Review

Brain Stimulation for Torsion Dystonia

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IMPORTANCE Dystonia is a heterogeneous neurologic disorder characterized by abnormal muscle contractions for which standard medical therapy is often inadequate. For such patients, therapeutic brain stimulation is becoming increasingly used.

OBJECTIVES To review the evidence and effect sizes for treating different types of dystonia with different types of brain stimulation and to discuss recent advances relevant to patient selection, surgical approach, programming, and mechanism of action.

EVIDENCE REVIEW PubMed was searched for publications on the clinical effect of brain stimulation in dystonia up through December 31, 2014. Recent meta-analyses, consensus statements, and evidence-based guidelines were incorporated. Emphasis was placed on deep brain stimulation (DBS) and randomized clinical trials; however, other stimulation modalities and trial designs were included. For each intervention the mean change in dystonia severity, number of patients studied, and evidence of efficacy based on American Academy of Neurology criteria were determined.

FINDINGS Strong (level B) evidence supports the use of DBS for the treatment of primary generalized or segmental dystonia, especially when due to mutation in the *DYT1* gene, as well as for patients with cervical dystonia. Large effect sizes have also been reported for DBS treatment of tardive dystonia, writer's cramp, cranial dystonia, myoclonus dystonia, and off-state dystonia associated with Parkinson disease. Lesser benefit is generally seen in dystonia secondary to structural brain damage. Other brain stimulation techniques, including epidural cortical stimulation and noninvasive brain stimulation, have been investigated, but generally report smaller effect sizes in fewer patients.

CONCLUSIONS AND RELEVANCE Patients with dystonia that is not adequately controlled with standard medical therapy should be referred for consideration of DBS, especially patients with generalized, segmental, or cervical dystonia. Other less-invasive stimulation modalities require further research before being considered a therapeutic alternative.

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Dystonia is defined as a neurologic disorder characterized by sustained or intermittent muscle contractions causing abnormal movements and/or postures. Dystonia is a heterogeneous group of disorders with many underlying causes both known and unknown. The most recent consensus guidelines[1] classify dystonia based on clinical presentation and etiology. Key clinical factors include patient age at onset, extent of the body affected, temporal pattern, and whether dystonia is the only major motor finding (isolated dystonia) or one feature of a broader disorder (combined dystonia). Etiologic classification relates to whether dystonia is inherited, acquired, or due to identifiable nervous system abnormalities. Different types of dystonia span the spectrum of this classification scheme from generalized childhood-onset dystonia due to genetic mutation (eg, *DYT1* gene mutation) to more focal adult-onset dystonia affecting the hand (writer's cramp), neck (cervical dystonia/torticollis), or face (cranial dystonia/Meige syndrome). Dystonia can arise secondary to brain insult, including stroke, trauma, or adverse medication effect (tardive dystonia) or as a symptom of other diseases, such as Parkinson or Wilson disease.

Pharmacologic therapies for dystonia, including anticholinergic agents, dopaminergic agents, benzodiazepines, tetrabenazine, and baclofen, generally provide modest symptomatic improvement and can cause significant adverse effects. A rare exception is dopa-responsive dystonia, which responds profoundly to treatment with levodopa. Botulinum toxin injections can provide symptomatic relief for targeted muscles; however, the injections must be repeated every few months, patients can become resistant or immune to the therapy over time, adverse effects (eg, weakness) are common, and the injections become both costly and impractical if many muscles are affected. Surgical interventions have included rhizotomy for severe cervical dystonia and ablation of the thalamus (thalamotomy) and/or basal ganglia (pallidotomy) for more generalized dystonias.[2] These ablative procedures can provide significant benefit, and pallidotomy is still used in select cases. However,

variation in lesion location or size can yield heterogeneous results and pose a risk of irreversible adverse effects, particularly with bilateral interventions.[2] Because of these limitations, deep brain stimulation (DBS) has emerged as the preferred surgical intervention for medically refractory torsion dystonia. The main advantages of DBS relative to ablation are (1) the effects of stimulation are reversible, yielding a significant margin of safety; (2) the stimulus can be titrated to clinical effect and modified as needed over time; and (3) bilateral interventions can be performed safely.

