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Deep brain stimulation for autism spectrum disorder

Stefano Marini, Lucia D'Agostino, Carla Ciamarra, Alessandro Gentile

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Abstract

Deep brain stimulation (DBS) is a medical treatment that aims to obtain therapeutic effects by applying chronic electrical impulses in specific brain structures and neurological circuits. Over the years, DBS has been studied for the treatment of many psychiatric disorders. Scientific research on the use of DBS in people with autism has focused this interest mainly on treatment-resistant obsessive-compulsive disorder, drug-resistant epilepsy, self-injurious behaviors (SIB), and aggressive behaviors toward the self. Autism spectrum disorder (ASD) includes a group of developmental disabilities characterized by patterns of delay and deviance in the development of social, communicative, and cognitive skills and the presence of repetitive and stereotyped behaviors as well as restricted interests. People with autism often have numerous medical and psychiatric comorbidities that worsen the quality of life of patients and their caregivers. Obsessive-compulsive symptoms can be found in up to 81.3% of people with autism. They are often severe, refractory to treatment, and particularly difficult to treat. SIB has a high prevalence in severely retarded individuals and is often associated with autism. Drug treatment of both autism and SIB presents a therapeutic challenge. To describe the current state of the art regarding the efficacy of DBS in people with ASD, a literature search was conducted for relevant studies using the PubMed database. Thirteen studies have been considered in this paper. Up to date, DBS has been used for the stimulation of the nucleus accumbens, globus pallidus internus, anterior limb of the internal capsule, ventral anterior limb of the internal capsule, basolateral amygdala, ventral capsule and ventral striatum, medial forebrain bundle, and posterior hypothalamus. In the total sample of 16 patients, 4 were adolescents, and 12 were adults. All patients had symptoms resistant to multiple drug therapy. Many patients taken into consideration by the studies showed clinical improvements as evidenced by the scores of the psychopathological scales used. In some cases, clinical improvements have varied over time, which may require further investigation. Among the new therapeutic perspectives, DBS could be a valid option. However, further, and more in-depth research is needed in this field.

Key Words: Deep brain stimulation; Autism spectrum disorder; Comorbidities; Drug

resistant; New therapeutic perspectives

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Core Tip: Deep brain stimulation (DBS) is a medical treatment that aims at obtaining therapeutic effects by applying chronic electrical impulses in specific brain structures and neurological circuits. Autism spectrum disorder comprises a group of developmental disabilities that are often associated with numerous medical and psychiatric comorbidities that worsen the quality of life of patients and their caregivers. Comorbidities often require multiple drug treatments with an increasing rate of treatment resistance. Thirteen studies have been considered in this paper. Up to date, DBS has been used for the stimulation of the nucleus accumbens, globus pallidus internus, anterior limb of the internal capsule, ventral anterior limb of the internal capsule, basolateral amygdala, ventral capsule and ventral striatum, medial forebrain bundle, and posterior hypothalamus. In the total sample of 16 patients, 4 were adolescents (all males), and 12 were adults (5 males and 7 females). All patients had symptoms resistant to multiple drug therapy. Only one patient was considered not a responder to DBS. Among the new therapeutic perspectives, as evidenced by the studies presented in this article, DBS could be a valid option. However, further, and more in-depth research is needed in this field.

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INTRODUCTION

Deep brain stimulation (DBS) is a medical treatment that aims at obtaining therapeutic effects of certain neurological and psychiatric disorders by applying chronic electrical impulses in specific brain structures and neurological circuits[1]. The modern beginning of DBS can be traced back to the work of Benabid, Pollak, and colleagues at the Joseph Fourier University in Grenoble in the 1980s[2], based on several decades of clinical work and biophysical discoveries[3]. The clinical success of DBS has opened the door to other neurostimulation therapies such as transcranial magnetic stimulation and has motivated an intense analysis of the neural circuits affected by neurological disorders such as Parkinson's disease[4]. The first use of DBS for a psychiatric indication was published by Nuttin *et al*[5] in 1999. Over the years, DBS has been studied for the treatment of obsessive-compulsive disorder (OCD) [6], tardive dyskinesia (TD)[7], treatment-resistant depression[8-10], Tourette's syndrome[11], treatment-refractory anorexia nervosa[12].

