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REVIEW

Efficacy and Safety of Neuromodulation Interventions for Autism Spectrum Disorders with Comorbidities: A Systematic Review

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Purpose: Autism spectrum disorder (ASD) is a neurodevelopmental disorder characterized by impairments in social communication and stereotyped, repetitive behaviors or interests. Neuromodulation interventions have been employed in ASD, which can improve behavioral and cognitive outcomes in ASD, especially relief of comorbidities, as shown in preliminary evidence. However, their efficacy and safety remain unclear owing to the lack of high-quality synthetic evidence. We aim to systematically evaluate the therapeutic potential of neurostimulation in ASD and explore its underlying mechanisms.

Patients and Methods: A narrative synthesis of peer-reviewed literature from 2000 to 2025 was conducted, sourced from the PubMed, Web of Science, and Cochrane Library. Seventy-three relevant studies were identified in this paper.

Results: Up to date, noninvasive brain stimulation has become a potential intervention to reduce autism-related symptoms and improve neuropsychological function in ASDs, while a marked alleviation of comorbidities including aggression, anxiety and epilepsy was observed following invasive brain stimulation interventions. Both of the neuromodulation techniques are believed to be safe and well-tolerated.

Conclusion: Neuromodulation interventions could be a hopeful option to improve patients' symptoms and control comorbidities of ASD. Further high-quality trials should be conducted to optimize long-term prognosis of ASD.

Keywords: autism spectrum disorder, comorbidities, noninvasive brain stimulation, invasive brain stimulation

Introduction

As a neurodevelopmental disorder characterized by impairments in social communication and stereotyped, repetitive behaviors or interests, autism spectrum disorder (ASD) affects approximately 1/100 children around the world.[1] Together with these core symptoms, co-occurring psychiatric or neurological disorders are more common in people with ASD, of which attention deficit hyperactivity disorder (ADHD), sleep difficulties, anxiety, depression, and epilepsy are fairly prevalent. Almost 70% of people with ASD experience at least one comorbid psychiatric disorder, whereas nearly 40% individuals may have two or more psychiatric disorders.[2] These coexisting disorders significantly contribute to reduced quality of life and increased mortality of ASDs.

The significant economic effect of ASDs emphasizes the need to explore effective interventions. Now, the major treatments of ASD are based on psychotherapy, such as early intensive behavioral intervention (EIBI), cognitive behavioral therapy (CBT), etc., while only small-to-medium effects of improvement have been achieved.[3] However, recent decades have witnessed a growing interest in neurostimulation techniques in the treatment of ASD. The

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stimulation techniques can be broadly divided into noninvasive brain stimulation (NIBS) and invasive brain stimulation (IBS). The procedures of NIBS are safe and well-tolerated and can be performed in ambulatory settings without requiring sedation. On the other hand, IBS techniques are neurosurgical procedures that implant pulse generators connected to the vagus nerve or brain structures.

In the neurobiology of ASD, it is believed that alterations in whole-brain connectivity during early neurodevelopment contribute to neuropsychiatric symptoms.[4] Some neuroimaging studies have observed abnormal growth in the cortical surface between 6 and 12 months of age and greater brain volume between 12 and 24 months of age in children who were later diagnosed with autism.[5] Neuropathologic studies have demonstrated the presence of an excitation-inhibition (E/I) imbalance within the cerebral cortex in ASDs.[6] Both NIBS and IBS could induce neural activation and modify abnormal brain activity by the use of electricity, which aligns with the pathological neuroplasticity in children with ASD. Additionally, as the major excitatory neurotransmitter in central nervous system, glutamate may be a key neurotransmitter involved in ASD, and abnormal increased levels of the amino acid in ASD patients have been described.[7] Multiple Ankyrin repeat domains 3 (SHANK3), a post-synaptic protein at excitatory glutamatergic synapses, plays a pivotal role in ASD symptoms,[8] and the whole-cell voltage clamp recordings of SHANK3 mutant mice showed that the disruption of the E/I balance may generally be attributed to an enhancement of the glutamatergic activity.[9] In 2021, Moxon-Emre et al found that rTMS treatment course could modulate glutamatergic levels in adults with ASD, which aligned with the hyperglutamate theory of ASD.[10]

Due to a lack of high-quality synthetic evidence, the application of neuromodulation interventions has not been recommended in the guidelines for ASD. Therefore, a systematic review of the up-to-date literature on the therapeutic uses of NIBS and IBS in ASD is still warranted. The primary objective of this systematic review is to evaluate the therapeutic efficacy of NIBS and IBS on core ASD symptoms and common comorbidities in ASDs, and the secondary objective is to assess the safety and tolerability of the interventions.

Materials and Methods

Study Eligibility

We conducted a systematic review of peer-reviewed international literature, utilizing the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[11] A comprehensive literature search was conducted on studies published from January 2000, to December 2024 (updated May 2025), in the PubMed, Web of Science, and Cochrane Library databases. Search terms indicated the diagnoses and interventions of interest: [autism OR autism spectrum disorder OR ASD OR autistic disorder OR autistic spectrum disorder OR Asperger's syndrome] AND [Transcranial Direct Current Stimulation OR tDCS OR Transcranial Electrical Stimulation OR Transcranial Alternating Current Stimulation OR Anodal Stimulation tDCS OR Cathodal Stimulation tDCS OR Repetitive Transcranial Electrical Stimulation]; [autism OR autism spectrum disorder OR ASD OR autistic disorder OR autistic spectrum disorder OR Asperger's syndrome] AND [repetitive Transcranial Magnetic Stimulation OR rTMS OR TMS OR Transcranial Magnetic Stimulation]; [autism OR autism spectrum disorder OR ASD OR autistic disorder OR autistic spectrum disorder OR Asperger's syndrome] AND [electroconvulsive therapy OR ECT OR Electroshock Therapy OR Electric Convulsive Therapy OR Electric Shock Therapy]; [autism OR autism spectrum disorder OR ASD OR autistic disorder OR autistic spectrum disorder OR Asperger's syndrome] AND [Vagus nerve stimulation OR VNS OR Vagal Nerve Stimulation]; [autism OR autism spectrum disorder OR ASD OR autistic disorder OR autistic spectrum disorder OR Asperger's syndrome] AND [Deep brain stimulation OR DBS].

Inclusion Criteria

Articles were included if they met the following criteria: (1) original research in a peer-reviewed journal, (2) the study sample included individuals with ASD, and (3) investigated noninvasive or invasive neurostimulation interventions as a therapeutic modality in the management of ASD via open-label trials, controlled trials, or crossover studies.

Exclusion Criteria

Articles were excluded if they met the following exclusion criteria: (1) focused on other disorders that were not ASD, (2) were published in a language other than English, (3) did not include interpretable data, or (4) performed a literature review or meta-analysis.

Screening and Selection of Studies

According to PRISMA guidelines, the literature was collected, read, screened, and extracted independently by two persons, following the principles of extraction. We assessed the reference lists of the retrieved papers to ensure that all relevant articles were included in our review and excluded additional articles that did not meet the inclusion criteria.

Quality Assessment

The selected studies were appraised for quality using the Joanna Briggs Institute (JBI) critical appraisal checklist.[12] The quality appraisal stage was done independently by two authors. The articles were then scored based on their quality scores and classified as having a quality score of less than 50% (low-quality studies), 50% to 75% (moderate-quality studies), or greater than 75% (high-quality studies). Due to the limited number of relevant reports, no studies were excluded based on their quality ratings. However, the quality ratings were used to guide the interpretation of the results.

Data Extraction and Synthesis

Two authors collaborated on each selected article. In cases of disagreement, the decision was made based on the opinion of a third member in the research team. Extracted contents include basic characteristics of the included literature, such as author, year, sample size, age, diagnosis, study design, intervention measures, procedure, outcome, and safety assessment indicators. Extracted data from the studies were analyzed through a narrative synthesis to explore the neuromodulation options for core symptoms and ASD-related comorbidities given the inclusion of a variety of study designs. We synthesized the trials grouped by the types of intervention (NIBS including TMS, tDCS, ECT vs IBS including DBS, VNS). Tables were constructed based on the information extracted, which include key study characteristics such as population, diagnosis, study design, intervention parameters, sham stimulation methods and outcomes.

Results

Study Characteristics

A total of 1722 records were retrieved through electronic and manual searches. Figure 1 shows a schematic overview of the study selection process. After removing duplicate results and excluding studies with irrelevant title and abstract, the results were reduced to 185. The rest of the studies were assessed for eligibility, and a further 112 studies were excluded for reasons indicated in the PRISMA flow diagram. Finally, 73 articles were included and analyzed in this study after excluding those records that did not fulfill the inclusion criteria. Of the total 73 articles, 57 studies primarily described NIBS interventions, and 16 studies described IBS interventions. 27/73 of the included articles were sham-controlled trials. Others included case reports or reviews of case series. The characteristics, design, technical parameters, and outcomes of the included studies are shown in Tables 1–4. The quality ratings of included studies are shown in Appendix 1, Appendix 2 and Appendix 3 in the Supplementary Material. The 25 selected studies were appraised for quality by utilizing the JBI critical appraisal checklist for randomized control trials (RCTs), 22 selected studies were appraised for quality and by utilizing the JBI critical appraisal checklist for case reports, 22 selected studies were appraised for quality by utilizing the JBI critical appraisal checklist for quasi-experimental studies. The majority of the studies (81%) were of a high-quality, 13 studies (19%) were of a moderate-quality. None of the studies were eliminated based on methodological quality evaluation outcomes as the authors wanted to compile a comprehensive list of all potentially effective therapeutic managements.

