note the complete withdrawal of medication after deep brain stimulation in four of the seven patients.

AE, adverse event; DBS, deep brain stimulation; F, female; GPi, globus pallidus internus; i.r., if required; M, male; n.a., not available; SE, standard error; SGCE, epsilon-sarcoglycan gene; VIM, ventral intermediate thalamicnucleus.

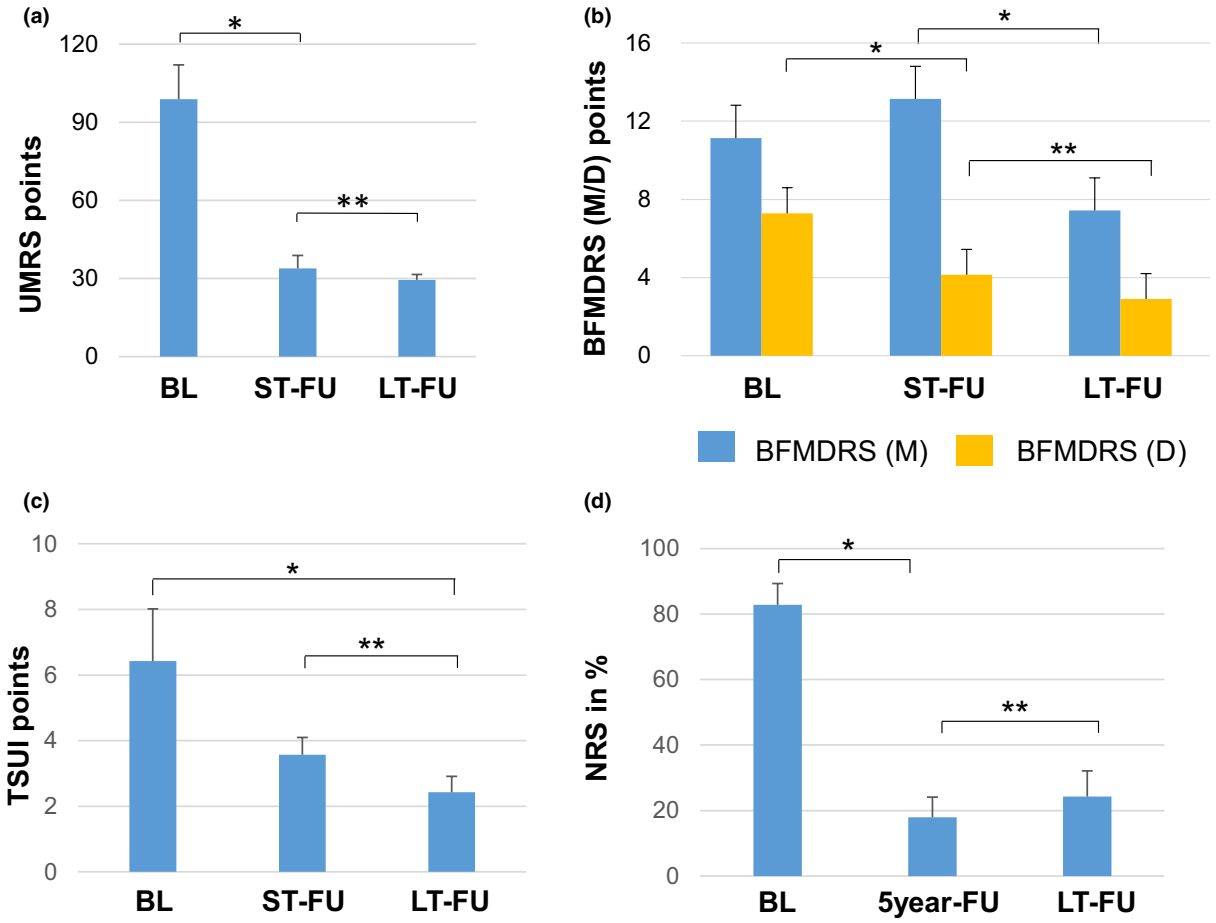

FIGURE 1 (a) Mean absolute myoclonus reduction in the Unified Myoclonus Rating Scale (UMRS) at baseline (BL), short-term follow-up (ST-FU) and last long-term follow-up (LT-FU). *p = 0.00415, **p = 0.00133. (b) Mean absolute Burke–Fahn–Marsden Rating Scale motor/disability (BFMDRS M/D) subscore at BL, ST-FU and last LT-FU. Motor score: *p = 0.01261. Disability score: *p = 0.0136, **p = 0.0092. (c) Mean absolute Tsui rating scal score (TSUI) at BL, ST-FU and LT-FU. *p = 0.02, **p = 0.03. (d) Mean absolute Numeric Rating Score (NRS) at BL, after ~5 years of stimulation and at LT-FU. *p = 0.0021, **p = 0.00067. Patients: n=7. [Colour figure can be viewed at wileyonlinelibrary.com]

was more variable across patients. Patient 6 developed new dystonic features, especially in the lower limb during VIM stimulation at ST-FU that was partially reversible at LT-FU with pallidal DBS when VIM stimulation was switched off. Improvement in dystonia was not significant at ST-FU with a mean reduction in motor BFMDRS of −1.2% ± 22.1% and reached 36.3% ± 10.2% at LT-FU. While cervical dystonic symptoms and dystonic tremor as evaluated by the Tsui rating scale showed a clinically meaningful but not statistically significant benefit of 27% (2.8 ± 0.5 points symptom reduction, p = 0.07) at ST-FU, DBS effects at LT-FU had improved significantly to 54% (4.0 ± 0.5 points symptom reduction, p = 0.02) compared to BL. Mean disability scores of the BFMDRS improved significantly by 44% ± 11.4% at ST-FU and 58% ± 14.8% at LT-FU (p = 0.043 and 0.027, respectively). Subjective postsurgical motor improvement compared to presurgical impairments rated by NRS showed a stable benefit of 76% ± 7.8% at LT-FU compared to 82.1% ± 6.2% (p = 0.0007 and 0.002, respectively) ~5 years after surgery.