Autism spectrum disorder (ASD) includes a group of developmental disabilities characterized by patterns of delay and deviance in the development of social, communicative, cognitive skills and the presence of repetitive and stereotyped behaviors as well as restricted interests[13]. In addition to core symptoms, people with ASD often have numerous medical and psychiatric comorbidities that worsen the quality of life of patients and their caregivers[14]. Obsessive-compulsive symptoms can be found in up to 81.3% of people with ASD. They are often severe, refractory to treatment, may be clinically confused with core symptoms of ASD, and are particularly difficult to treat[15,16].

Self-injurious behavior (SIB) has been defined as "behavior which produces physical injury to the individual's own body"[17]. SIB has a high prevalence in severely retarded individuals and is often associated with autism. Indeed, up to 42% of people with autism may exhibit repetitive SIBs[18]. Additionally, over 75% of children with SIB will have these behaviors persist into adulthood sometimes resulting in serious harm and even death[19-21].

In approximately two-thirds of cases, SIB is maintained by social variables[22], while in approximately one-quarter of cases, SIB occurs independently of social consequences [automatic reinforcement subtype, automatically maintained SIB (ASIB)][23]. ASIB is considered the most challenging subtype to treat, because the events that cause and maintain it are not known. Currently, ASIB is classified into three subtypes[24,25]. Subtype 1 ASIB is characterized by higher rates of SIB in conditions with minimal external stimulation. Subtype 2 ASIB is characterized by high or variable rates of SIB across high and low stimulation conditions. Subtype 3 ASIB is characterized by the presence of self-restraint[26].

Drug treatment of both autism and SIB presents a therapeutic challenge. Some drugs such as risperidone, aripiprazole, and fluoxetine have shown positive efficacy evidence for treating irritability in people with ASD but not for specifically reducing self-harm[27-30]. Currently, the most successful therapeutic strategies for SIBs are based on applied behavioral analysis techniques[31,32] combined

with pharmacological treatments with neuroleptics, mood stabilizers, sedatives, but some patients remain refractory[33].

The present work aims to describe the current state of the art regarding the efficacy of DBS in people with ASD.

A literature search was conducted for relevant studies using PubMed database. In drafting this paper, the authors decided to consider the published articles, classifying them according to the brain regions stimulated by DBS and not according to the pathologies treated.

There are clinical studies on animal models in the literature, but in this article, we will only consider human clinical studies, as we are more interested in the usefulness and efficacy of DBS in clinical practice.

Scientific research on the use of DBS in people with autism has focused this interest mainly on treatment-resistant OCD, drug-resistant epilepsy (DRE), SIBs, and aggressive behaviors toward self. Four studies in the literature have used DBS to treat OCD and other comorbidities in people with ASD [34-37] (see Table 1). Five studies investigated the efficacy of DBS in the treatment of SIB in people with autism[38-42]. A protocol for the application of DBS in children and young adults has recently been published, but the results are not yet available[43]. Furthermore, Heiden *et al*[44] published a retrospective study of the use of DBS in ten patients, including two patients with autism, but the results were not extrapolated for the different pathologies. This makes it impossible to consider the efficacy of DBS in the autistic patients included in the study. Torres *et al*[45] also published a study on the use of DBS for aggression in 7 patients, 5 of whom had autism. The results were not divided for a single patient not allowing to identify of the efficacy of DBS for autistic patients. Recently Benedetti-Isaac *et al* [46] published a follow-up study on the use of DBS in 5 pediatric autistic patients with aggressive behaviors resistant to drug therapy, but the results were not divided by single patient.

In the total sample of 16 patients, 4 were adolescents (all males), and 12 were adults (5 males and 7 females). All patients had symptoms resistant to multiple drug therapy. Generally, treatment resistance consists of three core components: Correct psychiatric diagnosis, adequate treatment, and symptoms not responding adequately despite treatment[47].

USE OF DBS IN PEOPLE WITH AUTISM

In patients with autism, the literature published so far has used DBS for the stimulation of the nucleus accumbens (NAc), Globus Pallidus internus (GPi), anterior limb of internal capsule (ALIC), ventral ALIC (vALIC), basolateral amygdala, ventral capsule and ventral striatum, medial forebrain bundle (MFB), posterior hypothalamus (PHyp).

