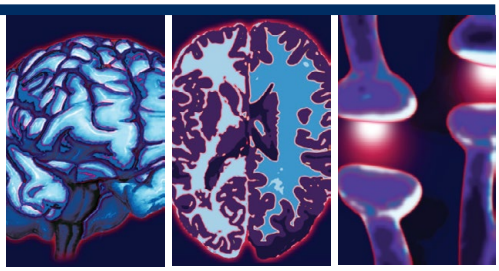
Commentary



Deep Brain Stimulation for Autism Spectrum Disorder: Current and Future Uses

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Summary

Autism spectrum disorder (ASD) is a common and often disabling neurodevelopmental disorder of childhood with limited treatments. Deep brain stimulation surgery (DBS) was recently reported to benefit self-injurious behavior in some patients with low functioning ASD. Currently understood involvement of frontal-basal ganglia circuits in the inhibitory control of movement, thoughts, perceptions, emotions and other functions suggest an important disturbance of this system in ASD. This, in turn, suggests that DBS has potential benefits for higher functioning ASD patients with disabling repetitive motor and non-motor aspects. Experience with DBS for related conditions Tourette syndrome and obsessive-compulsive disorder provides insights into potential benefits and potential DBS targets for ASD. It appears to be rational to pursue systematic research studies of DBS as a treatment for aspects of ASD beyond SIB, particularly other disabling repetitive motor and non-motor features.

Keywords: Autism; Basal ganglia; Brain circuitry; Deep brain stimulation; Surgery; Treatment

Autism spectrum disorder (ASD) is a common childhood neurodevelopmental disturbance. It has an estimated prevalence rate in the U.S. of 1:68 children [1]. Diagnostic criteria for autistic conditions are newly outlined in the fifth edition of the Diagnostic and Statistical Manual of Psychiatry [2]. Current consensus is that the key diagnostic features of ASD include persistent deficits in social communication and social interaction across multiple contexts, such as in social-emotional reciprocity, nonverbal communication or in developing, maintaining and understanding relationships, and restricted, repetitive patterns of behavior, such as stereotypies, repetitive phrases, insistence on sameness, rituals, fixated interests and abnormal reactivity to sensations.

The clinical manifestations of ASD can be quite varied in type and severity. It is likely that the diagnosis encompasses a number of different conditions that remain to be identified and differentiated. Both environmental and genetic etiologies have been described and the fact that a number of different genetic loci have been implicated highlights the etiological heterogeneity of ASD. While the underlying neurobiology of ASD remains largely unknown, dysfunction of a variety of brain circuits have been implicated, including those sub serving social cognition, facial processing, "theory of mind" (acquiring insight into the mental state of others), emotional, sensory and cognitive processing, and attention and focusing [3]. In addition, studies showing widespread decreased connectivity among cortical networks have pointed to a deficit in central processing coherence, potentially explaining why cognition in ASD is often focused on detail rather than global perceptions [4]. Disturbances in a number of neuroanatomic regions have been proposed, including cerebral cortex, cortical white matter, limbic system, and cerebellum/inferior olive [3]. Given the unfortunate lack of understanding of the pathogenesis of ASD, effective treatments

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are largely absent. Treatment for ASD has largely focused on behavioral therapies aimed at reducing disabling symptoms. Medications are sometimes used for symptomatic treatment, such as for self-injurious behavior, mood disturbances, obsessive-compulsiveness and involuntary movements. There are no existing therapies that are based on underlying brain mechanistic disturbances.

Deep brain stimulation (DBS) is a treatment approach that involves stereotactical surgical implantation of electrical leads into specific deep brain targets to provide, from an external generator, focal electrical neural network modulation. It historically evolved from stereotactic ablation/lesioning neurosurgery, but is preferred because the stimulation is adjustable and can be individualized to optimize benefits and minimize side effects and the stimulation can be turned off if needed. The first group of conditions for which DBS was successfully applied was the neurological movement (basal ganglia) disorders, particularly Parkinson's disease (PD), essential tremor and dystonia. The aim has been to correct abnormalities in frontal-basal ganglia circuitry.

