Dystonia

Subthalamic Nucleus Deep Brain Stimulation for Dystonia: Evidence, Pros and Cons

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The primary target for deep brain stimulation (DBS) for medication refractory dystonia has traditionally been the globus pallidus internus (GPi), however alternate targets have also been explored with the hope they might offer similar or superior outcomes with less side effects and reduced battery demands. Recent studies have shown comparable outcomes with both pallidal and subthalamic (STN) DBS, although the level of evidence is still superior for the GPi. There may not be an "optimal target" for all dystonia patients, with both targets offering the potential for excellent control of dystonia but more comparison studies are needed. In this review, we will discuss the history, efficacy, as well as target specific benefits and possible side effects of STN DBS for dystonia.

Keywords: dystonia, cervical dystonia, deep brain stimulation, subthalamic nucleus, secondary dystonia

INTRODUCTION

Over the last 10 years, STN DBS has emerged as a promising stimulation target for dystonia and has now been performed for various types, including isolated dystonia (1-4), dopa responsive dystonia (5), dystonic tremor (6), tremor associated with dystonia (7), tardive dystonia (8), neurodegeneration with brain Iron accumulation (9) and others. In this article, we will review the history of STN DBS for dystonia, the outcomes and discuss site-specific benefits and side effects in conditions such as isolated dystonia as well as acquired dystonia (10) Almost all studies report non-blinded outcomes and assess only STN as a target in a single cohort of patients. The debate if one target is superior (GPi or STN) for improving dystonia continues for any given individual but both targets offer the potential to provide excellent dystonia control. Other emerging targets (Thalamic/cerebellar) are also being explored. With newer imaging software and sensing systems now available, we are continuing to learn about the pathophysiology of dystonia and the mechanism of DBS across multiple "circuit nodes."

HISTORY OF STN DBS FOR DYSTONIA AND OUTCOMES

GPi DBS for dystonia was first reported in 1999, when neurosurgeon Philip Coubes reported improvement of an 8 year old girl with refractory status dystonicus (11). He later reported successful treatment of seven patients with generalized dystonia with bilateral pallidal DBS. Simultaneously Krauss et al reported successful treatment of three patients with refractory cervical dystonia (12). Pallidal DBS is now a recognized and validated therapy for medication refractory isolated generalized

TABLE 1 | Subthalamic nucleus DBS for Isolated dystonia.

Author	Number of pts	Type of study	Dystonia distribution	Length of follow up (*mean)	BFMDRS-M pre-op	BFMDRS-M post op	Mean % BFMDRS-M	QoL	BMFDRS-D pre-op	BFMDRS-D post op	BFMDRS-D mean %	TWSTRS–S Pre-op	TWSTRS–S post op	TWSTRS-S mean%	TWSTRS-D Pre op	TWSTRS-D post op
(25)	12	Case series	Generalized, 2 tardive	28.8	Exact scores not listed		86.6%									
(2)	4	Case series (blinded rater)	Cervical dystonia	12	24.3	33.3 (ND in 1 pt)		+	8	4.7		24.3	19.25		19.5	12.5
(4)	9	Prospective	Cervical dystonia	Included below, in long term data				+				53.1 (total score)	19.6 (total score)	62/9%		
(35)	4	Case series	Generalized dystonia s/p bilateral Pallidotomies	>32	Total BFMDRS 93	Total BFMDRS 33.8	Total 65.3%									
(34)	27	Retrospective	Generalized dystonia	68.4	49.2	10.3	79%	+	13.9	4.2	69%					
(37)	12	Prospective double blind cross over study	6 Cervical dystonia, 6 generalized, 1 multifocal	6			44%	±						50/9%		
(3)	20	Prospective	Cervical dystonia, generalized dystonia 4 pts DYT1 +	52	17.9	7	70.4%	+	5.4	2.6		41	13.7	66.6%		
(36)	14	Retrospective	Generalized dystonia	>360			91.4%	+			88.5%					
(38)	14	Retrospective	Meige syndrome	28.5	19.3	5.5	74%	+	15.6	6.1	60.9%					
(39)	15	Retrospective	Meige syndrome	14	Not listed			+			70.9% total BFMDRS score					
(40)	30 patients (16 STN and 14 GPi)	Matched retrospective cohort	Generalized	12	31.8	6.5	84%	+	9.8	2.7	74%					
(41)	32	Retrospective	Meige syndrome	16.3	17.9	3	80.7%		4	1	75%					
(42)	9	Retrospective	Pediatric generalized dystonia	120	49.5	2.25	90.4%		14	1.5	86.5%					
(43)	11	Retrospective	Meige syndrome	30	17.3	5.1	69.9%		20.3	5.7	71.7%					
(44)	15	Retrospective Meige syndrome	Meige syndrome	15	15.3	5.2	68.6%		6.9	3.5	51.7%					
(45)	(8 pts STN, 5 pts GPi, 1 dual stimulation)	Long term open label follow up (Schjerling cohort)	Generalized and cervical dystonia	120	Mean: 42.6 (including 8 pts w STN, excluding dual stim patient)	Mean 19.6	Mean 36% (23% for STN, 53% for GPi)				26% (26% for STN and 25% for GPi)					