In 2003, the US Food and Drug Administration granted a humanitarian device exemption for the use of DBS in primary generalized or segmental and cervical dystonia based on the relatively small number of patients thought to be surgical candidates and the robust clinical responses reported at that time, albeit in open-label assessments. The humanitarian device exemption requires that DBS for dystonia be performed with the oversight of a local institutional review board. Since 2003, the body of evidence supporting the use of DBS in dystonia has grown, including the results of 2 large randomized clinical trials, both performed in Europe.[3,4] To identify relevant publications, we performed a PubMed search through December 31, 2014, including the terms *dystonia and brain stimulation*, *dytsonia and DBS*, and *dystonia and TMS or tDCS*. Literature cited by identified articles was also incorporated. Herein, we review the current status of DBS for the treatment of dystonia, incorporating recent evidence-based guidelines,[5-8] meta-analyses,[9,10] and reviews.[2,11] The potential impact of investigational noninvasive brain stimulation techniques for dystonia is also discussed.[12]

Selecting Patients for DBS Therapy

Deciding which patients with dystonia are candidates for DBS therapy can be complex given the heterogeneous nature of the disorder, the varied responses to stimulation of different dystonia subtypes, and the potential risks of surgery. Given this complexity, DBS for dystonia is probably best performed through a dedicated multidisciplinary movement disorder center. Regarding patient selection, one may begin with the US Food and Drug Administration–approved indications, which are supported most strongly by the available evidence. Under the current humanitarian device exemption, DBS is approved only for the treatment of primary generalized, segmental, or cervical dystonia. The use of DBS to treat other dystonia subtypes is considered off-label; however, evidence is emerging that it may be effective.

The evaluation of patients with dystonia presenting for consideration of DBS should focus on (1) excluding conditions that would respond favorably to less-invasive treatments and (2) identifying factors predictive of a positive (eg, *DYT1* mutation) or negative (eg, secondary dystonia) response to stimulation. A levodopa trial should be performed in all patients with symptom onset before age 21 years and considered in patients with symptom onset before age 50 years to rule out levodopa-responsive dystonia. Testing for Wilson disease should be conducted in patients with suggestive features. Patients with focal or cervical dystonia referred for DBS owing to resistance to botulinum toxin therapy should be evaluated to ensure they would not benefit from more appropriately targeted or dosed injections. One can test for resistance by injecting a small amount of botulinum toxin into a forehead wrinkle and assessing for effect. Patients with psychogenic dystonia may be referred for DBS since they are often refractory to treatment. Differentiating psychogenic from organic dystonia is difficult and considered definitive only if symptoms resolve with psychotherapy.[13,14] Clinical features suggestive of a psychogenic cause include inconsistency over time, incongruence with organic dystonia syndromes, sudden onset, peak severity at onset, fixed or tonic features, and comorbid psychiatric disease or other psychogenic symptoms.[14] It is important to evaluate patients for fixed skeletal deformities, spasticity, and myelopathy, all of which may mitigate the patient's response to DBS. Similarly, the preoperative workup should include brain magnetic resonance imaging (MRI) to exclude structural abnormalities that could indicate a secondary dystonia or affect surgical targeting. Finally, screening for premorbid psychiatric symptoms or cognitive dysfunction is reasonable keeping in mind that globus pallidus pars interna (GPi) DBS has been used successfully in psychiatric patients with tardive dystonia and in some patients with cognitive impairment.[6] There is no evidence that DBS exacerbates these symptoms in patients with dystonia.

The proper timing of DBS surgery remains a controversial issue. In general, intervention should be considered once it is determined that medical therapy has failed to adequately control symptoms and before the development of fixed skeletal deformities or cervical myelopathy.[6] As recently as 2011, the Movement Disorders Society[6] concluded that there was insufficient evidence to recommend early surgery; however, accumulating data suggest that the earlier one intervenes with DBS, the better the outcome, especially in generalized dystonia due to mutation in the *DYT1* gene.[15] Precisely how early DBS should be performed is unclear, however, because there are scant data regarding surgical outcomes in children younger than 7 years or for symptom duration of less than 2 years.