While simplified, current neurophysiological conceptualizations suggest that frontocortico-striatal-thalamic-cortical circuits, so important in neurological movement disorders, serve a critical inhibitory ("braking") function for motor outputs. The frontal lobes and their basal ganglia connections importantly allow an individual to stop an action (frontal lobe damage characteristically causes behavioral disinhibition). Thus, in parkinsonian disorders characterized by bradykinesia there is excessive motor "braking" related to nigrostriatal degeneration and dopaminergic deficiency while hyperkinetic involuntary movements, such as chorea, tics and dystonia, are thought to be due to inadequate inhibition resulting in abnormal activation of neocortical motor areas (motor programs) and the expression of repetitive abnormal movements [5]. Such concepts have led to the successful application of DBS for movement disorders with targeting directed at influencing cortico-striatal-thalamic-cortical circuits to increase (e.g., globus pallidus interna [GPi] for dystonia) or decrease (e.g., subthalamic nucleus for PD) "braking" action on motor output. In Tourette's syndrome (TS), DBS has been successfully applied in the treatment of disabling medication-refractory tics, including self-harming tics and compulsions [6]. With this experience in mind, DBS treatment has been reported for 3 patients ASD. All were low-functioning and in each case the main indication was, like some of the initial uses of DBS for TS, severe, medication-refractory self-injurious behavior (SIB). The first case was treated in Germany [7]. He was a 13 year old boy with severe ASD, mental retardation, cerebral palsy and disabling SIB requiring permanent restraints. DBS involving the basolateral amygdala led to a gradual observed improvement of SIB over the first 10 months. Other aspects of ASD, including anxiety, response to auditory and visual stimuli and language improved (he said some words for the first time ever). The amygdala was selected as the target due to its known role in rage, fear and social processing. In addition, structural and functional disturbances in the amygdala and its connections have been reported to occur in ASD [8]. The last two reported cases were treated in the U.S. [9]. One was a 19 year old woman with mental retardation and severe ASD, diagnosed with monosomy 2q and trisomy 20p. She had self-injurious picking behavior and tardive dystonia due to prior antipsychotic medication treatment. DBS involving GPi bilaterally led to marked improvement in the SIB and dystonia which had been sustained past 1 year after treatment. The other case was a 17 year old boy with severe ASD, profound mental retardation, aggressive behavior and disabling SIB. Bilateral DBS involving the GPi and the anterior limb of the internal capsule resulted in substantial initial improvement in SIB, but the benefit disappeared after 6 months and was not regained despite multiple programming adjustments. Although not reported in these ASD cases with SIB, some patients with TS and SIB ended up repeatedly picking at their DBS wires and stimulator resulting in damage to the equipment and infection. This potential problem needs to be considered when applying DBS to the treatment of SIB in patients with ASD.

It is reasonable to consider whether DBS might be an effective treatment for higher functioning ASD patients with problems other than SIB that interfere with optimal functioning. Recent information indicates that the same cortical-basal ganglia circuitry implicated in neurological movement disorders and the target for neuromodulation by DBS is responsible for important "braking" actions on more than just movement [10]. Frontal-basal ganglia pathways

are now known to exert critical inhibitory control (stop signals) for thoughts/cognition, attention, impulses, emotions and complex actions and when disturbed can lead to inattention, distractibility, lability of mood, addictions, and obsessions and compulsions [10].

Although the basal ganglia has not been a brain location of great interest in ASD so far, the repetitive behaviors, interests and activities characteristic of ASD point to a key failure of cortico-striatal-thalamic-cortical inhibitory actions on motor, attentional, emotional and other systems in the condition. Inadequate "braking" of motor output in ASD is implicated by the common involuntary movements of tics, tic-like echolalia and repetitive idiosyncratic phrases, stereotypies, and SIB. There is a failure to inhibit excessive focusing on details or perseverative thoughts. Individuals with ASD often fail to dampen responses to environmental sensations, such as odors, tastes, textures, sounds or lights and there may be unusual interest in sensory aspects of the environment. There is often difficulty regulating emotions and also attention, with the presence of executive dysfunctions typical of basal ganglia disorders. Obsessive-compulsive features are commonly present in ASD, such as preoccupations with unusual objects, monotonous and repetitive activities, excessive smelling or touching of objects, an insistence on sameness, inflexible adherence to routines and rituals, intolerance to change, difficulties with transitions, and rigidity of thinking. Thus, neuromodulation of cortical-basal ganglia pathways by DBS may well be a rational approach for treating some of the repetitive actions and thoughts that can be disabling for patients with ASD.

In support of this possibility, there is a long history of psychosurgical brain ablation approaches in basal ganglia networks for severe obsessive-compulsive disorder (OCD), usually focused on the anterior cingulate, internal capsule, sub caudate tracts and rostral intralaminar and medial thalamic nuclei. More recently, the use of DBS for OCD has been the focus of systematic study by a multicenter collaborative group of research centers in the U.S. and others [11,12]. The U.S. Food and Drug Administration has issued a humanitarian device exemption for the use of DBS for refractory OCD. Several targets have been explored and refined. So far, stimulation of the ventral internal capsule/ventral striatum has the most data and has shown good response rates, even for the severely affected, medication-resistant subjects treated [13]. Given the common presence of obsessive-compulsive features in ASD and the documented success of DBS for severe OCD, it is reasonable to consider that similar benefits might occur for ASD patients with such symptoms. For OCD, all of the DBS targets employed appear to exert their effects at least in part by altering activity in the orbitofrontal cortex, anterior cingulate cortex and striatum [14]. The same targets studied for OCD may be rational for ASD given the apparent need to restore more inhibitory control on thoughts and actions.