+ refers to improved Quality of Life outcomes (QoL), - to negative outcomes in QoL. BFMDRS: Burke-Fahn Marsden Dystonia Rating scale. BMDRS-M + motor subscore, BFMDRS-D: disability subscore, TWSTRS: Toronto Western Spasmodic Torticollis Rating Scale. TWSTRS-S: motor severity subscore. TSWSTRS-D: Disability subscore. . Empty boxes means data not included in publication.

or cervical dystonia (13-20), with Level 1 evidence (21) and long term benefits documented a decade and more post implantation (22-24).

The earliest studies of STN DBS in dystonia were published in 2007 (25). Sun et al reported a single center retrospective case series of 14 patients with generalized dystonia (two patients w tardive dystonia and 12 with primary generalized dystonia) with robust response to STN DBS. The mean improvement on the Burke Fahn Marsden Dystonia Rating scale (26) (BFMDRS) was reported to be 88% with a mean follow up of 28 months. That same year, Kleiner-Fisman (2) et al reported outcomes in four patients with predominantly cervical dystonia treated with STN DBS. Blinded rating with BFMDRS and Toronto Western Torticollis Rating Scale (TWSTRS) (27) at 12 months showed significant improvement only in the TWSTRS. The majority of patients in this study had significant comorbidities including fixed skeletal abnormalities, likely limiting benefit.

These early studies, the observation that Parkinson's Disease associated dystonia could be improved with STN DBS (28, 29), and the limited benefit in some patients with GPi DBS (20), all prompted further investigation into the STN as an alternate dystonia target. Also, as the field gained more experience treating dystonia with GPi DBS, over time in some patients, new stimulation induced side effects began to be appreciated. This included development of bradykinesia most notably in previous non dystonic body regions, micrographia and other handwriting difficulties, trouble getting out of a chair, moving in bed, as well as gait changes (sometimes freezing of gait) (30-32). Often side effects could be managed with stimulation adjustments such as reducing frequency of stimulation (33), but not in all cases. This prompted wider interest in exploring alternative dystonia DBS targets including the STN.

STN DBS IN ISOLATED CERVICAL AND GENERALIZED DYSTONIA

Table 1 includes all published cases of STN DBS in isolated dystonia that describe four or more patients (25, 34-45). The first blinded prospective study of STN DBS in dystonia was published in 2011, describing one-year outcomes in nine patients with predominantly cervical dystonia (4). The total TWSTRS score improved a mean of 62.9%, with most of the improvements achieved by 3 months. STN DBS was well tolerated and there were no serious adverse events. Three patients experienced marked weight gain and all patients experienced transient stimulation induced dyskinesia. Later the same group published a continuation of this study, which then included 20 patients who were followed prospectively for 3 years (3). The cohort included a majority of cervical and craniocevical dystonia patients, but also included generalized, bibrachial, segmental dystonia subtypes, and some with a DYT1 mutation. At 36 months, BFMDRS motor score improved by a mean of 70.4% and the TWSTRS by 66%, similar to previously reported outcomes with bilateral pallidal DBS (13, 17-20). No significant device related complications occurred, but one patient experienced persistent dysphoria

when turning on the left STN lead. Non-responder rate was at 10%, which is lower than what has previously been described with pallidal DBS at 27% (12). Benefits noted by authors included more rapid improvement in dystonic symptoms with initiation of therapy as well as lower IPG drainage due to lower required stimulation settings. No reports of bradykinesia were reported, however, stimulation induced dyskinesia (SID) occurred as can be seen in other conditions treated with this target (46). A sub-study of the same cohort showed dystonia control was greater with high frequency subthalamic DBS compared to low frequency stimulation (47).

