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REVIEW PAPER

Pediatric indications for deep brain stimulation

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Abstract
Purpose Based on the success of deep brain stimulation (DBS) in the treatment of adult disorders, it is reasonable to assume that the application of DBS in the pediatric population is an emerging area worthy of study. The purpose of this paper is to outline the current movement disorder indications for DBS in the pediatric population, and to describe areas of investigation, including possible medically refractory psychiatric indications.
Methods We performed a structured review of the English language literature from 1990 to 2011 related to studies of DBS in pediatrics using Medline and PubMed search results.
Results Twenty-four reports of DBS in the pediatric population were found. Based on published data on the use of DBS for pediatric indications, there is a spectrum of clinical evidence for the use of DBS to treat different disorders. Dystonia, a disease associated with a low rate of remission and significant disability, is routinely treated with DBS and is currently the most promising pediatric application of DBS. We caution the application of DBS to conditions associated with a high remission rate later in adulthood, like obsessive-compulsive disorder and Tourette's syndrome. Moreover, epilepsy and obesity are currently being investigated as indications for DBS in the adult population; however, both are associated with significant morbidity in pediatrics.
Conclusion While currently dystonia is the most promising application of DBS in the pediatric population, multiple conditions currently being investigated in adults also afflict children and adolescents, and thus warrant further research.

Keywords Deep brain stimulation · Pediatric · Dystonia · Obsessive-compulsive disorder · Tourette's syndrome · Epilepsy · Juvenile parkinsonism · Obesity

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Introduction

The treatment of pediatric neurological disorders often arises from modifications of treatments of similar conditions in adult patients. The use of neurostimulator devices, such as deep brain stimulators, in pediatric patients has an interesting but limited history. Deep brain stimulation (DBS) is the surgical treatment of choice for many adult patients with advanced Parkinson's disease (PD) and other movement disorders and is under investigation for use in the treatment of psychiatric conditions like depression, obsessive compulsive disorder, obesity, and addiction [53, 58, 77, 92, 95]. The clinical, therapeutic effects of high frequency DBS appear to mimic those of stereotactic ablations, although modification (both activating and inhibitory) of neuronal activity and circuits may be the mechanism of action of DBS at varying frequencies [17, 32]. While DBS can produce effects similar to ablation, it also provides added safety and flexibility due to its reversibility and titratability [64, 122]. Based on results obtained in adult patients, it is reasonable to assume that the application of DBS in children is an emerging area worthy of further study.

While the application of DBS in adults continues to expand, pediatric indications for DBS have been more limited. Some have advised that this application in pediatric populations needs to be approached carefully [42], while others posit that DBS may be particularly suited to use in the developing brain. For example, its reversibility and titratability allow adjustment of the treatment throughout development and its relative preservation of anatomy without inducing significant tissue damage may allow for future treatment modalities even after DBS intervention [30]. Importantly, many of the adult patients who do not fare as well after DBS surgery for PD are elderly and have mild cognitive impairment prior to surgery [56]. This would not be as much of a concern in the pediatric population. Furthermore, as our understanding of the mechanism of DBS improves combined with the ability to dissect neural circuitry using novel techniques such as optogenetics [51, 75, 175], the applications of DBS in pediatrics will no doubt expand. Nevertheless, careful attention will need to be paid to the ethical and medical issues that apply to the pediatric community. Moreover, the purpose of this paper is to outline the current movement disorder indications for DBS in the pediatric population, and to describe areas of investigation, including possible medically refractory psychiatric indications

Deep brain stimulation for pediatric movement disorders

We performed a structured review of the English language literature from 1990 to 2011 related to studies of DBS in pediatrics using Medline and PubMed search engines. The search employed various combinations of key words, including "deep brain stimulation," "pediatrics," and "children," and we expanded the search to include the terms "movement disorders," "neuropsychiatric," "psychiatric," "basal ganglia," "nucleus accumbens," and "hypothalamus". The search was expanded using the "Find Similar" and "Find Citing Articles" features of Medline and the "Related Articles" feature of PubMed, as well as the bibliographies of selected publications. We only included studies of DBS performed in the pediatric population (<21 years of age) or studies which clearly delineated the data obtained from adult and pediatric populations. Twenty-four reports of DBS in this age group were found and are summarized in Table 1. We excluded studies of DBS performed in adults.

Dystonia

The most common indication of DBS in the pediatric population to date is dystonia. Dystonia is defined as a syndrome of sustained muscle contractions, frequently causing twisting and repetitive movements or abnormal postures [38]. Prevalence estimates for primary dystonia fall between 111 and 3,000 per million, depending on the population and age of onset [31]. Dystonias can be classified as primary, where dystonia is the only clinical sign of disease, or secondary, where dystonia is secondary to another disease process such as traumatic brain injury [18, 74, 110]. Primary dystonias can be generalized (primary generalized dystonia), segmental (affecting adjoining parts of the body), or focal (affecting one muscle or a group of muscles). Many primary dystonias have been found to be associated with genetic mutations and deletions [110]. Medical management includes levodopa, anticholinergics, baclofen, botulinum toxin injections, and others, but these options do not relieve symptoms in all patients [135].