Regarding the stimulation parameters of TMS and tDCS, there was a large variability. In the NIBS technique, most studies (31/46) chose the left/right dorsolateral prefrontal cortex (DLPFC) as the stimulation target. Four studies employed theta burst

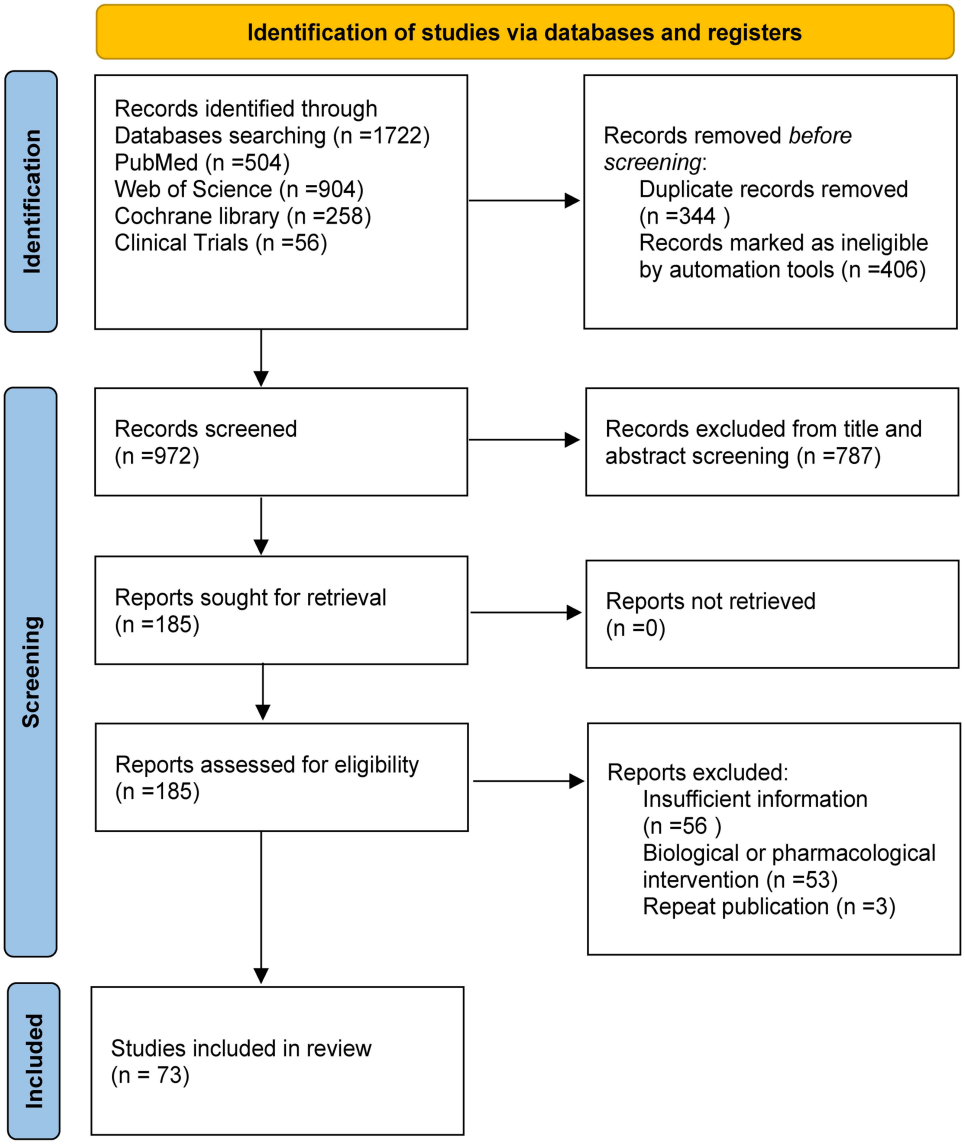

Figure 1 PRISMA 2020 flow diagram for systematic reviews which included searches of databases. From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71T.

stimulation (TBS) protocols, while the remaining 23 studies utilized more conventional rTMS approaches. The main stimulation frequencies were set at 0.5−1 Hz, and the duration of the procedure lasted from 2 to 18 weeks.

On the other hand, IBS, including DBS and VNS, mainly targeted improving the therapeutic effects of comorbidities or specific symptoms in ASD, such as drug-resistant epilepsy and self-injurious behaviors (SIB). A total of seven studies of VNS all focused on patients with both epilepsy and ASD. In 19 cases that were reported in 9 DBS literatures reviewed, validated targets in DBS contain the posterior hypothalamus (pHyp; 5/19),[71] ventral anterior limb of the internal capsule (vALIC; 3/19),[77] nucleus accumbens (NAc; 2/19),[73,74] globus pallidus internus (GPi; 2/19),[70,75] medial forebrain bundle (MFB; 2/19),[77] ventral capsule and ventral striatum (VC/VS; 2/19),[76] anterior limb of the internal capsule (ALIC; 1/19),[70] and basolateral amygdala (1/19).[69]

Efficacy

Noninvasive Neurostimulation

TMS

TMS is placed on the human scalp to activate the targeted cortex using rapidly changing extracranial magnetic fields.[78]

Table 1 Qualitative Summary of TMS Studies with Waitlist or Sham Controls for ASD

Research	N	Age	Diagnosis	Procedure			Outcome
				Frequency (Hz)	Target and Duration	Total Pulses	
[13]	13	17.2	High-functioning ASD	0.5	Left DLPFC, 3 W	900	Reduction in repetitive-ritualistic behavior as measured by the repetitive behavior scales following rTMS subjects; higher Gamma induced by the non-target stimuli in autistic subjects compared to controls at all sites
[14]	25	13.8	ASD	1.0	Bilaterally DLPFC, 12 W	1800	Significant improvement in discriminatory gamma activity between relevant and irrelevant visual stimuli following rTMS; significant improvement in the responses on behavioral questionnaires including irritability, repetitive behavior as a result of rTMS
[15]	13	15.6	High-functioning ASD	0.5	Left DLPFC, 3 W	900	Significant reduction in early cortical responses to irrelevant stimuli and increase in responses to relevant stimuli following low-frequency rTMS
[16]	20	36.6	Asperger's syndrome	1.0	Bilaterally pars opercularis/triangularis, 4 W	1800	Naming improved after rTMS of the left pars triangularis as compared with sham stimulation; naming latency lengthened after rTMS of the adjacent left opercularis.
[17]	45	13	ASD; IQ > 80	1.0	Left DLPFC, 12 W	1800	Significant improvement in both N200 and P300 components as a result of rTMS as well as significant reduction in response errors; significant reductions in both repetitive behavior and irritability according to clinical behavioral questionnaires
[18]	11	17.55	High-functioning ASD/Asperger's disorder	1.0	Left M1,/SMA, 3 W	900	Improvement in movement-related electrophysiologic activity following rTMS
[19]	20	13.5	High-functioning ASD	1.0	Bilaterally DLPFC, 12 W	1800	Significant post-TMS differences in the response-locked ERP such as ERN and behavioral response monitoring measures indicative of improved error monitoring and correction function
[20]	18	13.1	High-functioning ASD	0.5	Bilaterally DLPFC, 18 W	2880	Decrease in irritability, hyperactivity, stereotype behavior and compulsive behavior ratings following 18 TMS; a significant increase in cardiac interval variability and a decrease of tonic SCL
[21]	28	18-59	High-functioning ASD/Asperger's disorder	5.0	Dorsomedial PFC, 2W	1500	A near significant reduction in self-reported social relating symptoms and socially-related anxiety for post-treatment assessments
[22]	45	NR	ASD, mental retardation	1.0/8.0	Bilaterally premotor cortex, 6 W	900	A significant increase in eye–hand performances only when HFrTMS was delivered on the left premotor cortex

(*Continued*)

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Table 1 (Continued).

Research	N	Age	Diagnosis	Procedure			Outcome
				Frequency (Hz)	Target and Duration	Total Pulses	
[23]	54	14.5	ASD	1.0	Bilaterally DLPFC, 18 W	3240	Significant decrease in irritability, hyperactivity on the ABC, and stereotypic behaviors on the RBS-R following rTMS; ERP changes along with increased centro-parietal P100 and P300 (P3b) to targets are indicative of more efficient processing of information post-TMS treatment.
[24]	42	14.6	ASD	1.0	Bilaterally DLPFC, 18 W	3240	Significant improvements in behavioral and functional outcomes in the TMS-NFB group as compared to the WTL group
[25]	44	8-19	ASD	1.0	Bilaterally DLPFC, 18 W	3240	Excessive gamma oscillations and larger ERPs in ASD group as compared to the TDC group; decrease in irritability and hyperactivity scores and repetitive and stereotype behaviors
[26]	27	12.52	High-functioning ASD	0.5	Bilaterally DLPFC, 18 W	2880	Several parental behavioral rating scores improved including stereotypy, hyperactivity and inappropriate speech subscales of ABC, and in total score, ritualistic/sameness, stereotypy and compulsive behavior subscales of RBS-R post-TMS and showed a correlation with autonomic outcomes
[27]	10	9-17	ASD; Impairing restricted and repetitive behaviors	50	Right DLPFC, 3–15W	900	Significant improvements in RBS-R, YBOCS, WSCT and total time for completing Stroop test following iTBS; participants with lower baseline functioning experienced significant EF improvement in the active group.
[28]	124	13.1	High-functioning ASD	1.0	DLPFC, 6/12/18 W	180/ session	Improvement in discrimination between taskrelevant, task-irrelevant illusory figures and motor responses accuracy in an oddball test; significant reductions in aberrant behavior ratings and in both repetitive and stereotypic behaviors
[29]	40	22.58	High-functioning ASD/Asperger's disorder; significant EF impairment	20.0	DLPFC, 4 W	30000	No significant difference in CANTAB SWM total errors and BRIEF-MCI score; significant improvement in EF performance following active rTMS in ASDs with more severe adaptive functioning deficits
[30]	4	11-17	ASD	10.0	Left inferior parietal lobe, 3 W	9000	Trend-level improvements in measures of verbal fluency as well as in social responsiveness at follow-up; a modest improvement in social responsiveness which was sustained after 3 months of follow-up
[31]	38	14.4	ASD	1.0	Bilaterally DLPFC, 18 W	3240	A significant reduction of gamma responses to task-irrelevant stimuli following TMS treatment in ASD; a decrease in irritability, hyperactivity, and repetitive behavior scores