Three studies[33,34,39] have applied DBS to the NAc of people with autism and numerous comorbidities. Past literature has shown that the NAc may be a key structure for the control of OCD symptoms[48,49], in modulating aggression[50], and in improving the response to social stimuli in ASD [51].

Segar *et al*[34] showed the efficacy of DBS in a 24-year-old female patient with Kleefstra Syndrome with comorbidities of ASD, OCD, and Tourette-like symptoms. The clinical improvements mainly concerned the patient's compulsive behaviors, coprolalia, language, and social interaction, with marked improvement in the global assessment of functioning scores.

In 2019, Doshi *et al*[35] reported a 42-year-old woman with autism who underwent bilateral NAc DBS for control of severe OCD and aggression (violent outbursts against others and hitting and injuring others and herself) refractory to pharmacological treatments. In the days following the surgery, the patient had shown a marked difference in her behavior and eye contact, and appropriate laughter. Clinical improvements were consistent with improvements in administered psychopathology scale scores [Yale-Brown obsessive-compulsive scale (Y-BOCS), Hamilton depression scale, Hamilton anxiety scale, and social communication questionnaire].

Park *et al*[40] observed remarkable clinical improvements in a 14-year-old boy with ASD and SIB treated with bilateral NAc DBS. The clinical improvements (assessed with the Y-BOCS, clinical global impression scale, attention deficit hyperactive disorder rating scale, and social responsiveness scale), were accompanied by functional and structural changes in the brain after DBS, demonstrated using fluorodeoxyglucose positron emission tomography/computed tomography imaging. Furthermore, at the 2-year post-operative evaluation, the boy showed improved language comprehension and expression skills, and improved eye contact.

Two studies[38,41] have applied GPi DBS to people with autism to improve movement impairments. Stocco *et al*[39] applied GPi DBS to two people with ASD, severe stereotypies, and SIB (one patient simultaneously received DBS in GPi and the Anterior limb of the internal capsule). Only the patient who received GPi DBS had maintained clinical improvements over time, even reducing drug therapy. As suggested by the authors, GPi DBS may provide relief for severe pharmacologically unresponsive stereotypies in some patients. Indeed, the characteristics of the ideal patient to be subjected to DBS should be better explored.