As the patients were stimulated at different targets with uniform or combined VIM- and/or GPi-DBS during the course of their disease, we also briefly present the LT-FU with respect to the different type of stimulation target: in the patient with VIM-DBS (case 1), the main improvement was reached for myoclonus (72%, for more details see Table 2). In the patients with pallidal and thalamic DBS (cases 2 and 7), myoclonus was reduced by 61.8% ± 3.3% and motor BFMDRS showed a 17.9% ± 20.8% improvement at LT-FU. Finally, patients with sole pallidal DBS (cases 3–6) showed the most consistent changes with a 70.1% ± 5.3% reduction in myoclonus, 40.5% ± 15.1% improvement in motor BFMDRS and 85.7% ± 10.1% reduction in disability. Subjective postsurgical motor improvement reached 85% ± 9.5% after pallidal DBS at LT-FU.

Improvement in mood and QoL symptoms

Preoperative and postoperative BDI scores and QoL ratings (SF-36) were available from six of the seven patients. Mood did not change significantly with DBS (see Table S1). Overall SF-36 ratings reached 55 ± 4.6 points (range 0–100) at LT-FU in comparison to 45 ± 4.7 (range 0–100) points at BL. However, these overall differences as well as changes in the individual subitems of the SF-36 were

TABLE 2 Presurgical and postsurgical individual motor scores and subjective improvement post deep brain stimulation

Patient	UMRS (points)					BFMDRS (M/D)					TSUI (points)					SI %	SI %
	BL	FU 1	FU 2	FU 3	FU 4	BL	FU 1	FU 2	FU 3	FU 4	BL	FU 1	FU 2	FU 3	FU 4	~5 yrs	~12 yrs
1	137	39	30	26	38	8/11	7/4	7/4	8/5	4/8	9	6	6	4	3	95	70
2	63	19	23	19	22	6/3	6/3	6/3	6/3	3.5/2	4	3	2	2	2	80	50
3	106	42	33	43	29	12/6	9/3	10/2	5/1	7/0	13	5	5	6	5	80	100
4	87	29	32	-	25	11/7	4/2	2/2	-	2/1	10	3	3	-	2	80	100
5	81	57	63	48	36	11/7	13/6	13/6	11/5	8/0	4	3	3	3	2	50	80
6	153	34	30	30	29	22/14	18/6	47/11	44/7	19.5/6	2	2	3	2	2	100	80
7	65	26	26	26	27	8/3	7/1	7/1	7/1	8/3	3	3	3	3	1	90	50
Mean total ±SD	98.9 ± 32.4	35.1 ± 1.5	33.9 ± 12.3	32.0 ± 10.2	29.4 ± 5.3	11.1 ± 4.9/ 7.3 ± 3.7	9.1 ± 4.8/ 3.6 ± 1.9	13.1 ± 15.3/ 4.1 ± 3.4	13.5 ± 15.1/ 3.7 ± 2.4	7.4 ± 5.8/ 2.9 ± 3.1	6.4 ± 3.9	3.6 ± 1.3	3.6 ± 1.3	3.3 ± 1.4	2.4 ± 1.2	82.1 ± 15.1	75.7 ± 19.2