[32]	13	25.5	ASD, major depressive disorder	10.0	Left DLPFC, 25 sessions	75000	40% of participants achieved remission (HAM-D17 ≤ 7) after rTMS treatment; improvement in Informant clinical scales of core symptoms of ASD
[33]	78	8-17	ASD	50.0	Bilateral posterior superior temporal sulcus, 8 W	38400	Greater therapeutic efficacy following 8-week intermittent theta burst stimulation
[34]	29	18-50	High-functioning ASD	20.0	Left motor cortex (M1)	6000	Significant decrease in long-term depression (LTD) in the ASD group following rTMS, indicating hyperplasticity
[35]	56	6.34	ASD	1.0	Bilaterally DLPFC, 9 W	3240	Significant improvement in ABC scores following rTMS; rTMS provides changes in connectivity and behavior.
[36]	32	7.2/7.8	ASD, intellectual disability (IQ < 70)	1.0	Bilaterally DLPFC, 9 W	3240	Significant differences in RR and DET between the experimental group and the control group; discernible discrepancies in the ABC score pre- and post-rTMS for the experimental group
[37]	13	22.7	ASD	50.0	Bilateral posterior superior temporal sulcus, 18 W (a 16-weeks interval)	1200	Baseline social-communication symptoms, concurrent psychotropic medication use and IQ might modulate the effects of iTBS on the clinical symptoms and cognitive flexibility in ASDs.
[38]	15	7-12	ASD	5.0	Right inferior frontal gyrus, 10 days	NR	Increase in VABS subitem scores in the experimental group, including the receptive, expressive, domestic, and community scores; significant improvement in both the subitems of communication and daily living skills domain following 10 sessions of HF-rTMS combined with AOE in children aged 7–12 years with ASD
[39]	60	8-30	ASD	50.0	Left DLPFC, 8 W	9600	8-week inhibitory theta burst stimulation over the DLPFC is safe and feasible in ASD without co-occurring intellectual disabilities; no significant difference on clinical or neuropsychological measurements between active stimulation and sham condition

Abbreviations: N, number; W, weeks; DLPFC, dorsolateral prefrontal cortex; SMA, supplementary motor area; ABC, Aberrant Behavior Checklist; ERP, event-related potential; Y-BOCS, Yale-Brown Obsessive Compulsive Scale; CANTAB, Cambridge Neuropsychological Test Automated Battery; HAM-D, Hamilton rating scale for depression; VABS, Vineland Adaptive Behaviour Scale; NR, Not reported.

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Table 2 Qualitative Summary of tDCS Studies with Waitlist or Sham Controls for ASD

Research	N	Age	Diagnosis	Procedure			Outcome
				Anodal Location	Cathodal Location	Intensity (mA)	
[40]	10	9.8	ASD	Left DLPFC	Right supraorbital region	0.08 /cm^2	A significant improvement of mean vocabulary and syntax scores
[41]	20	6.4	Mild to moderate ASD (CARS-score 30–36.5)	Left DLPFC	Right shoulder contralateral to the anode	1.0	Significant improvements in two domains of ATEC (social and health/behavior domains) following active tDCS; significantly increase in PAF at the stimulation site
[42]	24	12.2	Mild to moderate ASD	Proximal right arm	Left DLPFC	1.0	Significant reduction in the total scores on the three clinical scales including ABC, ATEC and ADI-R during the first 6 months after treatment; significant increase in functional connectivity of the brain
[122]	12	32.1	High-functioning ASD	Bilaterally DLPFC	Bilaterally DLPFC	1.5	Significant improvement in working memory performance after balanced bilateral stimulation of DLPFC compared to sham
[43]	6	28.3	ASD	rTPJ	The ipsilateral deltoid	2.0	A significantly higher score on the verbal fluency test after receiving verum tDCS compared to sham tDCS
[44]	8	24.25	High-functioning ASD; dysexecutive syndrome	The right supraorbital area	Left DLPFC	2.0	Significant improvement in initiation and cognitive flexibility after tDCS
[45]	50	4-14	ASD	The left FC1 and the right FC2	Bilaterally supraorbital areas	1.0	Significant decreases in total ATEC scores, sociability sub-scores, behavioral, health, and physical condition sub-scores in the tDCS group
[46]	29	NR	ASD	The right temporal-parietal junction	NR	2.0	Anodal HD-tDCS significantly increased fixation time and fixation count in the mouth area.
[47]	12	25.08	ASD	The right vlPFC	NR	1.7	No improvements in cognitive flexibility following tDCS stimulation
[48]	14	10.7	ASD	vmPFC; r-TPJ	Left shoulder	1.0	Activation of the vmPFC with anodal tDCS significantly improved ToM in children with ASD compared with rTPJ tDCS and sham stimulation.
[49]	41	14-21	ASD; IQ≥60	Right supraorbital region	DLPFC	1.5	Significant improvement in the social function including enhanced emotion recognition and cognitive flexibility compared to sham tDCS
[50]	42	/	ASD traits (high-AQ scores)	rTPJ	Vertex (Cz)	2.0	Faster responses in the false belief and in the self-other judgments of mental features after a-tDCS in the high-AQ group
[51]	32	10.16	ASD	Left DLPFC	Right DLPFC	1.5	Significant improvement of autism symptom severity (ie, communication), theory of mind (ie, ToM 3), and emotion regulation strategies compared to the sham stimulation group
[52]	36	2.25	ASD	Left DLPFC	Right shoulder	1.0	Greater reductions in autism severity in the 5- tDCS and 20- tDCS groups than the control group at days 5 and 14, and months 6 and 12

[53]	60	14-21	ASD; IQ≥60	Right supraorbital	DLPFC	1.5	Significant improvement in overall social functioning and information processing efficiency during cognitive tasks in the active cathodal tDCS compared to sham tDCS
[54]	36	4-14	ASD	Bilaterally cerebellar hemispheres	Bilaterally supra-orbital area	1.0	Significant improvement in the brain complexity in ASD children with bilateral cerebellar anodal tDCS
[55]	105	14-21	ASD	Right supraorbital	DLPFC	1.5	A medium effect in improving the overall social functioning and a large effect in reducing RRB compared with the sham tDCS and waitlist control groups
[56]	26	NR	Low-functioning ASD; IQ < 70	DLPFC	Right supraorbital	1.0	Significant improvement in the duration, occurrence, and coverage of microstate A and the ABC scores after tDCS
[57]	30	NR	High-functioning ASD	Left DLPFC	Right shoulder	2.0	10 sessions of anodal tDCS to the left DLPFC led to improved nonverbal intelligence among individuals with ASD.

Abbreviations: CARS, childhood autism rating scale; ATEC, Autism Treatment Evaluation Checklist; ADI-R, Autism Diagnostic Interview; ToM, Theory of mind.

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Table 3 Qualitative Summary of ECT Studies for ASD

Research	Age/Sex	Diagnosis	No. ECT	Outcome
[58]	14, M	ASD, catatonia, depression	13 sessions	A full resolution of the catatonic symptoms (the return of speech, self-care skills, and activity levels) as well as the choreoathetoid movements and facial grimacing after 13 ECT sessions
[59]	17, M	ASD, catatonia, recurrent depression, mild ID	18	ECT improved mobility and facilitated food intake. The patient did not reach his premorbid level of functioning.
[60]	16, F	ASD, mental retardation, catatonia, SIB	25	After ECT 1, the patient was freely verbalizing, interacting, and playing with staff, and self-injury also showed marked reduction. After ECT 2, her catatonic stupor resolved, and she returned to her baseline 3- to 4-year-old functioning level.
[61]	8, M	ASD, mental retardation, prominent mood lability, SIB	>15	A consistent significant reduction in SIB during the 5 weeks of ECT; the patient was able to consistently work on daily structured academic tasks and engage in meaningful family activities.
[62]	18, M	ADHD, SIB	33	The patient attended college and was free of psychiatric symptoms. He continued with M-ECT every 2 weeks in combination with the aforementioned medications, for relapse prevention.
	19, M	High-functioning ASD	12	The patient responded gradually to a course of 18 bilateral treatments; Six months after discharge, he demonstrated only moderate reduction in symptoms of depression, psychosis, catatonia, and tics.
[63]	18, M	ASD, catatonia, congenital sensorineural deafness, mild mental retardation	12 sessions	The boy became more independent with his ADLs and there was no further aggressive outbursts at the time of discharge.
	16, M	ASD, moderate mental retardation, physical aggression	55	Behavioral problems were controlled after treatment number 6, such as reduced stereotyped movements, cessation of posturing, and fewer aggressive episodes.
[64]	19, M	ASD, mild mental retardation, depression, catatonia, SIB	>7	A consistent significant reduction in all problem behaviors including self-injury, aggression, and disruption during the 2 weeks treatment of bilateral ECT
[65]	14, M	ASD, mild mental retardation, catatonia	156	The motor, verbal and behavioral symptoms of catatonia improved throughout the treatments; The patient is now independent for all ADLs with normal oral intake and a 30-pound weight gain since discharge.
[66]	14, M	High-functioning ASD, catatonia	23	The patient achieved significant improvement with about 80% reduction of catatonia after the first phase of ECT, but relapsed due to the lack of maintenance ECT.
	21, F	ASD, catatonia	286	A steady progress in school meeting the goals of her individualized educational plan and a well tolerance after ECT
	17, M	Malignant catatonia	156	The verbal fluency improved and the patient could participate in daily educational programming after M-ECT.
[67]	21, M	ASD, catatonia, depression, SIB	220	Longitudinal cognitive and functional stability in M-ECT in ASD
[68]	16, M	ASD, catatonia, common variable immune deficiency, and von Willebrand disease	181	Treatment with ECT resulted in a gradual decrease in the intensity and frequency of aggression, but discontinuation of ECT precipitated relapse of symptoms.
	15, F	ASD, catatonia, macrocephaly, polycystic ovarian syndrome, and moderate cognitive impairment	105	Episodes of violent agitation decreased dramatically in number following ECT, but withdrawing ECT have resulted in return of spontaneous aggression, with notably decreased functioning.