Further support for the potential value of DBS in ASD comes from the exploratory use of this approach for Tourette's syndrome (TS) [11,12]. Tourette's syndrome has a number of similarities to ASD. Tics, OCD and attentional deficits are characteristic of both of these childhood-onset neurodevelopmental conditions. Research has pointed to some genetic, neurochemical, and neurophysiologic abnormalities similarities between TS and ASD. For example, genetic mutations linked to both disorders suggest the presence of an imbalance of inhibitory and excitatory brain neurotransmission. To date, DBS has been used around the world for TS patients with disabling tics despite optimal medication therapy [11,12]. In TS, appropriate patient selection criteria for DBS are being worked out and multiple anatomic targets have been employed with the best yet to be established, but nevertheless preliminary application has been successful for many patients. Perhaps relevant to ASD, stimulation of the thalamic centromedian nuclei (CM), the most commonly used target for TS, has been observed to have beneficial effects not only on tics but also for OCD, depression and anxiety [6]. Also, stimulation of a non-motor "limbic" target, the nucleus accumbens/anterior limb of internal capsule in TS, has led to reported improvement in tics [15]. Thus, stimulation of certain targets may lead to multidimensional clinical responses, something that will likely be important for ASD.

A type of non-invasive brain stimulation, repetitive transcranial magnetic stimulation in which intracranial electrical currents are generated by a rapidly fluctuating external magnetic field applied over the scalp, has also shown preliminary evidence of improving

symptoms and physiological measures in patients with ASD [16,17], which lends further support to the notion that electrical circuitry modulation with DBS may be a fruitful approach in the treatment of ASD. Indeed, the disordered circuits linked to ASD, such as those involved in social cognition, facial processing or theory of mind, might be amenable to a neuromodulation strategy with DBS.

For all its indications, DBS has largely been well-tolerated. Rates for potentially serious complications (stroke, hemorrhage, infection) are quite low in the hands of experienced neurosurgeons. Although the mechanisms of action remain unclear, DBS alters neuronal firing patterns, oscillatory/rhythmic activity, information transmission and coherence between different regions in the networks involved [11,12]. DBS may be introducing a new frequency of neuronal communication that interferes with pathological signals. Electrophysiological studies involving auditory stimuli have found that measured oscillatory activity is more frequently out of phase in individuals with autism compared to controls [18] and a deficit in central processing coherence may be present in ASD [4]. When used for OCD, depression and dystonia, clinical improvements after DBS gradually develop over several weeks suggesting that there are effects beyond those immediately influencing networks, such as plasticity changes. Different frequencies of stimulation can be used for neuromodulation for either activation or inhibition of neural circuits.

Based on many clinical characteristics of ASD, it appears rational to implicate inadequate inhibitory influences of the same or closely associated frontal-basal ganglia circuitry often successfully modulated by DBS for neurological movement disorders. As discussed above, experience with DBS for TS and OCD provide relevant information about potentially useful targets for ASD. Novel targets, such as the cerebellum, will need to be considered.

Rational target selection will be a critical aspect for the design of studies of DBS for ASD. It is likely that different targets will be appropriate depending on the most disabling aspect of this clinically heterogeneous condition for each subject. Some targets will be most appropriate for motor impairments and others for non-motor problems. Given the diverse manifestations of ASD, the incorporation of more than one target for stimulation may be logical. Clinical trials will need to carefully establish appropriate enrollment criteria to try to establish clinically homogeneous (e.g., diagnostic criteria, age, gender, severity, target symptoms, presence or absence of mental retardation) subject cohorts when possible. It is likely that subjects with higher functioning ASD than the ones treated with DBS so far will be appropriate candidates if they are impaired by only specific aspects of the disorder. Subjects with self-picking or scratching behavior should probably be excluded, unless SIB is the focus of treatment, due to potential risk of damage to DBS equipment. Valid and reliable endpoint measures are needed, particularly those that focus on functional outcomes. For DBS, control conditions, such as stimulator-off or sham treatment, and blinded assessments are needed. Ideally, biomarkers should be incorporated to help reduce subject heterogeneity, accurately stratify participants to the treatments studied, and utilize objective outcome measures. The application of neurosurgical procedures to neuropsychiatric conditions has always carried ethical and social implications. In studies of DBS for ASD appropriate ethical considerations must be addressed, including the informed consent/assent process for both subjects lacking capacity and those with impaired judgment and reasoning.

While unlikely to be curative, the application of DBS to ASD might be successful as symptomatic treatment for disabling features, particularly those involving repetitive behaviors and thoughts. In this way, DBS involving the GPi has proven successful in improving dystonia caused by a variety of conditions. Families will need to understand that DBS is not viewed as a "cure" for ASD, but rather a treatment to reduce disabling features and improve function and quality of life. The use of DBS in ASD might help sort out some of the phenomenological and etiological heterogeneity of the disorder, possibly by clarifying which particular circuitry is disturbed in individual patients.

In conclusion, current evidence suggests that a deficit in inhibitory action of frontocortical-basal ganglia circuitry is likely involved in some of the key features of ASD. Given the successful and safe modulation of such circuitry by DBS in related

conditions, particularly OCD and TS, a similar approach has prospects for benefits in ASD. It appears to be scientifically and medically rational to pursue careful, systematic study of the efficacy and tolerability of DBS in ASD, particularly for the disabling repetitive motor and non-motor features. Potential targets for initial study are suggested from prior experience with DBS for TS, OCD and the few patients with ASD already treated with this approach.

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