Surgical Procedure

The DBS device includes 3 key components: a stimulating electrode (also called a *lead*), an extension cable, and a programmable pulse generator (PG), which is similar to a cardiac pacemaker (**Figure 1**). The device is implanted in 2 stages. During the first stage, unilateral or bilateral leads are implanted stereotactically into a specific therapeutic target. By far the most common target for dystonia is the GPi (**Figure 2**), but other targets, including the subthalamic nucleus, have been studied.[8] During the second stage, which may be performed on the same day or later, the PG is implanted under the skin of the anterior chest wall or the abdomen and connected to the lead wire via subcutaneously tunneled extension cables. In most instances, bilateral implants are required; however, patients with hemidystonia may benefit from unilateral stimulation.

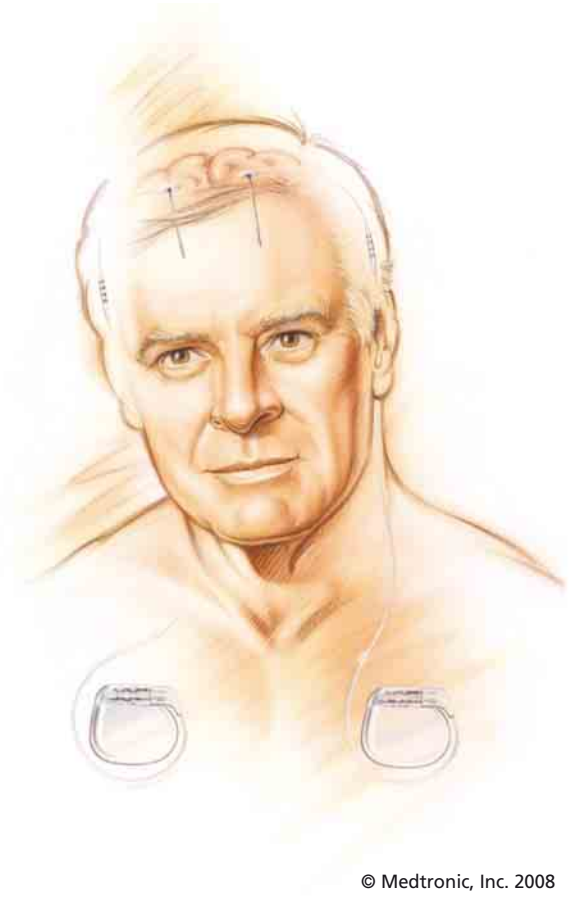
Lead insertions may be accomplished with a variety of image- and physiologically guided techniques, although use of a cranial-mounted stereotactic head frame remains the criterion standard against which all other techniques are measured.[7] Alternatives to the frame include frameless stereotactic targeting and direct, image-guided placement within the MRI scanner. Regardless of the targeting technique, target visualization is accomplished with MRI utilizing techniques that provide excellent delineation of the basal ganglia.[7] Intraoperatively, proper siting of the therapeutic target may be accomplished with single-unit microelectrode and/or local field potential recordings.[8] Traditionally,

these recordings are obtained with the patient fully awake; however, acceptable recordings can be obtained in patients under anesthesia, and some anesthetic agents may be better than others at not disrupting the typical patterns seen in an awake patient.[8] Once proper targeting is confirmed, the lead is inserted and the acute effects of stimulation are tested. Dystonia differs from Parkinson disease and essential tremor in that days or weeks of stimulation, rather than seconds or minutes, are usually required to achieve clinical response. Therefore, an improvement in dystonia symptoms in response to intraoperative test stimulation is not expected. Instead, test stimulation is used to assess for adverse effects that, if present, will appear immediately and should prompt repositioning of the lead. Once satisfactorily positioned, the lead is anchored at the skull using the surgeon's preferred technique.