Abbreviations: F/M, females/males; ADL, activities of daily living; ID, intellectual disability.

The size and direction of the effect can be controlled by varying the frequency and number of stimulation sessions. It is believed that low-frequency repetitive TMS (LF-rTMS, ≤1 Hz) reduces cortical excitability through the activation of inhibitory GABAergic interneurons.[79] This effect was observed in a series RCT studies and also supported by some open-label studies. In RCTs, Baruth et al assessed the effect of twelve 1 Hz rTMS, which showed significant improvement in discriminatory gamma activity at the early stages of visual processing in ASD.[14] Fecteau et al randomly assigned

Table 4 Qualitative Summary of DBS Studies for ASD

Research	Age/Sex	Indication for DBS	Diagnosis	Procedure		
				Targets	Stimulation Levels	Outcome
[69]	13, M	Life-threatening SIB	Severe Kanner's autism, SIB	Basolateral amygdala	2-6.5 V, 120 μs, 130 Hz	CGI 6→CGI 4 Improvement in symptoms of irritability (aggression, self-injury); improvement in self-regulatory skills in response to visual and auditory stimuli
[70]	19, F	Self-injurious stereotypies, tardive dystonia	ASD, aggressive behavior, mental retardation, progressive arthritis,multiple nevi, stereotypies	GPi	3.3 V, 120 μs, 80 Hz	JHMRS 46→JHMRS 4 (13 m) A remarkable improvement in motor stereotypies of 91.3%; a progressive improvement in stereotypies and tardive phenomenon
	18, M	Stereotypies	ASD profound mental retardation, anxiety, aggressive behavior	ALIC, GPi	ALIC: 2.0 V, 210 μs, 100 Hz; GPi: 2.5 V, 120 μs, 100 Hz;	JHMRS 467→JHMRS 19 (3 m)→JHMRS 67 (6 m) An initial improvement of 71.6% in the JHMRS within 3 months after the surgery; stereotypies slowly returned to baseline after 6 months.
[71]	27, M	Aggressive behavior	ASD, DRE, IAB, TBI, ID	pHyp	2.7 V, 90 μs, 185 Hz	OAS 9→OAS 1 The average seizure decrease percentage was 98.5% per month; significant improvement in quality of life
	20, M	Aggressive behavior	DRE, IAB, ID		2.7 V, 90 μs, 185 Hz	OAS 9→OAS 1 The average seizure decrease percentage was 99.5% per month; significant improvement in quality of life
	22, F	Aggressive behavior	DRE, IAB, ID		2.4 V, 90 μs, 185 Hz	OAS 11→OAS 0 The average seizure decrease percentage was 99% per month; improvement in quality of life and better access to special education
	35, M	Aggressive behavior	DRE, IAB, ID		3.0 V, 90 μs, 185 Hz	OAS 9→OAS 6 The average seizure decrease percentage was 50.8% per month; significant improvement in quality of life
	16,M	SIB	ASD, DRE, IAB, ID		2.8 V, 90 μs, 185 Hz	OAS 8→OAS 8 The average seizure decrease percentage was 100% per month; aggressive behavior was partially controlled for a month.
[72]	24, F	Disabling OCD, TS	ASD, OCD, TS, childhood hypotonia, developmental delay	Bilateral VC/VS	6.0 V, 90 μs, 130 Hz	GAF 20→GAF 50–60 Improvement in obsessive-compulsive behaviors, coprolalia, speech, and social interaction

(*Continued*)

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Table 4 (Continued).

Research	Age/Sex	Indication for DBS	Diagnosis	Procedure		
				Targets	Stimulation Levels	Outcome
[73]	14, M	SIB	ASD, SIB	Bilateral NAc	3.0–5.0 V, 90 μs, 130 Hz	CGI-S 6→CGI-S 4 ABC 106→ABC 40 CY-BOCS 22→CY-BOCS 7 Decreases in both the intensity and frequency of the SIBs; an improvement in expression and comprehension language skills, and also better eye contact
[74]	42, F	OCD, aggression	ASD, OCD, aggression	Bilateral NAc	2.6 V, 60 μs, 130 Hz	Y-BOCS 19→Y-BOCS 5 HAMD 20→HAMD 1 HAS 30→HAS 18 SCQ 26→SCQ 16 Significant symptom relief in OCD and aggressive behavior
[75]	19, M	Self-mutilation, several lacerations	ASD, ID, epilepsy, aggressive behavior	GPi	/	Remarkable improvement in TD symptoms, anxiety, restlessness, behavioral symptoms, and self-destructive behavior
[76]	44, M	Treatment-refractory OCD	ASD, OCD, MDD, tics	VC/VS	/	68% decrease in Y-BOCS; 66% decrease in MADRS; 75% decrease in YGTSS; marked reduction in OCD symptoms and depression, receiving positive feedback from his supervisor and peers
[77]	39, F	OCD	ASD, OCD, Depressive episodes	vALIC	/	Y-BOCS 33→Y-BOCS 12 HAMD 27→ HAMD 7 50% reduction of OCD symptoms following DBS, especially obsessions
	54, F	OCD	ASD, OCD	vALIC,then MFB	/	Y-BOCS 38→Y-BOCS 18 HAMD 30→ HAMD 4 Improvement in OCD symptoms and more than 50% reduction of Y-BOCS scores after repositioning the electrodes in MFB
	32, M	OCD, aggressive intrusions	ASD, OCD, ADHD	vALIC	/	Y-BOCS 31→Y-BOCS 23 HAMD 18→ HAMD 12 Some improvement of OCD symptoms following DBS
	31, F	OCD	ASD, OCD, Depressive disorder, OCPD, AN	vALIC	/	Y-BOCS 31→Y-BOCS 23 HAMD 18→ HAMD 12 Reduction of the oppressive feeling of obsessions, but improvement was barely reflected in lower Y-BOCS scores

(*Continued*)

Table 4 (Continued).

Research	Age/Sex	Indication for DBS	Diagnosis	Procedure		
				Targets	Stimulation Levels	Outcome
	51, M	OCD	ASD, OCD	MFB	/	Y-BOCS 34→Y-BOCS 0 HAMD 5→ HAMD 2 Obsessive compulsive symptoms disappeared entirely; improved confidence and less social shyness
	30, F	OCD	ASD, OCD, persistent depressive disorder, generalized anxiety disorder, unspecified personality disorder	MFB	/	Y-BOCS 34→Y-BOCS 22 HAMD 23→ HAMD 22 35% reduction of OCD symptoms following DBS

Abbreviations: DRE, drug-resistant epilepsy; IAB, intractable aggressive behavior; TBI, Traumatic Brain Injury; SIB, self-injurious behavior; TS, Tourette syndrome; MDD, major depressive disorder; ADHD, attention deficit hyperactivity disorder; ALIC, anterior limb of the internal capsule; GPi, globus pallidus interna; VC/VS, ventral capsule/ventral striatum; NAc, nucleus accumbens; MFB, medial forebrain bundle; JHMRS, John's Hopkins Motor stereotypy rating scale; CGI, Clinical Global Impression; CGI-S, Clinical Global Impairment-Severity; CY-BOCS, Children's Yale-Brown OC Scale; HAS, Hamilton Anxiety Scale; SCQ, Social Communication Questionnaire; MADRS, Montgomery-Å' sberg Depression Rating Scale; YGTSS, Yale Global Tic Severity Scale; AN, anorexia nervosa.

twenty adults to receive four sessions of 30-min 1 Hz of both active and sham rTMS stimulation over Broca's area, and naming skills improved after rTMS in Asperger's syndrome participants. Another early open-label study by Sokhadze et al (2009) found that 0.5 Hz of rTMS could improve the inappropriate neuron activation in response to non-target items and reduce repetitive-ritualistic behavior in ASDs.[13] In follow-up studies by Sokhadze et al, individuals with ASD who received 0.5 Hz rTMS over the DLPFC showed improvements in executive functioning, error correction, and a reduction in repetitive and stereotypical behaviors.[15] In 2012, by measuring event-related potentials (ERP) indices during attentional processing in 25 participants with ASD, they confirmed a significant improvement at early and later stages (eg, N200, P300) of visual processing as a result of rTMS, making it possible to deal with visuoperceptual abnormalities in autism.[17] Regarding how to choose the appropriate treatment sessions, Sokhadze et al assigned 124 high functioning ASD children using randomization to receive different number of weekly 1 Hz rTMS sessions (ie, 6, 12, and 18), and argued that the behavior improvements increased with the total number of sessions to some extent, and 18 sessions best facilitate cognitive control and attention.[28]