Intrathecal baclofen (ITB) administration has emerged as a surgical treatment option for both dystonia and spasticity in the pediatric population [126]. Baclofen is a GABA agonist that, in the case of dystonia and spasticity, is thought to exert its therapeutic effects on neurons in the spinal nerve roots and cortex. Baclofen can be administered orally, directly into the thecal sac, or intraventricularly. When administered orally, baclofen does not adequately cross the blood–brain barrier to impart its therapeutic effects. Thus, it is often administered directly into CSF, either as a bolus or as a continuous infusion, via a pump [7]. As a treatment for dystonia, both intraventricular and intrathecal baclofen (ITB) have been found to be associated with clinical improvement, although intrathecal administration has been more thoroughly examined [6, 8, 112]. In a trial of ITB for pediatric patients with dystonia, families of patients who received the treatment reported an increase in quality of life and ease of care of 86 %; reduced dystonia scores were also observed at follow-up of as long as 24 months [8]. Another study of patients receiving intraventricular baclofen for the treatment of generalized dystonia reported a reduction of mean Barry–Albright dystonia scores from 23 to 8 [6]. Secondary dystonias, such as those arising from cerebral palsy, tend to respond especially well to ITB therapy, while primary dystonias do not. Especially severe cases of dystonia, such as those associated with neurodegeneration with brain iron accumulation (NBIA), can respond suboptimally both to medical management and ITB. Risks associated with this treatment include surgical complications and baclofen withdrawal as a result of equipment malfunction, a potentially fatal event [7]. The incomplete efficacy of ITB therapy and pharmacotherapy in the treatment of dystonia has motivated the development of novel and more aggressive treatments such as DBS.

DBS has been approved under a humanitarian device exemption for use in the treatment of dystonias in both adults and children [98]. DBS of the globus pallidus internus (GPi) has been established as an effective, safe treatment for medically refractive dystonia in adults [166]. Choice of this target stems from the success of GPi

Table 1 List of reviewed articles along with relevant characteristics and findings from each

Authors	Year	Number of patients	Mean age	Condition	Neural target	Findings
Tormenti et al.	2011	1	6	Dopa-responsive dystonia (secondary to tyrosine hydroxylase deficiency)	STN	Dystonic movements improved, gained ability to speak single words, reduced dose and frequency of carbidopa/levodopa
Marks et al.	2011	14	14.95 (7.90–26.70)	Dystonia (secondary to cerebral palsy)	GPi	Significant improvement in BFMDM, BFMDD, in patients before and after reaching skeletal maturity
Mahoney et al.	2011	7	11.58	Dystonia (secondary to pantothenate-kinase-associated neurodegeneration)	Globus pallidus	Stabilization or reduction in BFMDRS, neuropsychological testing improved or stabilized in all but one subject
Haridas et al.	2011	22	13.4	PGD	GP	84 %, 93 %, 94 % median improvement in BFMDRS motor scores at 1, 2, 3 years' follow-up, respectively
Adamovicová et al.	2011	2	17	Dystonia (secondary to pantothenate-kinase-associated neurodegeneration)	GP	3 months post-surgery a 41 % and 81 % improvement in BFMDRS, 4 years a 51 % and 28 % in BFMDRS, respectively
Lai et al.	2010	1		Dopa responsive juvenile parkinsonism	STN	Improvement in tremor and bradykinesia for 6 months, response was not sustained past 6 months
Mehrkens et al.	2010	5	13	PGD	GP	83.5 % mean improvement in BFMRS at 36 months, no therapy-associated morbidity except for mild dysarthria (n=2)
Timmermann et al.	2010	23 (review)	23 (most pediatric)	Generalized dystonia secondary to neurodegeneration with brain iron accumulation	GP	28.5 % and 25.7 % improvement in dystonia severity at 2–6 months and 9–15 months, respectively
Hyam et al.	2010	1 (another was not pediatric)	7	PGD	GP	65 % decrease in BFMDRS at 6 months, patient got an infection with sustained improvement
Valldeoriola et al.	2010	22	30 (includes pediatric cases, but not aimed just at them)	Primary generalized or segmental dystonia	GP	Mean 40 % improvement in physical health-related quality of life scores; mean 38 % and 60 % reduction in disability and motor scores, respectively (BMDRS)
Borggraefe et al.	2010	6	14.3	PGD	GP	72.7 % and 71 % improvement in BFMDRS post-op and 14 months' follow-up, respectively
Jech et al.	2009	1	12	PGD (with status dystonicus)	GP	88 % reduction in BFMDS after 2 months
Elkay et al.	2009	1	19	Status dystonicus secondary to Batten's disease	GP	38 % reduction in BFMDRS score with stimulation
Borggraefe et al.	2008	1	8	Progressive, PGD	GP	97 % and 69 % improvement in movement and disability BFMDRS scores, respectively
Sato et al.	2008	1	9	Hyperkinetic movement disorder	GP, STN	Immediate termination of choreoathetosis and ballistic movements post-op, with return of attenuated symptoms at 18 months; STN stimulation had no effect on symptoms
Peker et al.	2008	1	11	Holmes' tremor secondary to thalamic abscess	Ventral intermediate nucleus of thalamus	90 % reduction in tremor at 2.5 years' follow-up
Mikati et al.	2008	1	11	PKAN	GP	67 % improvement in Bary–Albright dystonia scale; reversion to pre-operative condition after removal of device secondary to infection
Isaac et al.	2008	1	16	PKAN	GP	31.4 % improvement in BFMRDS score; maintained at 2 years' follow-up
Parr et al.	2007	4	11.75	PGD	GP	56 % (27–85 %) and 42 % (5–64 %) improvement in BFMRDS motor and disability scores at 6 months
Lenders et al.	2006	1	9	Autosomal recessive dystonia	GP	BFMDRS movement score decrease of 15 % with ability to walk unaided up to 500 m, at 2 years' follow up
Mariotti et al.	2005	12	15	PGD (±status dystonicus)	GP	46.7 % and 36.1 % mean improvement in BFMRDS movement and disability scores, respectively
Coubes et al.	2004	19	All <17 (average age not reported)	PGD	GP	84.7 % and 62.8 % improvement in BFMDRS clinical and functional score, respectively, at 2 years; children had a greater improvement in clinical BFMDRS score after 2 years (p=0.04)
Cif et al.	2004	1	8	Myoclonus–dystonia syndrome	GP	20-month follow-up showed 81 % improvement in Unified Myoclonus Rating Scale, 86 % improvement in BFMDRS
Thompson et al.	2000	2	9	Choreiform movement disorders	Nucleus ventralis intermedius	18-month follow-up showed "relief of movements"; 4-month follow-up showed improved function of choreic extremity with functional improvements