Following implantation, proper lead location can be confirmed and intracerebral hemorrhage excluded with either computed tomographic scanning or MRI. Brain MRI can be performed safely despite the presence of the implanted leads and allows one to better assess their anatomical position. Low-energy MRI sequences must be used to adhere to US Food and Drug Administration–mandated safety regulations, although standard (higher-energy) MRI sequences have been used in many patients without adverse effects.[7]

The second stage of the DBS surgery, during which the PGs and extension cables are implanted and connected to the leads, can be performed on the same day as the lead implantation but is often scheduled for 1 to 2 weeks after the operation. This stage is performed under general anesthesia. In patients requiring bilateral stimulation, an important question is whether to implant a single PG to power both leads or 2 single-channel PGs, 1 for each side. Although implantation of 2 PGs requires an extra incision and a slightly longer operation, single-channel PGs have a lower profile than dual-channel PGs and last longer. Further, the presence of 2 PGs provides some protection against sudden cessation of all stimulation therapy if one battery is suddenly exhausted[17] or needs to be explanted owing to infection. Although not approved for use in dystonia, the dual-channel rechargeable device, which has the lowest profile of all PGs, may minimize the risk of infection and reduce the frequency of PG replacements that may prove particularly valuable in treatment for children with generalized symptoms.

Figure 1. Illustration of Bilaterally Implanted Deep Brain Stimulation (DBS) Devices



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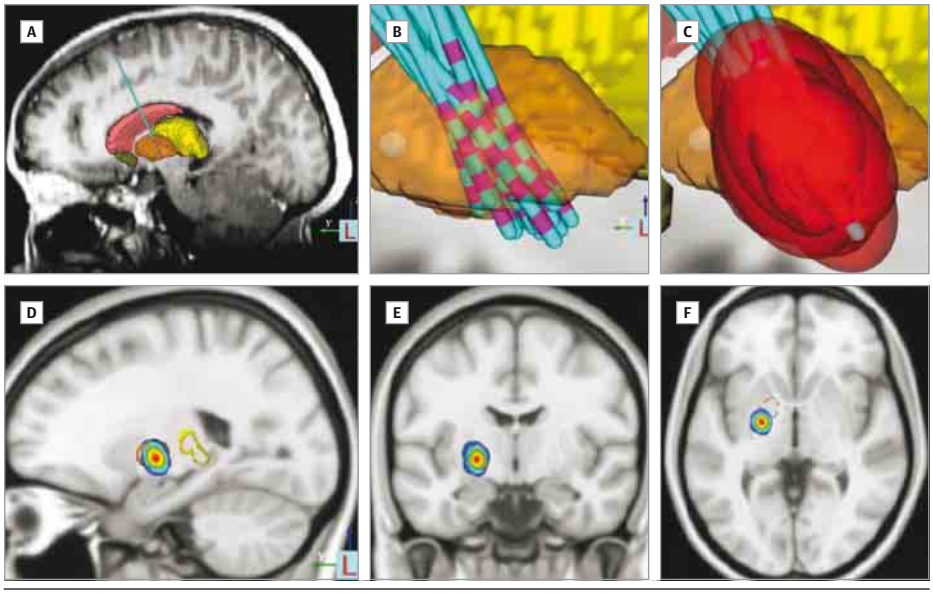
Each DBS device is composed of a stimulating lead in the brain, extension cable, and programmable pulse generator, usually implanted in the chest (used with permission from Medtronic, Inc).

DBS Programming

Immediately after lead implant, some patients experience a transient improvement in their dystonia; a phenomenon termed the *micro lesion effect*. Although less commonly observed in dystonia than in other disorders, when it occurs, this effect often heralds a good response to stimulation. Because the effect can last up to 3 weeks and complicate the assessment of stimulation response, some centers wait until after this period to begin programming.[5] Other centers begin programming immediately or wait 7 to 10 days after PG implantation, allowing time for the surgical incisions to heal. Of particular significance is patients who undergo implantation during a dystonic crisis, a potentially life-threatening situation in which a patient's dystonia acutely worsens and is manifest as severe, active, painful contractions that can lead to rhabdomyolysis, respiratory compromise, and other metabolic derangements. Small case series[5] suggest that DBS may help break dystonic crises more readily than medications alone. Under these circumstances, immediate activation of stimulation is warranted.