The longer-term (10 years) benefit of STN-DBS for generalized dystonia were retrospectively studied in a series of nine pediatric patients with generalized dystonia (42). The mean age at surgery was 15.9 years and the mean improvement in BFMDRS motor score was 77.1% at 1 year and 90.4% at 10-year. BFMDRS disability scores were also reduced by 87% at 10-year. Notably only two of the nine patients carried the TOR1A mutation for DYT1. As with several pallidal studies (48, 49), a negative correlation was found between the duration of disease to age of surgery ratio and the degree of BFMDRS motor and total score improvement. Stimulation related adverse events reported at 10 years included dysarthria, dysphagia ($n = 4$) and gait changes ($n = 4$). There were no significant surgery related side effects and, eight of the patients needed IPG replacement during follow up. One patient reported weight gain, and one patient experienced a lead breakage. Interestingly clinical efficacy was maintained after IPG depletion in one patient, and while the DBS was temporarily turned off in another, highlighting the possibility of STN DBS inducing functional brain changes even after cessation of neuromodulation (42), though this may not be target specific effect, as it has also been reported with pallidal DBS (50).

MEIGE SYNDROME

Evidence for both STN and GPi DBS in Meige syndrome (an adult-onset segmental dystonia manifesting predominantly with oromandibular dystonia and blepharospasm) remains primarily retrospective or based on case reports (38, 39, 43, 44, 51). The largest report has been from China describing 32 Meige syndrome patients treated with bilateral STN DBS with a mean improvement in the BFMDRS of 79%. Ten of the patients experienced stimulation induced dyskinesia. The mean voltage for development of dyskinesia was 1.7 V and stimulation of ventral STN was more likely to induce dyskinesia (41).

ACQUIRED AND NEURODEGENERATIVE DYSTONIA (FORMERLY SECONDARY DYSTONIA)

Tardive dystonia (TD) is a disabling and irreversible iatrogenic movement disorder typically caused by exposure to dopamine blocking agents. Often axial musculature is predominantly affected, such as neck, jaw and trunk (45). Robust, rapid and

sustained improvement of TD has been reported with pallidal DBS, with a mean percentage improvement in BMFDRS-motor sub score of 83% at a mean follow up of 41 months (46, 47). Similar outcomes appear to be possible with STN DBS with over 17 cases of TD treated with STN now published in the literature (26, 48-50). Deng et al reported long-term outcomes of 10 patients with tardive dystonia treated with bilateral STN DBS, with the mean follow up being 65 months (range 12–105 months). Mean improvement in BFMDRS motor sub score at last follow up was 88%. Patients showed a statistically significant improvement in Quality of Life as measured by the SF-36, and notably both Hamilton Anxiety Scale and Hamilton Depression scale displayed significant reductions (51). Several TD patient outcomes are described in mixed patient reports that also include patients with isolated dystonia describing, all with robust response to STN DBS(26)(48).

The STN has sometimes been targeted and implanted when the patient has existing damage to the pallidum noted on MRI(52) (53). Liu et al reported outcomes of three patients with PKAN implanted with STN DBS, with a mean improvement in BFMDRS motor scores of 58%, a more robust response than in the prior multicenter retrospective reports of GPi DBS in PKAN (54, 55) with authors suggesting the STN might be a good target especially for patients with prominent appendicular rather than axial dystonia (56). STN DBS has also been reported to be beneficial in two patients with Neuroacanthocytosis (57) including lingual dystonia (58).

Several case reports documenting outcomes of STN DBS for other cases of acquired or neurodegenerative dystonia have been published, with variable duration of follow up and efficacy (5, 9, 52, 53, 59-63). The improvement in dystonia rating scales is generally less robust than what is experienced in isolated dystonia (64), although meaningful improvements in quality of life is often seen- similar to what has been reported in pallidal DBS (**Table 2**).