pallidotomy in the treatment of patients with PD and generalized dystonia [54, 91]. Additionally, functional neuroimaging studies have revealed that GPi-DBS decreases activation of cortical areas that are normally hyperactivated in patients with dystonia [79]. In a randomized, controlled clinical trial with a sham stimulation arm, primary generalized dystonia (PGD) and segmental dystonias responded well to bilateral pallidal DBS, with significant improvements in disability, movement, and physical quality-of-life scores [80]. In addition to adults, this trial included a large proportion of pediatric subjects. Improvements in the Burke–Fahn–Marsden Dystonia Rating Scale (BFMDRS) movement score has been shown to last 36 months after the start of GPi-DBS [104]. GPi-DBS may also be effective for the treatment of focal cervical dystonia, as evidenced by two small series (n=2 and n=3) where decreased dystonia scores were seen up to 15 months after the start of DBS [73, 78]. Although dystonia is the most common pediatric indication for DBS, its effectiveness and safety in this population are not well established. Nevertheless, studies have reported favorable outcomes of GPi-DBS in pediatric patients with PGD as a result of the DYT1 mutation [30], which, according to a recent meta-analysis, appears to confer an advantage for symptomatic improvement compared with those without the mutation [21].

The durability of DBS has been supported by long-term trials [60]. In fact, one group has reported 10-year follow-up of a PGD patient who, at age 28, continues to enjoy the benefits of symptom reduction attributable to DBS [9]. General observations of these patients with ongoing stimulation include an increased effect in patients of a younger age and a maximum effect occurring about 3 years after implantation. One anecdotal report of improvement after DBS in a younger population suggests that intervention with DBS early in the course of PGD is advisable to prevent major disability and the suffering that goes with it [103].

DBS for secondary dystonias may not be as effective, given the variability in symptoms, comorbidities, and the fixed neurologic deficit associated with underlying structural abnormalities of the brain in these patients [37, 159, 166]. Secondary dystonias can arise as a consequence of trauma or neurological diseases like cerebral palsy (CP), NBIA, and Wilson's disease. In a small, uncontrolled series of patients with dystonia secondary to CP, DBS of the GPi was found to offer significant improvements in disability and movement scores [97]. However, lead placement and targeting were variable, which the authors attributed to inconsistencies in clinical manifestations and neuroanatomical abnormalities in the patients. Dystonia secondary to NBIA can be treated with GPi-DBS, but reductions in dystonia severity are generally not as durable or dramatic in degenerative conditions as for primary dystonias [159].

Tourette's syndrome

Tourette's syndrome (TS) is a neuropsychiatric disorder characterized by chronic motor and vocal tics that usually presents in childhood, often in combination with concomitant behavioral disorders including obsessive compulsive disorder (OCD) and attention deficit hyperactivity disorder [81]. Tics are brief movements or sounds that occur intermittently and unpredictably. They can arise from direct brain injury, but more often are associated with TS or other idiopathic tic disorders [157]. The tics associated with TS give relief of a premonitory sensation that is often localizable to the region of the tic and described as an itching, urge, or otherwise uncomfortable sensation [65, 82]. Tics can be vocal or motor, are commonly suppressible (under voluntary control), and are often mixed, occurring with varying frequency and intensity in any given patient, depending on environmental factors like stress, concentration, and social awareness [81]. Tic onset occurs at around 4–6 years of age followed by progressive increase in tic severity until an average of 10–12 years of age, followed by a decrease in intensity such that 50 % at age 18 were free of tics [19, 84]. The prevalence of TS in school-aged children ranges from 0.5 % to 3 % depending on the population studied and the clinical criteria employed [132].