BFMDRS (M/D), Burke–Fahn–Marsden Rating Scale (motor/disability subscore); BL, baseline; FU 1, follow-up at 6 months; FU 2, follow-up at 12 months; FU 3, follow-up after mean 5 years; FU 4, follow-up after mean 12 years (adapted from Gruber et al., 2010)[13]; SD, standard deviation; SI, subjective improvement; TSUI, Tsui rating scale score; UMRS, Unified Myoclonus Rating Scale.

statistically not significant except for the subitem ´general health´ that presented a significant reduction after ~5 years and at LT-FU compared to BL (p = 0.01 and 0.04, respectively) (for detailed scores see Table S1). Relative changes in BDI or SF-36 did neither correlate with motor improvements nor with myoclonus reduction, NRS and disability at LT-FU.

Safety

The main reason for surgical intervention after successful implantation was the replacement of the pulse generator (IPG) after battery exemption with on average 3.1 ± 0.6 IPG replacements (range 1–5) per patient over a period of 144 (range 83–234) months. The mean replacement interval (IPG lifespan) was 45.6 ± 5 (range: 24–84) months. Four of seven patients had switched to rechargeable stimulator devices at LT-FU. Since initial implantation, seven AEs were device-related and classified as serious AEs (SAEs) requiring hospital admission and surgical intervention. Due to insufficient benefit, patients 5 and 6 underwent explantation of the VIM-system and VIM-IPG, respectively. Stimulation-related side effects at LT-FU included dysarthria and dysphagia (n = 1) as well as gait disturbances (n = 1) (see Table 1).

DISCUSSION

Here, we present the longest retrospective follow-up study of a patient cohort with MD with bilateral pallidal and/or thalamic neurostimulation. This study describes sustained improvements of myoclonus in the UMRS and cervical dystonia in the Tsui after up to 20 years of DBS. Emphasizing the impact of DBS on MD patients on the functional level, motor improvements were accompanied by a significant reduction of disability in the BFMDRS at all follow-up visits and a significant overall patient-related motor benefit was reflected in the NRS (see Table 2). Overall, mean improvement of DBS motor effects was higher for myoclonus than for dystonia. Myoclonus usually manifests early in the course of the disease and often remains a highly disabling and stigmatizing symptom that is difficult to treat.[1,22] In our cohort, myoclonus responded well to VIM- as well as GPi-DBS with consistent effects at ST-FU and LT-FU of more than 50% reduction. Given the lower dystonia BL scores in comparison to myoclonus, the impact of DBS on dystonic symptoms, however, was more variable. The motor part of the BFMDRS revealed no significant change in dystonia at ST-FU and a mean but non-significant improvement of 35% at LT-FU in our cohort. However, it has to be kept in mind that baseline dystonia scores have been obtained under chronic use of combined oral medication as well as botulinum toxin injections or intrathecal baclofen. Medication could either be reduced and/or stopped after DBS (see Table 1), which can be considered a further functional benefit also with respect to the reduction of side effects due to chronic medication. Furthermore, several other

factors need to be considered: target selection for dystonia (VIM vs. GPi), body distribution of dystonia in MD patients, and potential AEs of thalamic DBS that may trigger or worsen dystonia in predisposed patients. After numerous trials have shown favorable short- and long-term motor as well as QoL improvements in dystonia, pallidal DBS is the preferred target.[8,23,24] Several studies report on similar outcomes after bilateral subthalamic stimulation (STN-DBS) in dystonia with sustained QoL improvements after 10 and more years, especially in patients with prominent cervical symptoms.[25,26] While VIM-DBS is an effective treatment option for tremor in Parkinson's disease and essential tremor, thalamic stimulation in dystonia is reasonable if the tremor is considerably more disabling than the dystonic features.[27,28]