As a patterned rTMS, intermittent theta burst stimulation (iTBS) is capable of producing a robust physiological plasticity effect in the human cortex.[80] Compared to rTMS, iTBS is shorter in duration and lower in intensity, making it a more convenient choice for sensitive populations, such as children. Ni et al conducted a series of RCTs to evaluate the feasibility and efficacy regarding iTBS. In 2021, they applied iTBS over the bilateral posterior superior temporal sulcus and found that longer courses of iTBS (8 weeks in total) may produce greater efficacy on core symptoms and social cognitive performance in children with ASD.[33] However, they also demonstrated that the impacts of multi-session iTBS on clinical symptoms may be affected by the psychotropic medication use and baseline autistic deficits.[37,39] In a case-control pilot study, Pedapati et al found a difference during the post-iTBS time course of M1 excitability between youth with ASD and their healthy peers, and this might become a potential physiological biomarker of cortical plasticity in ASDs.[81] Another open-label study in 2018 demonstrated improvements in restricted, repetitive behaviors, compulsions, and neurocognitive functioning following 15 sessions of iTBS targeting the right DLPFC in individuals with ASDs.[27]

Behavioral deficiencies, including characteristic symptoms of ASD, motor dysfunction, abnormal reactions to the sensory environment, and visuo-perceptual abnormalities, are common in ASD. Enticott et al conducted a double-blind RCT to demonstrate that deep rTMS to bilateral dmPFC improves social-related impairments.[21] A recent study demonstrated that rTMS could improve movement-related cortical potentials (MRCPs) and eye-hand performance in ASDs.[18,22] Decreasing sympathetic arousal indices has a positive correlation with repetitive and stereotypical behaviors of ASD, whereas rTMS

could reverse the effect by increasing parasympathetic tone. Casanova et al found that 18 sessions of low-frequency rTMS resulted in increased cardiac vagal control and decreased sympathetic arousal, which had positive and negative correlations with repetitive and stereotyped behaviors, respectively.[20,26] Otherwise, Wang et al proposed that 12 sessions of weekly inhibitory low-frequency rTMS, bilaterally applied to the DLPFC, will improve autonomic balance.[82]

rTMS could also be a potential therapy for individuals with ASD and comorbidities, which were validated through a series of pilot studies. Gwynette et al in 2010 concluded that 40% of participants with ASD and major depressive disorder achieved remission after rTMS targeting the left DLPFC.[32] Another Japanese research applied the iTBS treatment targeting the left DLPFC on ASDs with depressive symptoms, and the remission rate was 67%.[83] In 2022, 32 autistic children with intellectual disability who participated in a pilot study to receive 1 Hz rTMS treatment reported a positive influence on brain activity and behaviors.[36]

In recent years, several novel therapies have been developed. In 2023, an RCT study conducted on 15 children with ASD, and combined high-frequency rTMS with action observation and execution (AOE) treatment, which has recently emerged as a mechanism for promoting neuroplasticity in motor function.[38] Another pilot study by Sokhadze et al explored the effects of combining rTMS and neurofeedback in 20 children with ASD and 22 children in the waitlist groups, aiming to upregulate gamma oscillations and operantly condition them.[24] The study showed significant behavioral and functional outcomes compared to the waitlist groups. The results showed improvement in both the subitems of communication and the daily living skills domain. These findings highlight the promising therapeutic potential of TMS, and larger randomized trials are needed to inform clinical recommendations.

tDCS

Another mode of noninvasive neurostimulation is tDCS, which is a similar approach to rTMS but involves passing weak electric currents directly through two electrodes (in the range of 1–2 mA) instead of a coil.[84] It has been shown to modulate neuronal membrane potentials, such that neurons near the anode tend to fire more frequently, while those near the cathode may be less likely to fire.[85] Researchers proposed a series of RCT studies to observe the modulating effects of tDCS through various targets. Hadoush et al applied bilateral anodal stimulation over the left and right prefrontal and motor areas in 50 children with ASD diagnoses, which significantly improved social responsiveness (as evaluated by ATEC scores).[45] Additionally, another RCT study investigated the effects of bilateral anodal tDCS stimulation over the cerebellar hemispheres using resting-state electroencephalography (EEG).[54] Notably, the modulation increased the brain complexity in children with ASD, suggesting alternative neuromodulation pathways beyond traditional cortical targets. Salehinejad et al investigated the contribution of the vmPFC and right TPJ in theory of mind (ToM) abilities of 16 ASD children, which showed the vmPFC could be a potential better target region for the reduction of ASD symptoms.[48] Han et al applied multiple sessions of prefrontal tDCS coupled with cognitive remediation training, which resulted in a marked improvement in social functioning compared to the sham-tDCS group, as measured by the Social Responsiveness Scale-2nd edition (SRS-2), among 105 individuals with ASD.[53,55] In the choice of sessions, Auvichayapat et al compared the efficacy of 0, 5, and 20 sessions of tDCS over the DLPFC in 36 male children with ASD, which demonstrated that both 5- and 20-tDCS significantly reduced autism severity compared to the sham group with sustained improvements for 12 months, however, there was no significant difference between 5- and 20-tDCS groups.[52]

Due to higher levels of spatial focus and cortical excitability, high-definition transcranial direct current stimulation (HD-tDCS) was applied to better elucidate the causality of the correlation between brain excitability and behavioral or cognitive changes in individuals with autism.[86] Two RCT studies examined the effect of HD-tDCS over different targets. Qiao et al demonstrated that right TPJ anodal HD-tDCS can facilitate emotional face processing in 29 participants with high autistic traits.[46] Another RCT study compared the cognitive effects of active and sham anodal HD-tDCS over the right ventrolateral prefrontal cortex (vlPFC), although improvements in cognitive flexibility following stimulation were not observed.[47]

To assess neurophysiological correlates of ASD, some studies reported changes in EEG activity. An RCT study conducted by Amatachaya et al revealed that a single session of anodal tDCS over F3 increased peak alpha frequency (PAF), correlating with improved social and behavioral outcomes.[41] Differences in EEG microstates before and after tDCS were also compared in a pilot study, revealing a marked difference during the treatment period in children with ASD.[56] Integration with neuroimaging, such as fNIRS, allowed researchers to explore the possible neurophysiological mechanisms underlying the effects of tDCS.[49]

ECT

Catatonia has been increasingly recognized as a comorbid syndrome of ASD, which a meta-analysis in 2021 showed that 10.4% of individuals with ASD have catatonia.[87] ECT has been included in treatment algorithms for acute presentations of catatonia in autism, which was supported by a series of case reports.[88] Zaw et al reported in 1999 on a 14-year-old boy with catatonic stupor and autism who experienced remission of such with bilateral ECT, although the core symptoms of autism were not affected.[58] Ghaziuddin et al presented a 17-year-old white male with autistic disorder, depression, and catatonia who received a course of 18 ECTs, which proved life-saving due to his severe weight loss and declining self-care.[59] Similarly, Dhossche et al reported that two men responded to ECT in tics along with other catatonic symptoms and SIBs.[62] He further discussed 2 patients with ASD and mental retardation who experienced persistent symptoms of motor disturbance, functional decline, and episodic aggression.[63] Since 2008, Wachtel et al have reported a series of results about applying ECT in autistic adolescents to improve social activities and reduce SIBs.[60,61,64–67] A 10-year retrospective review of the use of ECT in ASD and/or intellectual disability (ID) analyzed 32 patients, of which 30 (94%) experienced a positive clinical response.[89] Therefore, if catatonia is present in ASDs, ECT may provide a safe alternative to pharmacotherapy or psychosurgery.

Invasive Neurostimulation

DBS

DBS is a surgical alternative that modulates specific brain regions and neurological circuits by applying chronic electrical impulses, which have been reported to be effective in treating hyperkinetic movement disorders. There are several studies on the effects of DBS on the aggressive behavior of ASDs, which mainly have focused on basal ganglia circuits. Sturm et al reported a 13-year-old boy with Kanner's autism and serious SIB, with DBS targeting the amygdaloid complex as well as the supra-amygdaloid projection system, and the stimulation of basolateral (BL) was proven to be beneficial to SIB, emotional, social, and cognitive symptoms of ASD.[69] Two studies targeted GPi DBS to improve movement deficits.[70,75] Kakko et al presented a 19-year-old male with ASD and ID, whose severe movement symptoms led to self-mutilation and sepsis.[75] After implanting electrodes in the GPi target, his anxiety, behavioral symptoms, and self-destructive behavior ceased remarkably. The other research evaluated the effects of stereotypies in two teenagers with autism after implanting electrodes in the GPi or anterior limb of the internal capsule (ALIC).[70] Both patients experienced an initial improvement in motor stereotypies of over 70% within the first few months after DBS surgery, but only one of them maintained this improvement during follow-up.