During programming, the clinician controls 4 stimulus factors: amplitude, pulse width, frequency, and the active contact. The goal is to find the combination of settings that improves motor function and/or reduces pain without causing adverse effects. Determining these settings is more difficult in dystonia than in essential tremor or Parkinson disease because the therapeutic benefit is often not apparent for weeks to months. Moreover, there is no consensus regarding the most efficient approach to achieving the optimal settings, although practical guidelines are available.[5] In general, one starts by activating each contact in isolation (monopolar stimulation), slowly raising the stimulus amplitude while examining for the threshold at which adverse effects (eg, muscle contractions, dysarthria, or worsening dystonia) occur. Some patients may also show acute beneficial effects, such as a reduction in dystonic tremor, identifying a preferred contact. If no beneficial effects are seen, one can conduct trial stimulation at each contact for longer periods (days to weeks) or select contacts located in the posteroventral GPi since prior studies[16] suggest that posteroventral GPi contacts are most likely to yield maximal benefit (Figure 2). Some centers select the contact at or immediately superior to that which produces phos-

Figure 2. Deep Brain Stimulation Target in the Globus Pallidus Based on Retrospective Analysis of the Site of Effective Electrode Contacts and Modeling of Stimulation Fields



Magnetic resonance imaging was used to identify the location of the deep brain stimulation electrode (shown as multicolored rod) in patients with generalized dystonia due to mutation in the *DYT1* gene (A) and coregistered into a common atlas space (B). The stimulation field for the effective electrode contact in each patient was modeled (C). A probabilistic volume in the posteroventral aspect of the globus pallidus pars interna was identified that could be used to guide future electrode placement or programming. Colors indicate the proportion of electrodes activating a given voxel location, with hotter colors corresponding with a higher probability of activation (D through F). Modified with permission from Cheung et al.[16]

phenes, indicating proximity to the optic tract, and others select the most ventral contacts that do not produce adverse effects at therapeutic voltage.

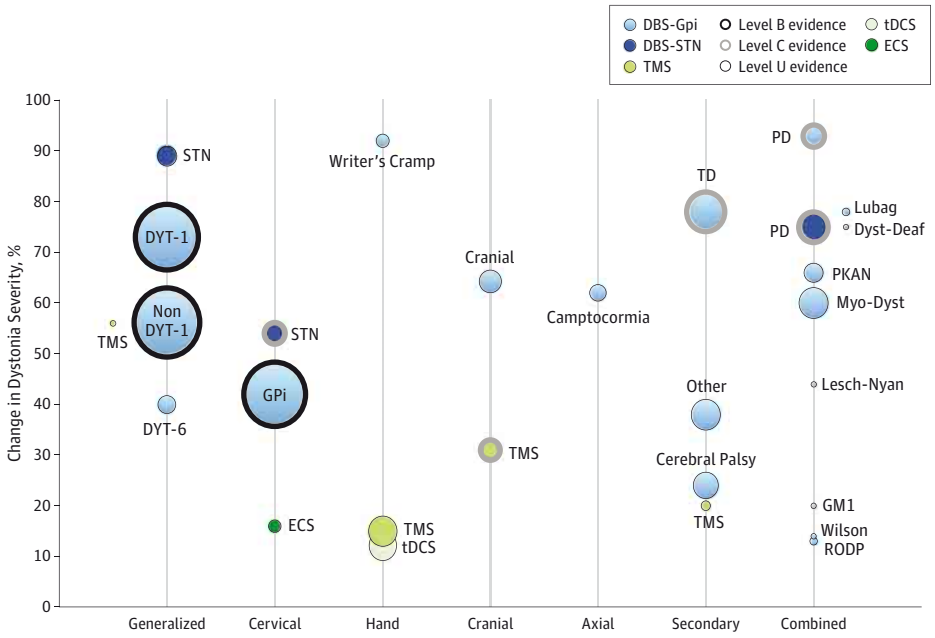
Unlike with Parkinson disease, in which one most often uses the lowest effective stimulus amplitude, increasing it as needed, many neurologists start with a relatively high voltage for dystonia, one just below the adverse effect threshold, and then decrease it to conserve battery power once benefit has been achieved. The most commonly used stimulation settings (frequency, 130-180 Hz; pulse width, 60-210 microseconds; amplitude, 2-5 V) are based on published trials,[5] although some evidence suggests that lower stimulation frequencies (60-80 Hz) may be equally effective in childhood dystonia while prolonging battery life. Patients return for evaluation and programming adjustments every few weeks for the first few months and then every 3 to 6 months for the first 1 to 2 years. Patient responses are often quantified using standardized scales, such as the Burke-Fahn-Marsden Dystonia Rating Scale or the Toronto Western Spasmodic Torticollis Rating Scale. Although useful for measuring improvement following DBS, these scales can be insensitive to small changes; therefore, assessment often must be individualized to address the patient's most disabling or bothersome symptom.