Current management strategies for TS include behavioral and medical interventions. Medical therapy includes, in order of priority, use of alpha-adrenergic agonists (e.g., clonidine, guanfacine), neuroleptics (e.g., haloperidol, risperidone), and the catecholamine blocking agent tetrabenazine, depending on severity of the tic disorder. The effectiveness of traditional and atypical neuroleptics has been confirmed in placebo-controlled trials [35, 134, 139, 144], but the side effects of these classes of D2 antagonists are significant and include sedation, parkinsonism, dystonia, tardive dyskinesia, weight gain, metabolic disorders, and others [130]. These side effects are important to consider when treating TS since chronic use of these drugs begins at such a young age and side effects like sedation may interfere with school work and metabolic effects may have a larger lifetime impact on health. Due to its localized effects, botulinum toxin (BTX) injection may be particularly effective in patients who report a prominent premonitory sensation and an isolated motor tic. The toxin is injected into a muscle group associated with the tic and has been shown to reduce motor tic severity by 39 % in a placebo-controlled study, but benefit from BTX in reducing vocal tics has not been established [83, 99, 147]. The side effects and varying efficacy of current medical management of tics in TS have motivated the development of surgical interventions like ablative surgery and DBS.

Ablative surgery has been under investigation for the treatment of intractable TS since at least 1961. Targets for

ablation have included the thalamus, cingulate gyrus, frontal, and pre-frontal cortex, and others [156]. Side effects include cognitive deficits, hemiparesis, confusion, dysarthria, dystonia, temporary loss of speech, and hemiballism [15, 156]. While some of these side effects were transient, others were permanently disabling, motivating the investigation of DBS as an alternative.

Reports of DBS for TS have largely been limited to the adult population, with the exception of case reports in adolescents. Targets of stimulation vary and include the anteromedial and posteroventral GPi [100], the centromedian–parafascicular (Cm–PoF) nuclear complex of the thalamus, the ventralis–oralis (Voa) complex of the thalamus [5, 128], the subthalamic nucleus (STN) [101], ventral capsule/ventral striatum (VC/VS), and nucleus accumbens (NAc) [174]. Reports of stimulation at these sites show improvement in tic symptoms and in many associated, non-tic symptoms of TS, like self injurious behavior and compulsions, depending on the target [24]. The thalamus is the most common target, as reported in one observational series of 18 patients, whereby tic severity was reduced by 64 % after Cm–PoF/Voa stimulation [142]. No adverse behavioral side effects were seen and improvements in comorbid obsessive compulsive behavior, OCD, SIB, and anxiety symptoms were substantial. A clinical trial of thalamic Cm–PoF/Voa–DBS for TS in which patients were blindly and randomly assigned to stimulation or non-stimulation arms showed a reduction in tic severity of 49 % at 1 year [5]. Side effects of DBS included gaze disturbances and reduced energy levels.

The NAc, with its central role in dopaminergic transmission, is a particularly interesting target for the treatment of TS because of the putative implication of dopamine in the pathogenesis of the disease (as evidenced by the effectiveness of D2 antagonists for treatment of tics) [123, 138, 152]. Stimulation of NAc in a single patient with intractable TS and comorbid OCD was reported to have substantially mitigated the motor and vocal tics as well as concomitant symptoms of OCD, evidenced by a decrease in the Yale Global Tic Severity Scale (YGTSS) and increase in global assessment of functioning [77]. In another single case report, a 38-year-old man with intractable TS and comorbid OCD showed a marked reduction in YGTSS total score, Yale–Brown Obsessive Compulsive Scale (YBOCS), and Rush Video Rating Scale, for 36 months after bilateral DBS of the NAc. Self-injurious behavior and smoking also resolved after the procedure [115]. In contrast to these positive reports, a patient with mild TS but severe OCD was more symptomatic after DBS of VC/VS [23].

DBS for TS in children has not been widely evaluated and case reports have been limited to adolescents, including a 16-year-old with intractable TS who improved substantially after bilateral GPi-DBS. Scores for tic severity decreased by 76 % (motor) and 68 % (vocal), and the impairment score decreased by 100 % at 6 months' follow-up with improvement in comorbid OCD symptoms and quality of life (SF-36) [143]. However, in another report of a 16-year-old with a similar clinical story, DBS of GPi was ineffective. The authors of this second case attribute the difference in outcome a variety of factors, including differences in drug treatment, the presence of an intellectual impairment, and the natural heterogeneity of TS [36]. In a larger series of mostly adult patients undergoing DBS for TS, two patients, ages 17 and 19, underwent Cm–PoF–DBS and, according to the YGTSS, experienced a reduction in tic severity of 69 % (the 17-year-old) and 45 % (the 19-year-old) [142]. No adverse outcomes were seen in these two patients. Anti-tic medication was still required after surgery in both. Long-term outcomes of more than a year have not yet been reported for this age group, and it is not known whether any of the operated patients may have had a reduction in symptoms as would be expected given the natural history of TS. Procedures and outcomes for DBS of these novel targets have not been well established, and thus, many of the side effects are unpredictable. The possibility of unintended psychiatric effects should not prevent the application of DBS to diseases like TS because patients in these situations gain significant symptomatic relief once the psychiatric problems are addressed. The range of these effects and procedures for avoiding and addressing them need to be well established as the field carves a largely cautious path to the application of DBS for TS in a wider pediatric population. In addition to these concerns about the side effects of DBS and the wide variety of targets available for stimulation, application of DBS for TS in young patients is complicated by the variability of disease course. It is reported that 33–50 % of children see a resolution of their tic symptoms at age 18, and about 75 % will see a marked reduction in tic symptoms at the same age [19, 84]. Given the likelihood that symptoms of TS will subside as those affected grow into adulthood, it may be inappropriate to extend DBS treatment for TS to children under a certain age before which it is impossible to determine a probability for symptomatic reduction as a part of the course of the illness.