In addition, the nucleus accumbens (NAc) has been demonstrated to be a key hub for the modulation of aggression and social response in ASD, which was supported by some case reports. Park et al applied bilateral NAc DBS in a 14-year-old boy with ASD and SIB.[73] The remarkable clinical improvement in the frequency of SIBs, as well as expression and comprehension language skills, was observed at the 2-year post-operative evaluation. The other case also targeted NAc as the electrode implantation location for a 42-year-old woman with autism and the comorbidities of obsessive-compulsive disorder (OCD) and aggression, which showed significant symptom relief for severe obsessive-compulsive behaviors, social communication, and stereotyped patterns at the 1-year follow-up.[74] In a middle-aged man with multiple comorbidities (including refractory OCD, epilepsy, tic disorder, autism, and major depressive disorder (MDD)), he received DBS targeted at the vc/vs and reported a significant reduction in OCD symptoms and depression.[76] In 2022, a case series first examined the effectiveness of DBS on OCD symptoms and the safety of DBS in patients with OCD and ASD specifically, which showed that 2/3 patients with OCD and comorbid ASD responded to DBS (decrease ≥35% in Y-BOCS).[77] A study conducted by Benedetti et al analyzed the impact of DBS targeting the posteromedial hypothalamus (pHyp) in nine patients with DRE and intractable aggressive behavior (IAB).[71] The results showed that seizure frequency and aggressiveness were significantly controlled after a follow-up of up to 4 years.

VNS

VNS therapy has been proven safe and effective in reducing seizure frequency and duration in individuals with pharmacoresistant epilepsy. Notably, ASDs have higher rates of epilepsy compared with individuals without ASD (21% in people with ASD and intellectual disability and 0.8% in a general population sample).[90] Preliminary studies also indicated that VNS may improve neurocognitive performance and quality of life in individuals with ASDs.[88,91] A cohort of 59 autistic patients was identified to assess seizure frequency and quality of life after being implanted with a pulse generator.[92] Notably, 58% of the autism patients experienced at least a 50% reduction in seizure frequency, and 76% reported improvement in alertness at 12 months of follow-up. In the largest study to date of VNS therapy in ASDs, there was no significant difference in seizure reduction between individuals with and without autism at 12 months post-implantation, but almost 62% of the patients in the autism group had greatly improved mood compared with the control group ($p = 0.0437$).[93] In addition, Wang et al conducted an observational study of 10 children with drug-resistant epilepsy (DRE) to confirm that VNS therapy makes seizure control stable and has a positive effect on autistic behaviors.[94] However, a prospective study in 8 autistic children with DRE indicated that seizure frequency had not decreased, and cognitive effects had not improved at the 2-year follow-up.[95] There is still limited data on VNS therapy in ASD, which emphasizes the need to evaluate the efficacy of this technique further. Figure 2 shows the indications of neuromodulation techniques and potential mechanisms that lead to the effects.

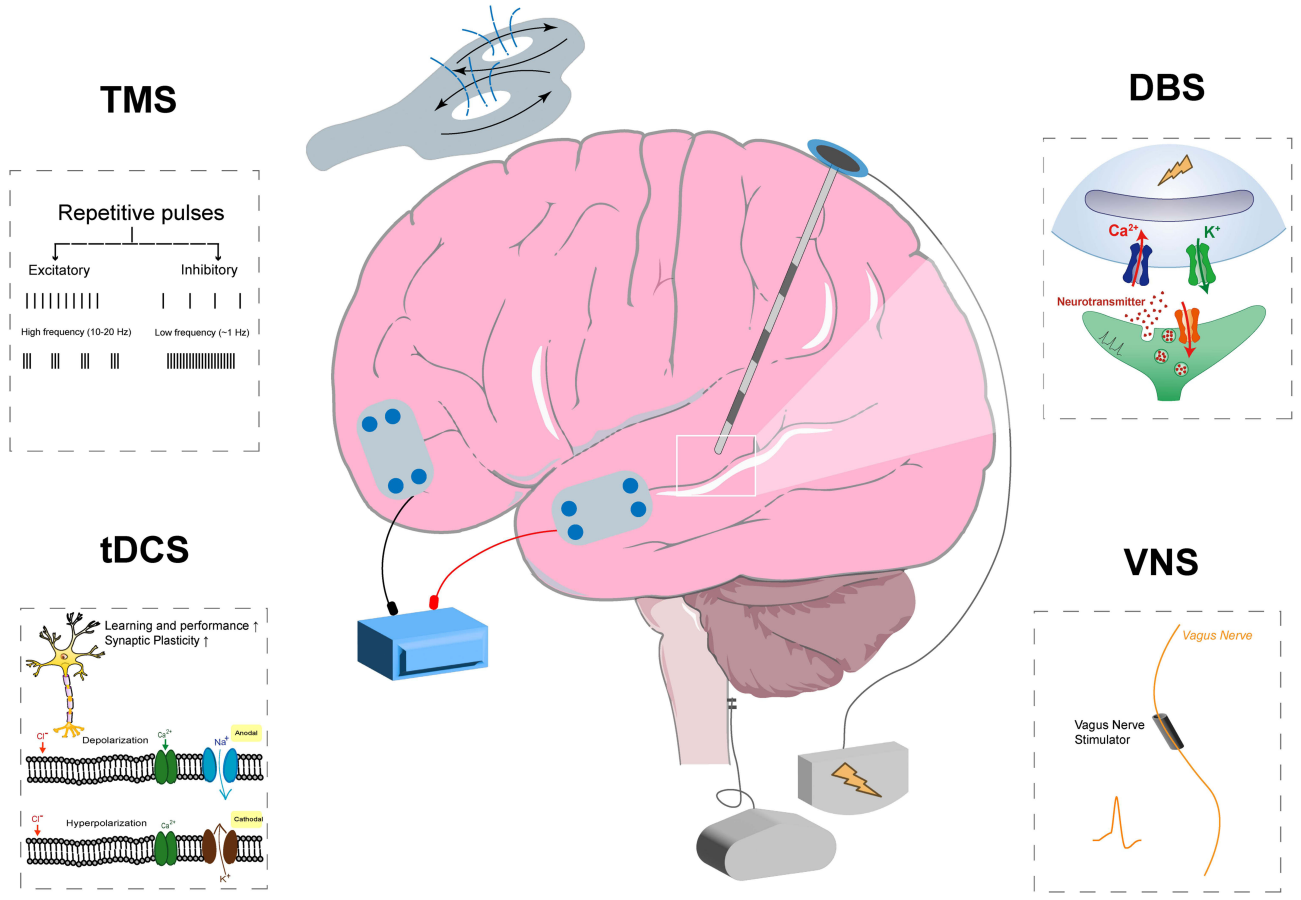

Figure 2 A schematic representation, mechanisms and indications of NIBS and IBS techniques. In TMS, HF-rTMS (5–20 Hz) induces to cortical facilitation, whereas LF-rTMS (≤1 Hz) reduces cortical excitability through the activation of inhibitory GABAergic interneurons; conditions treatable with TMS including: 1) social-related impairments; 2) executive function deficits; 3) abnormal reactions to the sensory environment; 4) combined with neurofeedback therapies; In tDCS, membrane potentials could be influenced at a cellular level under weak currents, which may improve neural plasticity and ability of learning and performance (upward arrow); conditions treatable with tDCS including: 1) social-related impairments; 2) cognitive flexibility deficits; 3) impairments in motor and behavioral skills; 4) combined with cognitive remediation training; in DBS, neurotransmitters are released in response to stimulation (the white box indicates the magnified area), leading to changes in synaptic plasticity; conditions treatable with DBS including: 1) Comorbidities: serious self-injurious behaviors, seizure, obsessive-compulsive disorder, depression; 2) motor stereotypies; in VNS, stimulation of the vagus nerve could influence the activation of noradrenergic system, which may promote enhancement of plasticity; conditions treatable with VNS including: 1) Comorbidities: pharmacoresistant epilepsy; 2) abnormal behaviors and emotional areas; 3) autistic behaviors, but the positive effect of VNS on autistic behaviors requires further evidence.

Safety

Noninvasive Neurostimulation

TMS and tDCS are considered quite safe even in pediatric populations. However, some potential risks for adverse side effects cannot be ruled out due to the heterogeneity of the patients. Induction of seizure represents the most serious adverse event related to TMS, with a reported risk of less than 0.01% across all patients and all paradigms. Other mild and transient side effects include mild headache, pain, and facial discomfort at the TMS application site.[29,33] Only minor adverse effects were observed during tDCS application, including mild skin irritation, short-term itchiness, and buzzing sensations.[42,44,49]

ECT is recognized to influence autonomic stability during electrical stimulation, which could bring the risk of potential arrhythmias.[96] Adequate IV hydration, commencing at least 12 hours prior to ECT treatment, likely reduced the risk, as conducted by Wachtel et al.[65] Additionally, common and self-limiting adverse effects associated with ECT include headache, muscle soreness, and post-procedural nausea or vomiting.[97] Cognitive side effects such as anterograde and/or retrograde amnesia are also frequently observed. These cognitive impairments could resolve in the weeks following treatment and have no significant difference compared to other groups.[98]

Invasive Neurostimulation

Few studies reported complications of DBS that interrupted therapy. One patient had an infection of the DBS system that required removal of the system.[77] A mild serous drainage was observed in a 27-year-old man around the electrode implantation site.[71] Another 24-year-old female also experienced a recurrence of symptoms due to lead fracture and dislodgement, which symptoms were alleviated with a new battery replacement.[72] Many studies have demonstrated the safety of VNS therapy, which can be delivered to adults as well as children.[99–101] Some reported adverse effects, such as intermittent coughing and hoarseness, are usually slight and transient.[95]

In summary, the safety of neuromodulation interventions has been demonstrated in numerous studies, with minimal side effects. The summary of adverse events reported in various neuromodulation techniques is shown in Table 5. However, nearly half of the existing studies have not reported adverse effects, while the remaining studies have often failed to use valid scales to assess adverse effects. Therefore, the risk of overall adverse events associated with neuromodulation techniques may be underestimated, especially in vulnerable populations. Future studies should utilize standard side effect questionnaires to evaluate the tolerability of the neuromodulation technique, and further long-term follow-up is also essential.