The trial-and-error approach routinely used for DBS programming was developed largely on the experience of providing treatment for patients with Parkinson disease and essential tremor for whom the therapeutic benefit at different electrode contacts can be rapidly assessed. Given the delayed therapeutic effects characteristic of dystonia, this process is clearly not ideal. Algorithms that allow one to identify the ideal contact and stimulation settings based on neuroimaging, brain connectivity, and modeling of the stimulation field could represent a major advance for programming DBS in dystonia in the near future (eg, Figure 2).[16]

Clinical Results

The results of the clinical studies of DBS for dystonia are summarized in the eTable in the Supplement and in **Figure 3**. Factors relevant for evaluating these clinical trial results include the magnitude of clinical benefit, number of patients studied, and level of the evidence that the intervention works better than placebo. To compile this summary, we borrowed heavily from meta-analyses[9,10] that incorporate the results of numerous individual trials. These data were then updated to include more recent studies or additional indications not covered by the original meta-analyses. Although much of the efficacy data were derived from open-label studies, prospective randomized clinical trials with double-blind assessments have been completed in patients with generalized or segmental primary dystonia and cervical dystonia, both demonstrating that GPi DBS is superior to sham stimulation.[3,4] Pallidal stimulation for generalized or segmental dystonia stands out as the best-studied therapy, with the most patients and largest effect sizes.[4,18] Greater clinical improvements have been reported in patients with the *DYT1* mutation than in patients with the *DYT6* mutation or with an unknown cause of their primary generalized dystonia, although the latter also do well. Improvement in severity scores following DBS for cervical dystonia is less impressive than in generalized dystonia; however, other clinical features (eg, pain and disability) may improve to a greater extent, yielding significant functional benefit.[3] Similarly, in patients with myoclonus dystonia, the improvement in myoclonus can be more dramatic than the improvement in dystonia severity (73% vs 53%).[10] Deep brain stimulation appears very effective for alleviating dystonia associated with Parkinson disease, tardive dystonia, and writer's cramp, although the latter is supported by limited evidence in few patients. Patients with secondary dysto-

Figure 3. Evidence of Efficacy for Brain Stimulation in Dystonia



Each bubble represents the evidence that a particular type of brain stimulation is effective for a particular type of dystonia. The position of the bubble along the y-axis indicates the mean improvement in dystonia severity; the size of the bubble, the number of patients studied; and the bubble outline, the quality of the evidence assessed by American Academy of Neurology criteria (level B, thick black outline; level C, thick gray outline; level U, no outline). Treatments with the best evidence of efficacy have larger bubbles higher on the graph and are outlined by darker lines. DBS indicates deep brain stimulation; Dyst, dystonia; DYT-1, generalized dystonia due to mutation in the *DYT1* gene; DYT-6, generalized dystonia due to mutation in the *DYT6* gene; ECS, epidural cortical stimulation; GM1, GM1 gangliosidosis; Gpi, globus pallidus pars interna; Myo, myoclonus; PD, Parkinson disease; PKAN, panthothenate kinase–associated neurodegeneration; RODP, rapid-onset dystonia parkinsonism; STN, subthalamic nucleus; TD, tardive dyskinesia; tDCS, transcranial direct current stimulation; and TMS, transcranial magnetic stimulation.

nia, particularly those with static encephalopathy, exhibit modest responses to DBS and more complication rates compared with patients with primary dystonia.[9] Nevertheless, a 24% reported mean clinical improvement in dystonia severity can still result in clinically meaningful benefit.[19]

In a comparison of surgical targets, GPi DBS is supported by higher-quality evidence in more patients and thus remains the target of choice.[8] However, small studies[20] of subthalamic nucleus DBS for dystonia have reported large effect sizes and potentially different adverse effect profiles, with a lower incidence of bradykinesia and a higher incidence of dyskinesia relative to GPi. Further work directly comparing the 2 targets is required before definitive conclusions can be made.