Juvenile parkinsonism

Idiopathic Parkinson's disease (PD), a progressive neurodegenerative disorder, is characterized by bradykinesia, resting tremor, rigidity, and postural reflex impairment most often with an onset of symptoms at about 60 years of age [85, 172]. At autopsy, neuronal degeneration can be found in a number of subcortical sites, especially the dopamine producing cells of substantia nigra in the mesencephalon, and throughout the brain there is an abundance of abnormal deposits in neuronal cytoplasm of the presynaptic protein alpha-synuclein in the form of immunostain-positive Lewy bodies. Juvenile parkinsonism (JP) is defined as the development of parkinsonian symptoms or signs before the age of

21, while young-onset PD is defined as onset between the ages of 21 and 40 [131, 141]. Patients with JP experience many of the same symptoms as older-onset PD patients, including tremor, bradykinesia, and focal dystonia [140]. Although JP usually resembles adult-onset PD clinically, including a variable natural history and levodopa responsiveness, the etiology of JP is more likely to be genetic. For example, mutations in the parkin and PTEN-induced putative kinase 1 (PINK1) genes have been found in these patients and their families. Additional etiologic factors, such as exposure to possible environmental toxins, have been postulated [158]. Pharmacotherapy of PD and JP includes a variety of dopamine replacement or dopamine enhancing strategies, using the dopamine precursor levodopa and other drugs. Unfortunately, as seen in adults with advanced PD, L-dopa treatment is associated with adverse motor effects such as dyskinesias, focal dystonia, and motor fluctuations. These adverse effects emerge within only a few years of treatment initiation in adult-onset PD [65], and in one group of JP patients, adverse effects were observed after a median time of only 6 months [140]. Given the early onset of JP, this brevity of treatment efficacy with L-dopa is potentially a more significant problem than in the treatment of adult onset PD. Thus, alternative treatments to reduce or delay the development of these motor side effects would be important in the treatment of JP.

DBS of the STN and GPi has been highly successful in the treatment of a subpopulation of patients with adult onset PD [43]. DBS has not been reported for pediatric treatment of JP, but has shown some success in limited reports in adults with PD secondary to mutations that are often implicated in JP. In one series, seven adult patients with two parkin mutations responded well to STN-DBS and after 12 months required lower doses of L-dopa than a control group of PD patients medically managed without surgery [90]. In another series of early onset PD patients undergoing bilateral STN-DBS, those with mutations in the parkin or PINK1 gene were found at 3-year follow-up to respond similarly to historical controls with idiopathic PD [111]. Given that such mutations—and others yet to be identified—are increasingly being found in patients with JP, DBS may be an appropriate therapeutic approach in carefully selected cases. Of course, application of DBS to pediatric JP patients will hinge on determining the underlying disease process in each case. While DBS may offer symptomatic relief in pediatric patients with parkin and/or PINK1 mutations, it may not have the same effectiveness in patients with JP secondary to other causes like mitochondrial disease, environmental exposure, or other neurodegenerative conditions. If DBS is found to be effective in cases of parkin- or PINK1-associated JP, genetic analyses and assessment of family history will be important in the routine evaluation of potential DBS candidates to ensure proper patient selection.

Deep brain stimulation for pediatric psychiatric disorders

OCD

Obsessive-compulsive disorder (OCD) is a heterogeneous neuropsychiatric disease characterized by obsessional symptoms and compulsive acts that cause distress and interfere with daily activities [1, 4]. The cognitive behavioral model of OCD states, roughly, that obsessions cause significant distress while the associated compulsions reduce this distress. The DSM-IV certifies the diagnosis of OCD in children even without insight into the unreasonableness of their obsessions, as is normally required for diagnosis in adults [1]. Comorbidities, including anxiety, depression, and eating disorders, are common with a diagnosis of OCD, occurring in nearly 70 % of OCD patients over a lifetime [66]. OCD has a significant impact on the pediatric population, with an age of onset commonly at about 10 years and a prevalence in children and adolescents of up to 3 %, with subclinical rates of OCD at about 19 % [151, 162]. While 40 % of individuals experience a remission of symptoms, those with early-onset and high severity are at increased risk for persistent disability [148, 151].