Table 5 Adverse Events Reported in Various Neuromodulation Techniques

Research	Neuromodulation	Adverse Events Reported
[14]	TMS	"itching" sensation around the nose; a mild, transient tension-type headache
[16]	TMS	Stiff neck; Subtle disorientation; Sleepy; Dizziness; Trouble concentrating; Headache
[29]	TMS	Mild-to-moderate adverse events: headache, pain, nausea, nose bleed, congestion, laceration
[47]	TDCS	Minor symptoms: pins/ needles, face pain, fatigue
[60]	ECT	Posturing resumed after ECT was postponed due to retinal detachment surgery
[68]	ECT	Attempts to taper off ECT coincided with return of aggression symptoms
[89]	ECT	Mild headache, myalgia
[72]	DBS	Symptoms recurred lead fracture and dislodgement
[76]	DBS	The patient continued to experience functional impairment during the first year after surgery, resulting in weight gain of 34 pounds.
[77]	DBS	Patient 1: hypomania, tics, impulsivity, agitation; Patient 2: infection of DBS system, requiring explantation and reimplantation, suicide attempt.
[95]	VNS	Intermittent hoarseness; increased physical violence toward others in a patient
[102]	VNS	Transient hoarseness during stimulation

Discussion

In this review, we comprehensively and systematically evaluate the clinical efficacy and safety of neuromodulation interventions in patients with ASD and other comorbidities. Finding innovative therapies is a fundamental aspect for individuals with autism and comorbid conditions resistant to conventional treatments. It demonstrates that both NIBS and IBS can help to improve neuropsychological function and reduce core symptoms of ASD as potential adjunctive therapies. A series of RCT and pilot studies demonstrated that NIBS may improve specific core or associated symptoms related to an alteration in the functioning of a specific cortical region or circuit, but the optimal stimulus parameters still remain unclear. On the other side, IBS are primarily aimed at alleviating severe comorbidities associated with ASD, such as SIBs, refractory epilepsy, major depressive disorder, etc. Due to the inherent risks of invasive interventions, current clinical studies are mostly case reports and observational studies, indicating a lack of higher-level clinical evidence. There remains significant heterogeneity in clinical phenotypes between studies, particularly in terms of patient profiles, study designs, stimulation protocols, and outcome measurements. Overall, the lack of standardized protocols for the neuromodulation techniques makes it difficult to compare different results directly. Therapeutic use of neuromodulation interventions would likely be described as possibly effective. Researchers should corroborate their findings with larger sample sizes and longer follow-up to recognize true benefits of neuromodulation interventions. Some potential breakthroughs such as TI should also be considered carefully in the treatments of autism, which could provide a deeper understanding of the mechanism of ASD.[103]

A major hypothesis suggests that the behavioral symptoms of ASD are explained by abnormal resting-state functional connectivity (rsFC), especially long-range disconnection that may occur as a result of developmental events.[4] Growing evidence indicates that sociability, cognitive, and sensorimotor impairments are related to abnormalities of distributed networks, rather than of single brain loci.[104] Social behavior is mediated by a distributed, large-scale network of multiple brain structures, including areas of the prefrontal cortex, subcortex, and areas that integrate information, which is commonly observed to be dysfunctional in individuals with ASD.[105] An fMRI study showed that deficits in the mesolimbic reward pathway (especially key subcortical nodes including VTA and NAc) contribute to impaired social skills in childhood autism.[106] Collectively, these studies suggest the presence of disrupted neural pathways before the emergence of behavioral symptoms in patients with ASD and might provide clues about the underlying neural mechanisms of autism, thus suggesting that stimulation approaches may yield promising results, as they seem to be able to modulate the brain's functional connectivity via normalizing the E/I balance.

TMS and tDCS can induce activity in neurons and changes in neuroplasticity via generating magnetic fields or weak currents, which is believed to reverse underlying neuroplasticity deficits in autism.[107] To gain a deeper understanding of the short-term and long-term effects of tDCS and TMS on ASD, more well-designed, longitudinal, randomized, double-blind, sham-controlled trials with an adequate follow-up period after treatment are needed. In 2017, Grossman et al developed Temporal Interference Stimulation (TI) to stimulate further specific deep brain regions, which could produce an LF envelope and modulate the activity of neurons.[103] We believe that TI is a promising technology for treating ASD due to its superior focus and steerability. Further animal experiments and clinical trials are required to be conducted.

There has been increasing interest in the overlap of catatonia and ASD.[108,109] Over the past decade, an increasing number of reports have shown the swift and well-tolerated resolution of catatonia with ECT.[110] Although the mechanism by which ECT relieves catatonia remains unclear, several hypotheses have been proposed. The neuroendocrine studies of melancholia found that repeated seizures normalize hypothalamic-pituitary-adrenal axis functions and correct neuroendocrine abnormalities, which may offer a standard explanation for autism.[111] Another mechanism originates from a study showing the increase in new brain cells after induced seizures.[112] Future research and clinical application are needed to expand our knowledge regarding optimal utilization of ECT in ASDs with catatonia and treatment-refractory SIB.

In IBS, with direct intervention in pathological neural circuits, DBS has changed the way that brain disorders are treated and understood and is considered one of the most promising therapeutic applications for clinical neuroscience.[113–115] In line with our expanding understanding of pathophysiology, the DBS community has moved toward developing "connectomic" neurosurgical targeting approaches. A connectomic analysis in 8 patients with ASD and extreme behaviors revealed a shared functional network upon which 3 of the DBS targets converge (NAcc, VC/VS, pHyp), which provided crucial

insight into the brain networks involved in symptom improvement with DBS.[116] Of note, DBS has now been used in ASDs only to treat comorbid conditions, which have obtained optimal results for drug-resistant OCD and SIBs.[69,76,77] Positive effects on core symptoms of ASD have only occasionally been reported.[72,73] Therefore, among the emerging therapeutic approaches, DBS represents a promising intervention for alleviating comorbidities associated with autism, potentially enhancing both clinical outcomes and quality of life for patients.

Epilepsy has been the most frequently studied topic among the physical conditions that co-occur with ASD. It is reported that almost 60% of EEG records from children with ASD have interictal spikes, and a higher percentage of interictal spikes in the frontal lobe.[117–119] Due to the high comorbidity rate between ASD and epilepsy, both diseases possibly share common pathophysiological properties. A hypothesis suggests that early-life seizures induce an imbalance in the excitatory/inhibitory (E/I) ratio in specific brain regions, which may alter the dynamic flexibility of brain connectivity in ASDs.[120,121] The effects are putatively mediated by the vagus nerve's numerous interconnections with brain structures thought to be involved with mood and emotional regulation. Meanwhile, VNS could be paired with well-established, existing rehabilitative interventions, holding potential to treat dysfunction that accompanies neurodevelopmental disorders.[123] Future clinical trials are crucial for evaluating the benefits of paired VNS therapies.

However, most studies were case reports and open-label trials, with low levels of evidence for clinical application. Ethical and legal concerns persist regarding potential misuse of DBS or VNS, which reminds us to carefully assess the risk-benefit ratio of invasive therapies.

In the future, more advanced techniques such as functional imaging and connectomics will be needed to evaluate the impact of neurostimulation interventions for ASDs, thereby optimizing clinical responses.

Limitations

This systematic review has certain limitations. First, we drew conclusions based on a limited sample size, and most included studies were case reports and not controlled studies. Given that we did not consider any limitations regarding the study design or the age or sex of participants, these results must be interpreted with caution regarding the potential effect of confounding factors. Second, many studies have not been designed using clear and objective primary clinical endpoints. The clinical outcome measures that have been utilized are often subjective self- or observer-based reports, which threaten to mask or undermine assessment of change. Third, ASD is often associated with co-occurring psychiatric or neurological disorders, and this can likely generate confounding effects in clinical neuromodulation studies. Overall, we have attempted to include all relevant research in this work to provide a comprehensive picture of the current state of this new therapeutic field, in order to review its findings and describe its strengths and weaknesses.

Conclusion

Recent decades have witnessed a growing interest in the efficiency and safety of neurostimulation interventions for autism, yet stronger evidence base for treating ASD in individual studies are needed. The current quality for neuromodulation interventions in ASD is mixed, which requires a wider range of such a clinically heterogeneous population to test the validity and reliability of these measures, thereby increasing the generalizability of the results. Therefore, further studies should focus on establishing a solid consensus regarding optimal stimulation parameters, cumulative doses, stimulation targets and longer follow-up duration for neurostimulation in ASD, which may provide patients with highly personalized and targeted therapeutic strategies.