Dystonia in MD mainly affects the neck and the upper extremities,[1] and recent studies in dystonia patients have shown that body distribution of dystonic symptoms is a crucial factor for DBS outcome with cervical symptoms responding less in ST-FU and LT-FU.[23,29] Changes in cervical dystonia may also be less well reflected using the BFMDRS. We have to note that in our patients, ratings for cervical dystonia according to Tsui showed a significant improvement of 54% at LT-FU. Importantly, one of our patients developed new dystonic features several months after initiation of VIM-DBS, while symptoms had been stable for many years before surgery. In this patient dystonia improved after cessation of thalamic stimulation and initiation of pallidal DBS.[13] Interestingly, Wang et al. observed a similar case of deterioration of dystonia after thalamic DBS with resolution after pallidal stimulation.[30] While they speculate on potential influences of different genetic backgrounds of the patients, possible plastic changes due to thalamic stimulation might play a role in a potentially vulnerable population as well. Overall, our results are in line with the meta-analysis by Rughani and Lozano[31] showing greater improvements in myoclonus scores compared to dystonic scores after DBS in MD. They reviewed 40 patients with MD and DBS out of 17 reports that all together reported on a statistically significant greater improvement in myoclonus compared to dystonia after surgery (including our dataset after ~5 years of stimulation). Additionally, this study found that myoclonus was similarly responsive to pallidal or thalamic stimulation while treatment of dystonic symptoms was significantly more successful after GPi-DBS compared to VIM-DBS.[31] Keeping in mind the small number of patients, the largest reduction of dystonia at LT-FU in our cohort was reached in those patients receiving GPi stimulation alone, while myoclonus has been reduced with VIM- and GPi-DBS. Interestingly, four of the initial five patients with VIM- and GPi-DBS presented with only pallidal stimulation at LT-FU because of dysarthria and/or gait difficulties related to thalamic stimulation. Patient 5 desired explantation of the VIM electrodes after selective testing of each target and clear superiority of pallidal stimulation on MD symptoms. Exclusive pallidal stimulation was not associated with loss of overall benefit and, even more importantly, stimulation-associated side effects were reported to a lesser extent compared to ST-FU and quadripolar stimulation (see Table 1), further supporting pallidal DBS as the preferred target for MD. In adulthood, severity of motor manifestations is referred to as relatively static.[32] In line with this, cessation of DBS in our cohort at 5-year follow-up showed a reoccurrence of motor symptoms to the level similar to presurgical scores with gradual deterioration of myoclonus and dystonia within hours and days (16–168 hours).[13] Systematic OFF-testing was not part of the LT-FU. Stimulation parameters were stable over time in our patients without relevant elevation of stimulation amplitude, as a possible indirect sign for development of tolerance. This is in line with the recently published data of nine patients with proven SGCE mutation by Kosutzka et al.[33] The group showed a 94% reduction of myoclonus and an accompanying 71% improvement of dystonic symptoms after ~9 years of pallidal DBS.[33] The overall results of this group are better than the improvements in our cohort. Next to the negative putative impact of VIM-associated side effects in our three patients with additional thalamic stimulation, this might be influenced by the different age of the patients at LT-FU with an average age of 41 years in the Kosutzka group versus 62 years in our cohort. Furthermore, Rhughani et al. reported on a strong trend towards better stimulation results in patients with a younger age at surgery and shorter disease duration.[31] In our cohort, patients were aged about 51 years at surgery and had a disease duration of about 44 years while the patients in the Kosutzka study were about 20 years younger. No statistically significant correlation between age at onset, age at surgery, disease duration and motor outcome was found in our cohort, most likely due to the limited variability with a relative old age in all patients. Although patient numbers are limited in both studies since MD is a rare disease, our results further underline the importance of early diagnosis and treatment for severely affected MD patients.