OCD is purported to arise from a disturbance of cortico-striato-thalamo-cortical circuits as evidenced by numerous functional and structural imaging studies, including diffusion-tensor imaging of the white matter tracts and measurements of metabolic activity in various regions in these circuits [26, 61, 136, 137]. A meta-analysis of functional imaging of OCD abnormalities has suggested that there are reliable increases in the apparent activity of the head of the caudate nucleus in subjects with OCD but that this difference does not directly provide evidence of involvement of this region in the pathogenesis of the disease. Many brain structures purportedly involved have not been found to be consistently hypo- or hyper-activated in OCD subjects when compared with controls [170]. In addition to abnormal functional anatomy in the pathogenesis of OCD, genetic influences have also been identified. Twin studies have found monozygotic and dizygotic concordance rates that suggest a substantial genetic determinant in the development of obsessive compulsive symptoms [124]. Biochemical dysregulation of serotonin is suggested by the therapeutic effectiveness of selective serotonin reuptake inhibitors (SSRIs), but the results of SSRI therapy in this setting have not been consistent [63, 121].

In a meta-analysis of randomized, controlled treatment trials for OCD, cognitive behavioral therapy (CBT) was found to have a large effect size of 1.45, while pharmacotherapy was associated with a more modest, but still significant, effect size of 0.48 [169]. As such, first line treatment for OCD is always CBT with an emphasis on exposure-

response prevention [45, 47]. Pharmacotherapy is often administered in conjunction with psychotherapy, and includes the SSRIs fluoxetine, fluvoxamine, paroxetine, and sertraline, the non-selective serotonin reuptake inhibitor, clomipramine, and as second-line drug therapy, atypical antipsychotics [70, 96]. The effect size of pharmacotherapy, although modest, has been found to be significantly higher than placebo, and response rates, defined as at least a 25 % reduction in YBOCS scores, range from 42 % to 53 % for the SSRIs used in OCD treatment [47, 96]. Thus, since approximately 50 % of patients with OCD do not respond to accepted pharmacologic treatments, more aggressive therapies for OCD are clearly needed.

Stereotactic ablation has been applied for the treatment of OCD in both the pediatric and adult population. Procedures have included anterior capsulotomy, cingulotomy, frontal leucotomy, and subcaudate tractotomy [87]. There have been no controlled trials. According several case reports and to a 2010 review of stereotactic psychosurgery in adults, anterior capsulotomy was, in general, the most effective of the procedures, with cingulotomy second [67, 71, 87, 88]. The use of the anterior capsule as a target for ablation treatment stems from both structural and functional imaging demonstrating its putative involvement in OCD pathophysiology [62]. The data on successful anterior capsulotomies in the pediatric population are limited to single case reports. In one of these, anterior capsulotomy abolished all obsessions and compulsions in an 18-year-old with 8-year history of OCD [29]. Although much less evidence is available regarding the potential for neurosurgical intervention for treatment of aggressive behavioral disorders, the role of stereotactic amygdalotomy is under investigation in some centers [113].

As with many applications of ablative neurosurgery, the benefits of DBS in OCD as a reversible, adjustable, and safer alternative have become attractive. The use of DBS for the treatment of OCD has been reviewed elsewhere, and its application to the pediatric population has been limited [62, 105]. DBS has been applied to the treatment of OCD in adults and received a humanitarian device exemption from the FDA in 2009 for the treatment of OCD [105]. Neuroanatomical targets have included the anterior capsule and the NAc [46, 49, 52, 53, 59, 116], the STN [93], and the inferior thalamic peduncle (ITP) [68]. Improvement of symptoms after implanting DBS ranges from 38 % (YBOCS score at follow-up) [46] to complete remission [44, 94] depending on the anatomic target and patient population.

A four-center open trial of VC/VS-DBS for OCD reported significant reduction in symptoms along with functional improvements in over 60 % of patients in the trial [52]. An encouraging outcome of the trial was the improvement in results as the study progressed and which may have been due to increased experience with targeting, patient selection, and post-surgical management. Target selection is still under investigation. The rationale of targeting the NAc in DBS for OCD is the implication of reward-system dysfunction in OCD. The results of a functional imaging study assessing NAc activity in OCD patients suggested that patients with OCD may not be able to make beneficial choices because of altered NAc activity during reward anticipation [39]. Additionally, bilateral stimulation of the NAc in a rat model has exhibited a reduction in the firing rate of the orbitofrontal cortex, a region where hyperactivity has been implicated in the pathogenesis of OCD [22, 102]. This involvement of the reward system in obsessive behavior, along with the results of animal studies, has motivated the exploration of NAc-DBS for OCD. Results of small uncontrolled studies of bilateral NAc-DBS for OCD have shown response (defined as a Y-BOCS decrease of 35 % or more) rates ranging from 50 % to 100 % [13, 33, 46, 153]. In a 10-month, double-blind study of STN-DBS for OCD, stimulation was shown to confer a significant reduction in Y-BOCS scores and a significant increase in Global Assessment of Functioning scale when compared to sham stimulation [93].

Despite some promising evidence, the use of DBS to treat OCD, even in an adult population, is still in its infancy. Application of DBS to the pediatric population has not been widely reported since many children remit spontaneously as they grow up. Furthermore, the combination of cognitive behavioral therapy and pharmacotherapy for OCD achieves approximately a 50 % remission rate [125], thereby setting a high standard for comparison with other, more innovative and invasive treatments. Therefore, DBS could play a role as an alternative therapy in carefully selected adults and even children who are refractory to the best medical and psychological treatments up [10, 151].