STUDIES DIRECTLY COMPARING PALLIDAL AND SUBTHALAMIC DBS IN DYSTONIA

To date, two prospective crossover studies of STN and GPi DBS in isolated dystonia have been conducted. The first reported by Schjerling et al performed a prospective double blind crossover study of 12 patients with focal, multifocal or generalized dystonia (37). Electrodes were implanted bilaterally in both the GPi and STN and each patient then randomly assigned to receive either 6 months of pallidal or subthalamic stimulation, followed by stimulation of the other target for the subsequent 6 months. No statistically significant difference in dystonia motor outcomes was found. Both targets showed improvement in dystonia motor severity and quality of life measures. All 12 patients accepted six-month subthalamic stimulation, compared to only seven with pallidal DBS. Among those who rejected pallidal stimulation, due to worsening dystonia, three accepted dual GPi and STN stimulation (unblinded). In 2022, a long-term open label follow-up results of the same cohort including some additional subjects was published (45).

Twenty-one patients enrolled in the protocol, of which nine had generalized dystonia and 12 had cervical dystonia. Eighteen patients completed the one-year randomization study. Eleven patients chose chronic subthalamic stimulation; six chose pallidal stimulation and one patient opted for dual target stimulation. Fourteen out of 18 patients participated in the long-term follow up study, with a mean follow up of over 10 years. Efficacy between targets was reported to be similar with a mean improvement of 36% in BFMDRS motor sub score and a similar safety profile. Mean duration of dystonia prior to surgery was 19.3 years and age at time of surgery 50.1. The group of patients with cervical dystonia were significantly older than the group with generalized dystonia. Age at surgery predicted a smaller improvement in movement score. Duration of dystonia prior to surgery negatively correlated with improvement in motor score, although not significantly. The authors commented, the more rapid response in dystonia with STN DBS might have favored its use compared to GPi DBS (45).

The second prospective study by Liu et al investigated the response of short-term (several days) pallidal or subthalamic stimulation in eight patients with isolated dystonia (65). The group implanted electrodes into all four nuclei, performed test stimulation using externalized leads, with determination of optimal target and removal of less efficacious electrodes prior to IPG implantation, around 10–14 days after the initial surgery. Stimulation was performed in three phases; patients were randomly assigned to receive either pallidal or subthalamic DBS, followed by a sham phase, followed by the other target. Stimulation parameters were increased until maximal benefit or side effects occurred at which parameters were left static for 24 h prior to rating scale assessments. There was no statistical difference in BFMDRS motor sub score outcome with a mean improvement of 50.6% with pallidal and 43.7% with subthalamic DBS; however, a higher incidence of adverse events including dyskinesia and dysphoria were noted in the STN group. These side effects were generally mild and responsive to adjustments. The main side effects associated with STN DBS were dyskinesia in five patients and dysphoria in two patients. Permanent target selection was then made based on benefit and side effect profile. Of the eight patients, only one patient received subthalamic stimulation long-term (1 year follow-up) (65). Given the smaller size of the subthalamic nucleus and the more rapid response rate, it is not surprising that more side effects occurred with STN stimulation and thus the study design may have favored pallidal stimulation.

Several retrospective cohort studies have also compared target outcomes. Lin et al performed a single center matched retrospective cohort study of 14 GPi and 16 STN DBS generalized dystonia patients implanted over a three-year period. Five patients were lost to follow up. Both targets achieved significant motor symptom improvement at 12 months, with a mean improvement in BFMDRS motor subscore of 84% with STN and 72% with GPi DBS. STN DBS was noted to have a more rapid onset of improvement within the first month from programming initiation as well as significantly lower amount of total energy delivered but showed that pallidal stimulation was more effective in treatment of axial symptoms. Both targets improved quality of life (40). Tian et al performed a retrospective

TABLE 2 | Subthalamic nucleus DBS for acquired and neurodegenerative dystonia. BFMDRS: Burke-Fahn Marsden Dystonia Rating scale. BMDRS-M + motor subscore, BFMDRS-D: disability subscore.