Table 1 Summary of deep brain stimulation studies for autism spectrum disorder

Ref.	Patients' age/sex	Diagnosis and comorbidities	Indications for DBS	DBS targets	Pre-BDS scores	Post-BDS scores	Main outcomes
Segar <i>et al</i> [34]	24, F	KS, OCD, ASD, epilepsy	Biting hands, picking skin	NAc	GAF 20	GAF 50-60	Clinical improvements mainly for compulsive behaviors, coprolalia, language and social interaction
Doshi <i>et al</i> [35]	42, F	OCD, ASD, epilepsy	OCD, aggression	NAc	Y-BOCS 19, HAMD 20, HAS 30, SCQ 26	Y-BOCS 5, HAMD 15, HAS 18, SCQ 16	Marked improvements in OCD symptoms, aggressive behavior, eye contact and appropriate laughter
Park <i>et al</i> [40]	13, M	ASD, Developmental Delay	Self-mutilation, face-hitting	NAc	CGI-S 6; ABC 106; CY-BOCS 22; K-ARS 54; SRS 101	CGI-S 4; ABC 40; CY-BOCS 7; K-ARS 36; SRS 98	Decreased in SIB and improvement in verbal communication
Stocco <i>et al</i> [39]	19, F	ASD, ID, monosomy 2q and trisomy 20p	Self-picking, Severe stereotypes	GPI	JHMRS 46	JHMRS 4	Marked improvement in the SIB and dystonia
	17, M	ASD, ID, anxiety	Punching of arms and legs, biting, Severe stereotypes	GPI and ALIC	JHMRS 67	JHMRS 19	Substantial initial improvement in SIB, but the benefit disappeared after 6 mo and was not regained
Kakko <i>et al</i> [42]	19, M	ASD, ID, epilepsy, TD	Aggression, self-mutilation, lacerations	GPI	NR	NR	TD symptoms were markedly improved. The anxiety, behavioral symptoms had ceased
Sturm <i>et al</i> [38]	13, M	Kanner's Autism, ID, infantile cerebral palsy	Self-aggression	Basolateral amygdala	Parental score of 6	Parental score of 2	Decreased in SIB and core symptoms of the autism spectrum in the emotional, social, and cognitive domains
Davis <i>et al</i> [36]	44, M	OCD, ASD, MDD, tics, epilepsy	OCD, aggression	Ventral capsule/ventral striatum	Y-BOCS, MADRS, YGTSS	Y-BOCS, MADRS and YGTSS scores decreased by 68%, 66%, and 75% respectively	The clinical improvements were maintained, albeit with fluctuations, after 3 yr. No effect on core symptoms of ASD
Graat <i>et al</i> [37]	39, F	OCD, ASD, Depressive episodes	OCD	vALIC	Y-BOCS 33, HAMD 27	Y-BOCS 12, HAMD 7	50% reduction of OCD symptoms following DBS, especially obsessions
	54, F	OCD, ASD	OCD	vALIC, then MFB	Y-BOCS 38, HAMD 30	Y-BOCS 18, HAMD 4	Initially did not benefit from DBS. Thereafter OCD symptoms improved and decreased by more than 50%
	32, M	OCD, ASD, ADHD	OCD, aggressive intrusions	vALIC	Y-BOCS 31, HAMD 18	Y-BOCS 23, HAMD 12	Partial responder probably due to several transient side effects of DBS
	31, F	OCD, ASD, DD, OCPD, AN	OCD	vALIC	Y-BOCS 34, HAMD 30	Y-BOCS 32, HAMD 27	Only some subjective improvements
	51, M	OCD, ASD	OCD	MFB	Y-BOCS 34, HAMD 5	Y-BOCS 0, HAMD 2	Obsessive-compulsive symptoms disappeared entirely. Improved confidence and less social

	30, F	OCD, ASD, PDD, GAD, UPD	OCD,	MFB	Y-BOCS 34, HAMD 23	Y-BOCS 22, HAMD 22	shyness 35% reduction of OCD symptoms following DBS
Benedetti-Isaac <i>et al</i> [41]	27, M	ASD, TBI, epilepsy	Aggressive behavior towards self	PHyp	OAS 9	OAS 1	Improvements in seizures, in aggressive behavior, in quality of life, in daily living skills
	16, M	ASD, epilepsy, Developmental Delay	Self-aggression	PHyp	OAS 8	OAS 1	Aggressive behavior controlled for a month. After 2 mo it reappeared as before surgery

ABC: Antecedent, behavior, consequence; ADHD: Attention deficit hyperactive disorder; ALIC: Anterior limb of internal capsule; AN: Anorexia nervosa; ASD: Autism spectrum disorder; CGI-S: Clinical global impressions-severity; CY-BOCS: Children's Yale-Brown obsessive-compulsive scale; DBS: Deep brain stimulation; DD: Depressive disorder; F: Female; GAD: Generalized anxiety disorder; GAF: Global assessment of functioning; GPi: Globus Pallidus internus; HAMD: Hamilton depression scale; HAS: Hamilton anxiety scale; ID: Intellectual disability; JHMRS: Johns Hopkins motor stereotypy rating scale; K-ARS: Korea attention deficit hyperactive disorder rating scale; KS: Kleefstra syndrome; M: Male; MADRS: Montgomery-Asberg depression rating scale; MDD: Major depressive disorder; MFB: Medial forebrain bundle; NAc: Nucleus accumbens; NR: Not reported; OAS: Overt aggression scale; OCD: Obsessive-compulsive disorder; OCPD: Obsessive-compulsive personality disorder; PDD: Persistent depressive disorder; PHyp: Posterior hypothalamus; SCQ: Social communication questionnaire; SRS: Social responsiveness scale; TBI: Traumatic brain injury; TD: Tardive dyskinesia; UPD: Unspecified personality disorder; vALIC: Ventral anterior limb of the internal capsule; Y-BOCS: Yale-Brown obsessive-compulsive scale; YGTSS: Yale global tic severity scale.