Deep brain stimulation for treatment of pediatric obesity

Obesity

With over 17 % of American children overweight, and an additional 16 % at risk for becoming overweight, pediatric obesity is a significant public health problem [119]. Moreover, obesity in childhood is associated with a multitude of comorbidities, including type 2 diabetes, heart disease, and an overall increased all-cause mortality [114]. A landmark article in 2005 put the effects of obesity in perspective: because of the obesity epidemic in the USA, the life expectancy of Americans may for the first time decrease in the twenty-first century [120]. In response to this epidemic and to the ineffectiveness of lifestyle changes and other conservative measures, bariatric surgery has become an attractive option for the treatment of adolescent obesity [20, 160]. The criteria for treatment with bariatric surgery are roughly the

same for adolescents as for adults: BMI >35 with a serious comorbidity, or a BMI >40 with only mild comorbidities [129]. In adolescents, Roux-en-y gastric bypass has exhibited a mean 35 % reduction in BMI and almost complete resolution of complications of obesity, such as hypertension and sleep apnea [20]. Despite the benefits of bariatric surgery in this population, peri- and postoperative complications have been reported, and depending on the specific procedure, the complication rate may outweigh possible benefits, particularly for laparoscopic gastric bands [127]. Gastric banding was associated with a high revision rate of 33 % in adolescents in one study [117]. Nutritional deficiencies especially after malabsorptive procedures such as gastric bypass are concerning [11]. These nutritional problems can be prevented with strict compliance and treatment with vitamins. However, the long-term effects of this are unknown in pediatric subjects.

DBS for the treatment of obesity has been explored as an alternative to bariatric surgery. Targets under investigation have included nuclei of the lateral and ventromedial hypothalamus, as well as the NAc [58, 171]. Exploration of these targets has been motivated by findings of changes in functional activity in the hypothalamus and the ventral striatum (where the NAc is located) in obese patients when compared to lean subjects [118, 164]. A detailed discussion of these target choices has been published elsewhere [58]. While the rationale for targeting hypothalamic regions is based on hypothalamic involvement in homeostasis, feeding behavior, and energy expenditure, the rationale for targeting the NAc is based on the reinforcing properties of high-calorie food [58, 154].

Deep brain stimulation for the treatment of epilepsy

Epilepsy

Epilepsy, defined as two or more unprovoked seizures more than 24 h apart in a child over 1 month of age [2], affects about 1 % of all children up to age 16, with children under the age of 1 at the highest risk [145]. Children with developmental disabilities like cerebral palsy, autism, and mental retardation are at a much higher risk for developing epilepsy [14, 34, 50, 76, 161]. Of children that develop epilepsy, about half will have persistent, lifelong illness [146]. The seizures associated with epilepsy, if not controlled, impact negatively on quality of life, employment, martial relationships, and socioeconomic status [145]. Patients with epilepsy report significant concern regarding their independence, ability to drive, and maintain employment [48]. Current treatment modalities for epilepsy in adults include pharmacotherapy with anti-epileptic drugs (AEDs), surgical resection of a seizure-producing brain region, vagal nerve stimulation (VNS), and DBS. AEDs function to decrease neuronal excitability by increasing GABAergic neurotransmission, decreasing glutamatergic neurotransmission, and modulating ion channel behavior and signaling pathways [69, 133]. Unfortunately, while these drugs offer relief to many patients with epilepsy, up to a third of patients undergoing AED treatment will continue having seizures, and for many patients who do remit, achieving remission can take more than 10 years [146]. Even if AEDs effectively suppress all seizure activity, most cause adverse effects, including cognitive impairment, loss of bone density, gum hyperplasia, risk of fetal maldevelopment during pregnancy, and disruption of sleep architecture, among other problems [72].

In patients whose epilepsy is refractory to pharmacotherapy, surgical procedures to resect or disconnect regions of the brain implicated in seizure production are established forms of therapy. Commonly resected regions include the anteromedial temporal lobe and focal regions of the neocortex; disconnection procedures include corpus callosotomy and multiple subpial hemispherectomy [149]. In a large multicenter study of epilepsy surgery, resection procedures were associated with a 75 % remission rate within a year and an increase in overall quality of life [150]. A meta-analysis of epilepsy surgery found that resective surgeries effect a 27–66 % rate of seizure remission, while callosotomies resulted in only a 35 % seizure-free rate [155]. Unfortunately, many refractory epilepsy patients are not surgical candidates and these procedures are associated with a risk of permanent neurologic deficits or death in nearly 4 % of cases [2]. VNS was approved as an adjunct to pharmacotherapy for adults and adolescents age 12 and over with refractory partial onset seizures [106]. The procedure is associated with up to a 50 % reduction in seizure frequency [3], but many patients will not be seizure free.