Author	Number of pts	Type of study	Cause	Length of follow up (months)	BFMDRS motor pre-op	BFMDRS motor post op	Percentage improvement Motor subscale	BFMDRS disability pre-op	BFMDRS Disability post op
(59)	9	Case series	2 pts Tardive, 3 post hypoxic, 1 post-traumatic, 1 Kernicterus 1 lesion lentiform nucleus 1 unknown	3–36		Only reported outcomes in 3 patients w satisfactory outcomes, 6 patients only "mild to modest improvement"	90% (only 2 pts with tardive and post traumatic dystonia responded)		
(52)	1	Case report	Methylmalonic acidemia	9	105	Notes marked improvement in dystonia not reflected in BFMDRS			
(9)	1	Case report	PKAN	36	Total BFMDRS 115	Total BFMDRS 18			
(5)	1	Case report	Dopa responsive dystonia				No scores listed. "improvement in dystonia noted from L STN DBS stimulation, (contralateral DBS removed due to infection)		Reduced medications, improved weight post op
(60)	1	Case report	Fahr's disease	24	105	*improvement not captured by BFMDRS	Meaningful improvements Per parents	30	*not captured w scale
(64)	2	Case series	GM1 Gangliosidosis Type 3, dystonia and parkinsonism	0.5	Pt 1:86 Pt 2: 29	Pt 1: 62 Pt 2: 29	STN leads added to help akinesia in patient 1, dual GPi and STN leads placed in pt 2		
(63)	1	Case report	Tardive dystonia	156	70.5	0	100%	28	0
(56)	3	Case series	PKAN	22–44	42	20.3	58.3%		
(53)	2	Case series	Post Hypoxic/ischemic	9	Total BFMDRS 70	Total BFMDRS 43.5	45.3%		
(8)	10	Case series	Tardive dystonia	65	36	7.6	88%	10.4	2.6
(61)	2	Case series	Post traumatic dystonia		24.5	8	65.5	13	3.5
(62)	3	Case series	Post Infarct dystonia	38	34	25.3	25.5%	8.3	6.7
(57)	2	Case series	Chorea acanthocytosis	12	41.3	17	58.9%	14	9

study of 17 consecutive patients treated with DBS for Meige syndrome that included 11 patients treated with STN DBS. Outcomes for both targets were similar, with a mean improvement in BFMDRS-motor score of 69.9% for STN and 71.7% for GPi DBS. BFMDRS disability subscore improvement was 71.6% with STN and 68.4% with GPi DBS. The stimulation voltage was significantly higher as expected in the GPi group (43).

There have been several meta-analyses published comparing outcomes. Tsuboi et al in 2020 summarized the evidence of STN (N = 24) versus GPi DBS (N = 184) for cervical dystonia. Only articles reporting TWSTRS outcomes were included. The authors concluded approximately 80–90% of patients with cervical dystonia are expected to experience a clinically meaningful improvement (defined as more than 25% improvement in TWSTRS) in symptoms following DBS of either target and that both STN and GPi DBS improve motor symptoms, disability, and pain, with similar efficacy. A meta-regression of long-term outcomes of isolated dystonia treated with either pallidal or subthalamic DBS was published in 2019. Authors included papers reporting baseline and follow-up BFMDRS scores up to three or more years and that included 10 or more patients. Three studies of STN DBS and 19 studies with GPi DBS were included. Treatment of both STN and GPI DBS, dystonic symptoms were improved and efficacy was maintained at 3 years. The results showed a positive correlation between a greater treatment effect and shorter disease duration. Authors observed greater improvement in the STN subgroup on univariate regression

analysis, but due to the high correlation/association between disease duration and DBS target, no difference in relative efficacy in BFMDRS outcomes between sites was found (66).

Some groups have explored using a dual targeting strategy with bilateral GPi and STN in neurodegenerative dystonia. Two patients with secondary parkinsonism and dystonia due to GM1 Gangliosidosis showed greater improvement with STN versus the GPi stimulation (64). Ozturk et al reported outcomes of pallidal versus subthalamic DBS in acquired and neurodegenerative dystonia in studies published between 2005 and 2020. The authors found 72 studies reporting outcomes of 264 cases treated with pallidal DBS (average follow up 19 months) and reported a mean BFMDRS improvement of 52%. Ten studies of STN DBS in acquired or neurodegenerative dystonia were identified, reporting outcomes in 146 secondary dystonia cases. The mean BFMDRS improvement was 66% (minimum 28%, maximum 98%) with an average follow up of 20 months (67).

SPECIFIC CONSIDERATIONS FOR NEUROMODULATION IN DYSTONIA

Relative to other movement disorders, patient selection and DBS programming can be more difficult in dystonia. The etiology of dystonia is sometimes unclear and the dystonia clinical features can vary widely (i.e., dystonia phenotype, distribution, age of onset, genetic status), Prognostic factors associated with better outcomes from DBS in dystonia include DYT1 genetic status (68), shorter disease duration (48) and absence of fixed skeletal abnormalities(69). Given the rapid evolution of dystonia genetics and with more available genetic testing, other prognostic markers are likely to emerge in the future.