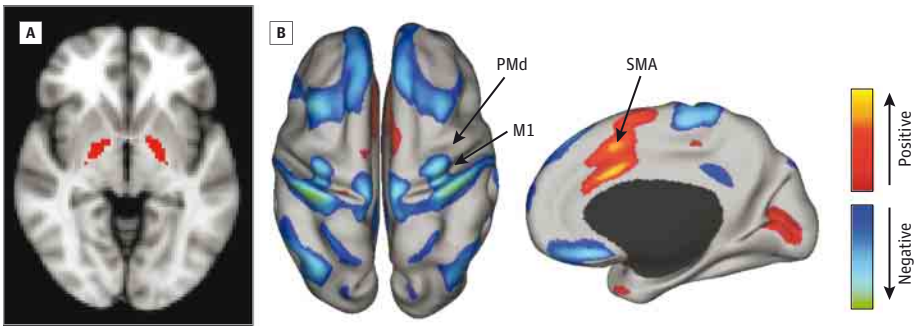
Regarding the time course of improvement, months of DBS may be required before any clinical benefit is observed and full benefit may not be realized for 1 year or longer. Phasic or active dystonic movements generally improve more rapidly than do fixed dystonic postures. In cervical dystonia, pain induced by muscular contractions may improve before and independent of any change in head position. Because of the relatively static nature of most dystonia subtypes, the response to DBS appears to be durable. Longer-term follow-up has documented continued benefit out to 5 years[21] and even 10 years.[17]

Risks

Deep brain stimulation poses 3 types of risk: surgical, stimulation related, and hardware related. For all patients who undergo DBS (including those with Parkinson disease and tremor) the risk of intracranial hemorrhage is reported to be approximately 3%, the risk of permanent neurologic morbidity is approximately 1%, and death within 30 days of surgery is 0.4%; however, these rates are likely to be lower in patients with dystonia who are significantly younger on average than patients with Parkinson disease or essential tremor. The rates of hardware malfunction or infection requiring rehospitalization vary but can be as high as 10% over time.[5] In a recent trial[3] of DBS for cervical dystonia, the risk of serious adverse events was 26%; of these, 8% failed to resolve. Adverse events related to stimulation include slurred speech and parkinsonism, although these effects generally resolve with cessation of therapy or adjustments in stimulation settings.[17] Although not common, suicide has been reported[3,17] in patients with DBS for dystonia, generally in patients with presurgical suicidal ideation. Some diseases, including cerebral palsy and dystonia secondary to structural lesions, may have a higher complication rate owing to a greater number of medical comorbidities.

Of all the potential complications associated with DBS, infection is the most common and can be disheartening in patients who have achieved a robust treatment response. In most instances, infected components must be explanted, temporarily interrupting therapy. Because most infections occur at the chest pocket, rapid removal of the PG and the extension, followed by aggressive antibiotic therapy, can salvage the brain lead, thereby minimizing the risk and difficulty of reimplantation. Children younger than 15 years are particularly prone to infection; therefore, lower profile implantable PGs may be advantageous in this group.

Figure 4. Location and Functional Relationship Between Invasive and Noninvasive Brain Stimulation Sites in Dystonia



A, The globus pallidus pars interna, the primary target of deep brain stimulation for dystonia, is shown in red. B, Resting-state functional connectivity with this deep brain stimulation site identifies positive and negative correlations on the surface of the brain potentially amenable to noninvasive brain stimulation. Prior targets of noninvasive brain stimulation are identified including primary motor cortex (M1), dorsal premotor cortex (PMd), and supplementary motor area (SMA). Modified with permission from Fox et al.[24]

Alternatives to DBS

Although highly effective in properly selected patients, DBS therapy involves risks, discomforts of surgery, and long-term limitations. Difficulties posed by the chronically implanted device include ongoing risk of infection, skin breakdown, wire breakage, device malfunction, and periodic battery replacement surgery and/or device recharging. Furthermore, DBS currently precludes the use of body MRI under any conditions and brain MRI can be performed only under restrictive conditions. These risks and limitations are motivating research into less-invasive brain stimulation alternatives, such as epidural cortical stimulation, in which electrodes are implanted on the surface of the brain, and completely noninvasive techniques, such as transcranial magnetic stimulation and transcranial direct current stimulation. Although use of these latter techniques in dystonia remains investigational, we include them in this review to provide a comparison between modalities and because dystonia patients who are candidates for DBS increasingly express interest about these alternative technologies (eTable in the Supplement and Figure 3).