Because of the ineffectiveness of many of the treatment options currently available, DBS has been investigated as a treatment option for epilepsy [57, 86]. The Papez neural circuit has been described as a route that links hippocampal output via the fornix and mammillary nuclei to the anterior thalamic nucleus. Projections from the anterior thalamic nucleus then travel through the cingulum bundle to the parahippocampal cortex and complete the circuit by returning to the hippocampus. Animal studies have supported the role of this circuit in seizure occurrence [107–109]. Alterations in the Papez circuit have been observed in multiple forms of epilepsy, and its components have become the targets of investigation of DBS for epilepsy, including hippocampus, anterior thalamic nucleus, and mammillary bodies in the Papez circuit, as well as the centromedian nucleus of the thalamus, STN, caudate nucleus, and cerebellum [12, 16, 25, 27, 28, 41, 89, 163, 165, 167, 168, 173].

DBS of the anterior nucleus of the thalamus (ANT) has been the most widely investigated target. A recent multicenter, randomized, controlled clinical trial of DBS of the anterior thalamic nucleus in adults with medically refractory

epilepsy (SANTE) showed a significant 29 % greater reduction in a group stimulated than in a control group with stimulation turned off, while over 12 % of patients became seizure free for at least 6 months [40]. Adverse events from the stimulator implant included implant site parasthesias, pain, and infection; five deaths were reported in the study—none was found to be device related. Although the low rate of remission in this study was disappointing, these patients had failed medical treatment with at least three AEDs and were completely disabled from their illness.

While such results are promising, they are not readily generalizable to a pediatric population. Aside from a few small studies in which an adolescent was included, no data have been published on the use of DBS to treat epilepsy in children. A slight consensus favors ANT as the preferred anatomic target, but other targets need to be explored.

Discussion

Published information covered in this review of the uses of DBS in treating neurologic disorders in children shows promise across a broad clinical spectrum. Medically intractable and severe dystonia is now routinely treated with DBS, and newer applications of DBS in the pediatric population is sure to expand in the near future as evidence from empirical observation and clinical trials I accumulates. A case can be made for early surgical intervention in progressive dystonia as a way of preventing long-term musculoskeletal deformities and functional disability [103]. Furthermore, appropriately early intervention in levodopa responsive juvenile PD is a legitimate therapeutic option to enhance quality of life in young patients facing an uncertain future. However, more evidence is required before DBS can be widely recommended in treating this rare disorder.

Clinical trials of DBS in patients with primary dystonia, especially those with the DYT1 mutation, have been generally positive and have strengthened the rationale for considering DBS when medical therapy is unsatisfactory. Safety is always an issue with surgical intervention, but complication rates have been lowered acceptably with steady advances in surgical technology and the use of sophisticated computerized devices for target identification. With information from such trials, the full scope of outcome and safety data can be weighed by clinicians debating the use of DBS for pediatric dystonia. The relief of symptoms and potential prevention of irreversible motor impairment have made dystonia the most accepted application for DBS in the pediatric population.

OCD and TS, unlike primary progressive dystonia, are associated with a fairly high remission rate by early adulthood [84, 151]. Arguments for the use of DBS in children for diseases that will eventually decrease in severity will need to include a rationale for possible persistence and for marked disability during symptomatic periods. For example, severe OCD or TS (or TS with comorbid obsessive-compulsive symptoms) can cause significant disability as children go through school-age years particularly due to social isolation [151]. If medical therapies are ineffective, it is probable that uncontrolled OCD and TS may markedly hinder a child's social and educational development, irrespective of the possibility of remission late in childhood. DBS offers the possibility of significant relief during a critical transitional time in the life of an affected child, and thus clinical trials should be considered to investigate the role of DBS in treating severely symptomatic TS. Future research on the use of DBS for neuropsychiatric disease in children will need to include the development of reliable methods of assessing disability and the probability of persistent disease.

Neither epilepsy nor obesity are indications for which DBS has been well established in the adult population, and thus they are not yet ready for application in the pediatric population. Despite the fact that randomized clinical trial data have been published for the use of DBS to treat epilepsy, its value is currently unclear. The results of the SANTE trial of using ANT-DBS for epilepsy in adults showed that the treatment is safe, but that it does not result in full remission in 88 % of patients. Challenges that this DBS application faces are wide and range from the choice of an appropriate target (of which there are many proposed) to the types of epilepsy syndromes best treated with DBS. The value of DBS for treating obesity in adults and children is likewise speculative at this time. With a paucity of human data for this application and the lack of consensus on a target for stimulation, research at the level of adult treatment and animal models will need to be performed before pediatric application is pursued.

In addition to the concerns about the effectiveness and safety of DBS in children, the battery life of the internal pulse generator (IPG) portion of a DBS device is of considerable concern for this young population. In a recent analysis, the battery life of a non-rechargeable IPG in treating PD in adults can vary from 9 to 44 months, depending on the neurologic condition, settings, type of device, intensity of use, and number of previous IPG replacements the patient has had [55]. A battery change involves a brief surgical procedure to change the replace the IPG. The young age of pediatric patients would require a considerable number of such battery changes over a lifetime, and as such, these patients will be exposed to a higher risk of surgical complications than adults. As the use of DBS in the pediatric population expands, minimizing exposure to surgery will be important as the IPGs of these patients are maintained. The development of transdermally rechargeable IPGs will be an important step forward for patients who stand to endure many battery changes over the course of treatment of their chronic disease.

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