CONSIDERATIONS IN TARGET SELECTION

Specific limitations with pallidal DBS include higher energy stimulation and thus higher IPG drainage, although IPG lifetime and availability of rechargeable systems make this a less important consideration in target selection currently. The rate of hemorrhage during DBS lead implantation maybe slightly higher with pallidal DBS implantation, although thankfully the hemorrhage rate is low across both targets (70). The sometimes slow and insidious onset of benefit with pallidal stimulation can also offer challenges for DBS programmers, given the lack of immediate feedback while programming in some cases. STN DBS may offer a more rapid response and be helpful in optimizing stimulation parameters in a more timely fashion (4).

STIMULATION INDUCED DYSKINESIA

While GPi DBS has been reported to cause bradykinesia (30, 32), STN DBS can cause stimulation induced dyskinesia (SID) as previously reported with STN DBS in PD (71), Obsessive Compulsive Disorder (72) and Huntington's disease (73).

Similar SID can also occur with STN DBS in dystonia as we have mentioned (46, 41). The phenomenology of these hyperkinetic movements can be both varied and complex and can complicate optimizing DBS programming. Bledsoe et al reported athetotic movements of fingers, chorea, rapid jerks as well as more sustained dystonic posturing (46). These movements often occurred in previously non-dystonic or hyperkinetic areas. Importantly all patients in this case series did experience SID with initial programming; however, some experienced delayed onset of SID several months after last programming session. The latter is an important finding as it should prompt programmers to evaluate the patient in the OFF stimulation state, to establish if the new hyperkinetic movements are due to SID versus spread or worsening of dystonia. Programming strategies proposed to combat SID included slow increase in amplitude of stimulation, use of bipolar configuration as well as activating the dorsal contacts (4, 46). Programming the dorsal STN using interleaving has previously reported to be anti-dyskinetic in PD, likely due to activation of pallidofugal fibers (74) can also be applied. The dorsolateral STN has been reported to offer optimal dystonia control (40). Newer segmented directional leads may also help minimize SID with more exact stimulation delivery.

WEIGHT CHANGES

Weight gain has frequently been reported with STN DBS for PD (75) and similar changes have been reported with some patients treated with STN DBS for dystonia and appears to be target specific (76). Three of nine patients in Ostrem et al initial prospective trial experienced 10% increase in body weight (4).

NEUROPSYCHIATRIC CONSIDERATIONS

Neuropsychological outcomes after STN DBS are scarce. In the prospective study of STN DBS for dystonia, no consistent neuropsychological deficits occurred. Although transient worsening of depression was observed in several patients, the Beck depression Inventory (77) did not worsen at 12 months (4). Contrarily, the Hamilton Depression Scale and the Hamilton Anxiety Scale showed significant reduction at last follow up (>5 years) in 10 patients treated with STN DBS for TD(79). Although there have been many published reports of cognitive concerns in vulnerable patients after STN DBS in PD (79, 80), a study of working memory and attention using a dual task paradigm in eight cervical dystonia patients both ON and OFF STN DBS showed no significant worsening of cognitive function (81). Multiple studies have reported sustained improvement in quality of life post STN DBS in dystonia, usually reported by the SF-36 questionnaire (36, 78).

ROLE OF RESCUE LEADS

A multi-center cohort study of 132 patients with DYT1 dystonia treated with pallidal DBS found a suboptimal (less than 30%

TABLE 3 | Pros and cons of STN or GPi DBS for dystonia.

Target	STN	GPi
Benefits	More rapid onset of action	Class I evidence for isolated dystonia with proven long term benefit
	Lower IPG drainage	
Limitations	Less robust evidence	Stimulation induced bradykinesia
	Stimulation induced dyskinesia	Delayed onset of clinical benefit
	Possible weight gain	Slightly increased rate of hemorrhage

IPG, implantable pulse generator.

improvement in BFMDRS) long term response in 8% (11 patients). All 11 of these patients experienced an initial response of more than 30% postoperatively, with subsequent worsening. Younger age of onset, faster disease progression and cranial involvement were felt to represent a more aggressive phenotype of DYT1. Off stimulation evaluation showed worsening of dystonia, despite missing the 30% improvement threshold, thus indicating some continued benefit. All 11 patients underwent further DBS surgeries, either targeting the STN or the GPi, Additional leads did not offer meaningful improvement, if the initial leads were optimally placed (82).