Compared with DBS, noninvasive brain stimulation and epidural cortical stimulation have been studied[12] in a far smaller number of patients and with lower effect sizes. There exists significant heterogeneity in trials of noninvasive stimulation for dystonia. Targets have included the premotor cortex, primary motor cortex, and the supplementary motor area. Stimulation has been applied at rest and during specific tasks, which may prove important as evidenced in at least one study[22] of patients with musician's dystonia. The only randomized clinical trial without an accompanying conflicting report evaluated transcranial magnetic stimulation to the anterior cingulate/supplementary motor area for blepharospasm.[23] How targets used for noninvasive brain stimulation relate to those used for DBS is a topic of active investigation[24] (**Figure 4**).

Mechanism and Future Directions

At present it is unclear how electrical brain stimulation yields therapeutic benefit in dystonia or any disorder, which is an important limiting factor in the further development of the therapy. Research directed at this question is hampered by restrictions imposed by the US Food and Drug Administration regarding the performance of brain MRI in patients with implanted DBS devices and the ethical complications surrounding the use of radioligands for performing serial positron emission tomography, particularly in children. To address this gap in our knowledge, efforts are under way at multiple centers, including ours, to develop low-energy functional MRI techniques to study the acute and long-term effects of DBS.

The fact that the clinical response to DBS is delayed for days or weeks and that some patients who have received DBS treatment for many years may not experience a return of symptoms for prolonged periods of time after stimulation ceases, suggest that in dystonia, DBS may induce neuroplastic changes that are as yet unknown. Increasingly, dystonia is conceptualized as a neural network disorder[25,26] and brain stimulation as a network-based therapy.[24] As such, brain connectivity and network considerations may help us to better understand stimulation effects and guide the discovery of new therapeutic targets and the selection of optimal contacts and settings for stimulation within a target. Recent evidence[27] suggests that disrupting pathologic oscillations within these networks plays a role in alleviating phasic dystonic movements. The disruption of pathologic rhythms occurs rapidly with the onset of stimulation and, consistent with this notion, phasic movements in dystonia can respond quickly to DBS. However, fixed dystonic postures that take longer to respond may require brain network reorganization, which is a more slowly developing process.

The recent approval of the first responsive neural stimulating device for the treatment of refractory epilepsy has heightened expectations for the development of closed-looped DBS systems for the treatment of other conditions including dystonia. Analogous to on-demand cardiac pacemakers, these devices generate therapeutic impulses only when an abnormal rhythm is detected. The battery-conserving properties of such an approach could prove particularly valuable in dystonia, which often responds only to stimulation parameters that deplete batteries quickly.

Finally, despite increasing interest in noninvasive stimulation for dystonia, it is clear that significant additional research is needed before these therapies replicate or even approximate the responses currently achieved with DBS. Critical factors that may limit the ability of these noninvasive techniques to achieve signifi-

cant results in dystonia include the fact that (1) at present, only the cortex may be targeted unlike DBS, which targets subcortical structures; and (2) these noninvasive techniques provide intermittent stimulation, which may be insufficient to achieve the desired clinical response. Studies[24] of brain connectivity may allow for identification of noninvasive targets connected to deep brain structures (Figure 4). Moreover, noninvasive stimulation might be combined with a particular physical activity to induce network plasticity in a shorter amount of time.[22] Finally, noninvasive techniques combined with functional imaging studies may reveal cortical regions of interest that may be amenable to stimulation via chronically implanted stimulating devices.

Conclusions

Patients with dystonia not adequately controlled with standard medical therapy should be referred for consideration of DBS, especially patients with generalized, segmental, or cervical dystonia. Deep brain stimulation may also provide benefit in patients with other dystonia syndromes including tardive dystonia, writer's cramp, cranial dystonia, myoclonus dystonia, and off-state dystonia associated with Parkinson disease. Less-invasive brain stimulation modalities may circumvent some of the risks and limitations of DBS but require further research before being considered a therapeutic alternative for dystonia.

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Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: Fox.
Critical revision of the manuscript for important intellectual content: All authors.
Study supervision: Alterman.

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