Tardive dyskinesia (TD) is probably the most severe form of extrapyramidal symptoms (EPS) secondary to antipsychotic drugs, manifesting usually after months or years of therapy with involuntary choreiform movements and dystonia, frequently affecting the face and tongue[52]. While there are drug treatments for TD, it is often chronic and irreversible. Furthermore, patients with intellectual disabilities (ID) are more susceptible to EPS[53]. Past literature has shown encouraging evidence of DBS in the treatment of dystonic cerebral palsy in children[54]. GPi DBS in a young adult diagnosed with ASD and ID markedly improved TD symptoms[42]. The anxiety, restlessness, behavioral symptoms, and self-destructive behavior have ceased. Furthermore, the patient's skills, especially communication skills, have returned to the level before the presentation of aggressive seizures.

In 2013 Sturm *et al*[38] treated a 13-year-old boy with ASD and SIB with DBS in the amygdaloid complex and supra-amygdaloid projection system. The implantation of the electrodes in the two areas had been made necessary to testify that possible mechanical irritations, micro-lesions or inflammations in the projections of the amygdala were not effective in controlling the symptoms. Only stimulation of the basolateral nucleus of the amygdala proved effective in improving self-harm and core symptoms of ASD in the emotional, social, communicative, and cognitive domains in a 24-mo follow-up.

Davis *et al*[36] subjected a 44-year-old man with treatment-resistant OCD, major depressive disorder, ASD, and tics to DBS. DBS targets were represented by the ventral capsule and ventral striatum. After 3 years, the clinical improvements obtained within 6 mo of the surgery were maintained, albeit with fluctuations. Indeed, the scores on the Y-BOCS and the Montgomery-Asberg depression rating scale indicated that his symptoms were in the mild range, while the scores on the Yale global tic severity scale were much improved. On the other hand, as expected by the authors, full resolution of symptoms was never achieved and the patient continued to experience the clinical features of ASD.

In 2022, Graat *et al*[37] published the results of six patients with refractory OCD comorbid with ASD who underwent DBS of the vALIC or MFB. The efficacy of DBS on obsessive-compulsive and depressive symptoms was tested with the Y-BOCS and the Hamilton depression rating scale, respectively. Considering Y-BOCS scores, four patients were responders (> 35% decrease Y-BOCS), one patient was a partial responder (25%–35% decrease Y-BOCS) probably due to transient side effects of DBS, and one patient was a non-responder (< 25% decrease Y-BOCS), even though she had subjective symptom improvements.

After considering previously published studies[55,56] on the evidence of surgical treatment of the PHyp in aggressive drug-resistant behaviors, Benedetti-Isaac *et al*[41] published the results of PHyp DBS in 5 patients with DRE associated with intractable aggressive behavior. Only two patients among those recruited were also affected by ASD. A 27-year-old man with ID associated with severe autism, reported improvement in quality of life, better access to special education, and improvements in daily living activities. On the other hand, the aggressive behavior of a 16-year-old boy with ID and severe autism, was partially controlled for a month, but after 2 mo it reappeared as before surgery despite stimulation.

Only one study[37] reported adverse effects of DBS. One patient showed severe transient side effects: an infection of the DBS system that required removal of the system and, at a later stage, a suicide attempt (overdosed of quetiapine). Suicidality resolved without changing stimulation settings. Other

transient adverse effects were represented by restlessness, hypomania, tics, impulsivity, agitation, forgetfulness, cramp/joint pain, headache, memory complaints, agitation, hallucinations, and delusions.

CONCLUSION

The multiple comorbidities associated with ASD and the drug resistance in some patients lead to a decrease in the quality of life of patients and their family members or caregivers. To date, DBS has been used in people with autism solely to treat comorbid conditions. Despite encouraging results for the treatment of drug-resistant diseases, positive effects on core symptoms of ASD have only occasionally been reported. Finding new and innovative treatments is a fundamental aspect for those who take care of people with autism and comorbid conditions resistant to conventional treatments. Among the new therapeutic perspectives, as highlighted by the studies presented in this article, DBS could be a valid option to improve the management of disabling pathologies comorbid with autism and consequently the quality of life. However, further, and more in-depth research is needed in this field.

FOOTNOTES

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