DISCUSSION

Both pallidal and subthalamic bilateral and unilateral DBS are FDA approved under the Human Device Exemption (HDE) for treatment of drug refractory isolated dystonia, including generalized, cervical and hemidystonia in patient's age seven and above. (https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfhde/hde.cfm?id=H020007).

Pallidal DBS has Level I evidence for both generalized and cervical dystonia(18, 83) whereas STN DBS has level IV for generalized dystonia(3) and level III for cervical dystonia(4). Over 80 patients with generalized, 24 with cervical, 87 with Meige syndrome and 17 with tardive dystonia treated with STN DBS have been reported in the literature (**Table 1, 2**). Most studies have concluded outcomes after STN DBS in dystonia to be similar to GPi DBS. Challenges now exist for clinicians to choose from multiple effective targets for dystonia—much like we have for other disorders (PD, and off label Tourette syndrome and obsessive-compulsive disorder) (84-86), See **Table 3**. Not discussed in this review is also the application of thalamic DBS for dystonia (87) and dystonic tremor (88), cerebellar DBS (89, 90) as well as cortical stimulation (91) which may increase clinical options in the future. Although dystonia subtypes are often grouped together on the basis of their motor manifestations, pathogenesis may differ among the subtypes. Current understanding of the neuroanatomical basis of dystonia have evolved from a focus on dysfunction of the basal ganglia to include a broader motor network model involving the basal ganglia, cerebellum, cerebral cortex, and other brain regions (92). Important concepts in the pathophysiology include the impairment of sensorimotor integration, a loss of inhibitory control on several levels of the central nervous system including the basal ganglia, cortex and brain stem as well as changes in synaptic plasticity (93, 94). Reduced function of the indirect pathway with decreased pallidal inhibition of the thalamo-cortical circuitry as well as hyper functional activity of the direct basal ganglia pathway has been proposed to contribute to abnormal motor cortical excitability in dystonia (95). In addition, primate research has shown the STN receives substantial direct cortical projections, *via* the "hyperdirect" pathway(96) and cortical areas projecting to the STN have been implicated in dystonia pathophysiology(97).

Recent research has also highlighted the importance of the cerebellum in the genesis of dystonia (98). Previously it was thought the basal ganglia and cerebellum only communicated through higher order cortical relay and functioned somewhat independently by relaying projections to cortical areas *via* separate thalamic nuclei, however recently a is a disynaptic connection from the motor STN, *via* pontine nuclei, to the cerebellar cortex has been described (99, 100). Additionally, the cerebellar dentate nucleus has a disynaptic connection, *via* the intralaminar nucleus of the thalamus, directly to the striatum (100).

It is interesting that such diverse therapeutic effects are possible from multiple DBS targets and can improve both hypokinetic and hyperkinetic movement disorders. The exact mechanism of how DBS exerts its therapeutic effect remains unknown but evidence is mounting that DBS is suppressing pathological oscillatory activity within these brain networks (101). Current DBS systems have the ability to record local field potentials (LFP) from target nuclei and low frequency theta activity (3–8 Hz) has been shown to be associated with dystonia and suppressed by therapeutic DBS (102). Theta spectral activity has been recorded from both STN (103) and GPi (104) targets and correlated with clinical severity (105, 106). A recent proof of principle study showing adaptive DBS of the STN in cervical dystonia controlled by cortical theta oscillation showed improved clinical rating compared to continuous DBS as well as increased peak amplitudes without inducing SID (107).

CONCLUSION

Deep Brain stimulation represents a powerful treatment option for dystonia, regardless of target. The optimal target for neuromodulation remains unknown and future head-to-head studies are needed. Thus far, pallidal DBS still has significantly more robust evidence over STN DBS. Other emerging targets outside

of the basal ganglia known to be important n dystonia, such as the cerebellum has also gained recent attention. Modulating brain circuits by targeting one of several different nodes within the network can offer powerful symptomatic benefit. Given that targeting multiple areas within the circuit have been shown to both disrupt the abnormal pathological oscillatory activity and offer robust and similar clinical efficacy, clinicians are now faced with determining a final target based on multiple factors including the best side effect profile, ease of surgical targeting, and programming for an individual patient. Emerging tools including improved imaging approaches such as connectomics as well as more sophisticated neurophysiology may help guide ideal nodes to target with DBS on an individual basis in the future.

AUTHOR CONTRIBUTIONS

CONFLICT OF INTEREST

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