Only a few studies to date have also assessed non-motor effects of DBS in MD.[13,33-35] Contarino et al. reported on a cohort of five patients with pallidal stimulation and worsening of psychiatric symptoms in most patients after surgery.[34] Although, a comparison of health related QoL and emotional well-being with preoperative scores was not possible, Kosutzka et al. found transient depression in the postoperative period, but noted a relatively low prevalence of neuropsychiatric problems highlighting good social adjustment and QoL at LT-FU.[33] In our cohort, scores for Mood and QoL were not improved with DBS compared to BL but equally important did not deteriorate over time (see Table 1). Relative changes in BDI or SF-36 did neither correlate with motor improvements, myoclonus reduction, NRS or disability at LT-FU. Gruber et al. found isolated statistical improvements in the SF-36 subitems ´general perception of health´ and ´change of health´.[14] In our cohort, only the subitem ´general health´ of the SF-36 had significantly improved at LT-FU. With regard to this, it is necessary to keep in mind that patients in the present cohort had a mean age of 63 (range 53–80) years and several comorbidities at the time of follow-up. Patient 1 had experienced multiple strokes with consequent hemiparesis and incontinence, patient 7 experienced gait abnormalities and pain due to lumbar spinal stenosis, and patient 5 was diagnosed with chronic depression already before DBS. Given these confounders, several other subratings, however, indicate relevant and persisting

improvements in everyday life in our cohort at LT-FU. Subjective rating of impairment due to MD symptoms resulted in a 76% benefit at LT-FU with only a slight deterioration compared to ST-FU (82%). The ´functional test´ of the UMRS revealed a significant 60% reduction of impairment (p = 0.0009) and the disability score in BFMDRS had improved up to 58% at LT-FU. Furthermore, reduction of motor impairments was accompanied by a relevant and continuing reduction in symptomatic medication at LT-FU (see Table 1). As the association of MD and psychiatric comorbidities may presumably exert a relevant impact on scores like the BDI and SF-36, further studies additionally focusing on more specific preoperative and postoperative psychiatric rating scales covering, for example, anxiety, OCD and depression, will be needed.

Limitations of this study include the small sample size in the context of a rare disease, the non-blinded evaluation of stimulation benefits, and a probable interrater variability due to the retrospective character of the ST-FU data analysis. Nevertheless, the present results do not only extend predominantly anecdotal evidence of beneficial long-term effects of DBS in patients with MD but also provide extensive assessment of motor features (myoclonus, dystonia), disability, QoL and mood in a very long follow-up on an older MD population. Furthermore, this study provides data on combined thalamic and pallidal stimulation in MD and supports the GPi as the best DBS target on a long follow-up in a real-world setting.

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WOA Institution: Charite Universitatsmedizin Berlin

Blended DEAL : ProjektDEAL

CONFLICT OF INTEREST

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AUTHOR CONTRIBUTION

Patricia Krause: Conceptualization (lead); Data curation (lead); Formal analysis (lead); Funding acquisition (lead); Investigation (lead); Methodology (lead); Project administration (lead); Resources (equal); Software (equal); Supervision (lead); Validation (lead); Visualization (lead); Writing-original draft (lead); Writing-review & editing (equal). **Kristin Koch:** Data curation (supporting); Formal analysis (supporting); Methodology (supporting); Software (equal); Validation (supporting). **Doreen Gruber:** Conceptualization (equal); Data curation (supporting); Formal analysis (supporting); Methodology (equal); Project administration (equal); Resources (equal); Software (equal); Validation (equal); Writing-review & editing (equal). **Andreas Kupsch:** Conceptualization (equal); Methodology (equal); Resources (equal); Writing-review & editing (equal). **Alireza Gharabahi:** Methodology (equal); Writing-review & editing (equal). **Gerd-Helge Schneider:** Methodology (equal); Resources (equal); Writing-review & editing (equal). **Andrea Kühn:** Conceptualization (lead); Data curation (equal); Formal analysis (equal); Methodology (lead); Resources (equal); Supervision (lead); Validation (equal); Visualization (equal); Writing-review & editing (lead).

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions. Additional data that support the findings of this study are available in the supplementary material of this article.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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