Data Sharing Statement

All data extracted or analyzed during this study are included in the manuscript and the supplementary materials.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

References

1. Zeidan J, Fombonne E, Scorah J, et al. Global prevalence of autism: a systematic review update. *Autism Research*. 2022;15(5):778–790. doi:10.1002/aur.2696
2. DeFilippis M. Depression in children and adolescents with autism spectrum disorder. *Children*. 2018;5(9):112. doi:10.3390/children5090112
3. Koenig K, Levine M. Psychotherapy for individuals with autism spectrum disorders. *J. Contemp. Psychother*. 2011;41(1):29–36. doi:10.1007/s10879-010-9158-9
4. Lord C, Brugha TS, Charman T, et al. Autism spectrum disorder. *Nat Rev Dis Primers*. 2020;6(1):5. doi:10.1038/s41572-019-0138-4
5. Hazlett HC, Gu H, Munsell BC, et al. Early brain development in infants at high risk for autism spectrum disorder. *Nature*. 2017;542 (7641):348–351. doi:10.1038/nature21369
6. Rippon G, Brock J, Brown C, Boucher J. Disordered connectivity in the autistic brain: challenges for the "new psychophysiology". *Int J Psychophysiol*. 2007;63(2):164–172. doi:10.1016/j.ijpsycho.2006.03.012
7. Rojas DC. The role of glutamate and its receptors in autism and the use of glutamate receptor antagonists in treatment. *J Neural Transm*. 2014;121(8):891–905. doi:10.1007/s00702-014-1216-0
8. Nisar S, Bhat AA, Masoodi T, et al. Genetics of glutamate and its receptors in autism spectrum disorder. *Mol Psychiatry*. 2022;27 (5):2380–2392. doi:10.1038/s41380-022-01506-w
9. Chiesa M, Nardou R, Lozovaya N, et al. Enhanced glutamatergic currents at birth in Shank3 KO mice. *Neural Plast*. 2019;2019:2382639. doi:10.1155/2019/2382639
10. Moxon-Emre I, Daskalakis ZJ, Blumberger DM, et al. Modulation of dorsolateral prefrontal cortex glutamate/glutamine levels following repetitive transcranial magnetic stimulation in young adults with autism. *Front Neurosci*. 2021;15.
11. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. *BMJ*. 2009;339:b2700. doi:10.1136/bmj.b2700
12. Porritt K, Evans CB, Loveday C, et al. Systematic reviews of qualitative evidence. In: Aromataris E, Lockwood C, Porritt K, Pilla B, Jordan Z, editors. JBI Manual for Evidence Synthesis; 2024.
13. Sokhadze EM, El-Baz A, Baruth J, Mathai G, Sears L, Casanova MF. Effects of low frequency repetitive transcranial magnetic stimulation (rTMS) on gamma frequency oscillations and event-related potentials during processing of illusory figures in autism. *J Autism Dev Disord*. 2009;39(4):619–634. doi:10.1007/s10803-008-0662-7
14. Baruth JM, Casanova MF, El-Baz A, et al. Low-Frequency Repetitive Transcranial Magnetic Stimulation (rTMS) modulates evoked-gamma frequency oscillations in Autism Spectrum Disorder (ASD). *J. Neurother*. 2010;14(3):179–194. doi:10.1080/10874208.2010.501500
15. Sokhadze E, Baruth J, Tasman A, et al. Low-frequency repetitive transcranial magnetic stimulation (rTMS) affects event-related potential measures of novelty processing in autism. *Applied Psychophysiology and Biofeedback*. 2010;35(2):147–161. doi:10.1007/s10484-009-9121-2
16. Fecteau S, Agosta S, Oberman L, Pascual-Leone A. Brain stimulation over Broca's area differentially modulates naming skills in neurotypical adults and individuals with Asperger's syndrome. *Eur. J. Neurosci*. 2011;34(1):158–164. doi:10.1111/j.1460-9568.2011.07726.x
17. Casanova MF, Baruth JM, El-Baz A, Tasman A, Sears L, Sokhadze E. Repetitive Transcranial Magnetic Stimulation (rTMS) Modulates Event-Related Potential (ERP) Indices of Attention in Autism. *Transl. Neurosci*. 2012;3(2):170–180. doi:10.2478/s13380-012-0022-0
18. Enticott PG, Rinehart NJ, Tonge BJ, Bradshaw JL, Fitzgerald PB. Repetitive transcranial magnetic stimulation (rTMS) improves movement-related cortical potentials in autism spectrum disorders. *Brain Stimulation*. 2012;5(1):30–37. doi:10.1016/j.brs.2011.02.001
19. Sokhadze EM, Baruth JM, Sears L, Sokhadze GE, El-Baz AS, Casanova MF. Prefrontal neuromodulation using rTMS improves error monitoring and correction function in autism. *Applied Psychophysiology and Biofeedback*. 2012;37(2):91–102. doi:10.1007/s10484-012-9182-5
20. Casanova MF, Hensley MK, Sokhadze EM, et al. Effects of weekly low-frequency rTMS on autonomic measures in children with autism spectrum disorder. *Front Hum Neurosci*. 2014;8:851. doi:10.3389/fnhum.2014.00851
21. Enticott PG, Fitzgibbon BM, Kennedy HA, et al. A double-blind, randomized trial of deep Repetitive Transcranial Magnetic Stimulation (rTMS) for Autism Spectrum Disorder. *Brain Stimulation*. 2014;7(2):206–211. doi:10.1016/j.brs.2013.10.004
22. Panerai S, Tasca D, Lanuzza B, et al. Effects of repetitive transcranial magnetic stimulation in performing eye-hand integration tasks: four preliminary studies with children showing low-functioning autism. *Autism*. 2014;18(6):638–650. doi:10.1177/1362361313495717
23. Sokhadze EM, El-Baz AS, Sears LL, Opris I, Casanova MF. rTMS neuromodulation improves electrocortical functional measures of information processing and behavioral responses in autism. *Front. Syst. Neurosci*. 2014;8:134. doi:10.3389/fnsys.2014.00134
24. Sokhadze EM, El-Baz AS, Tasman A, et al. Neuromodulation integrating rTMS and neurofeedback for the treatment of autism spectrum disorder: an exploratory study. *Applied Psychophysiology and Biofeedback*. 2014;39(3–4):237–257. doi:10.1007/s10484-014-9264-7
25. Sokhadze E, Casanova M, El-Baz A, Farag HE, Li X, Wang Y. TMS-based neuromodulation of evoked and induced gamma oscillations and event-related potentials in children with autism. *NeuroRegulation*. 2016;3(3):101–126. doi:10.15540/nr.3.3.101
26. Sokhadze G, Casanova M, Kelly D, Casanova E, Russell B, Sokhadze E. neuromodulation based on rTMS affects behavioral measures and autonomic nervous system activity in children with autism. *NeuroRegulation*. 2017;4(2):65–78. doi:10.15540/nr.4.2.65

27. Abujadi C, Croarkin PE, Bellini BB, Brentani H, Marcolin MA. Intermittent theta-burst transcranial magnetic stimulation for autism spectrum disorder: an open-label pilot study. *Rev Bras Psiquiatr*. 2018;40(3):309–311. doi:10.1590/1516-4446-2017-2279
28. Sokhadze EM, Lamina EV, Casanova EL, et al. Exploratory study of rTMS neuromodulation effects on electrocortical functional measures of performance in an oddball test and behavioral symptoms in autism. *Front. Syst. Neurosci*. 2018;12:20. doi:10.3389/fnsys.2018.00020
29. Ameis SH, Blumberger DM, Croarkin PE, et al. Treatment of Executive Function Deficits in autism spectrum disorder with repetitive transcranial magnetic stimulation: a double-blind, sham-controlled, pilot trial. *Brain Stimulation*. 2020;13(3):539–547. doi:10.1016/j.brs.2020.01.007
30. Assadi M, Dave J, Leone P, Redjal N, Curtin A. Enhancement of behavioral and linguistic outcome measures in autism spectrum disorder through neuro-navigated transcranial magnetic stimulation: a pilot study. *J Clin Neurosci*. 2020;74:151–154. doi:10.1016/j.jocn.2020.02.005
31. Casanova MF, Shaban M, Ghazal M, et al. Effects of transcranial magnetic stimulation therapy on evoked and induced gamma oscillations in children with autism spectrum disorder. *Brain Sci*. 2020;10(7):423. doi:10.3390/brainsci10070423
32. Gwynette MF, Lowe DW, Henneberry EA, et al. Treatment of adults with autism and major depressive disorder using transcranial magnetic stimulation: an open label pilot study. *Autism Res*. 2020;13(3):346–351. doi:10.1002/aur.2266
33. Ni HC, Chen YL, Chao YP, et al. Intermittent theta burst stimulation over the posterior superior temporal sulcus for children with autism spectrum disorder: a 4-week randomized blinded controlled trial followed by another 4-week open-label intervention. *Autism*. 2021;25 (5):1279–1294. doi:10.1177/1362361321990534
34. Desarkar P, Rajji TK, Ameis SH, et al. Assessing and stabilizing atypical plasticity in autism spectrum disorder using rTMS: results from a proof-of-principle study. *Clin Neurophysiol*. 2022;141:109–118. doi:10.1016/j.clinph.2021.03.046
35. Kang J, Li X, Casanova MF, Sokhadze EM, Geng X. Impact of repetitive transcranial magnetic stimulation on the directed connectivity of autism EEG signals: a pilot study. *Med Biol Eng Comput*. 2022;60(12):3655–3664. doi:10.1007/s11517-022-02693-y
36. Kang J, Zhang Z, Wan L, Casanova MF, Sokhadze EM, Li X. Effects of 1Hz repetitive transcranial magnetic stimulation on autism with intellectual disability: a pilot study. *Comput. Biol. Med*. 2022;141:105167. doi:10.1016/j.compbiomed.2021.105167
37. Ni HC, Lin HY, Chen YL, et al. 5-day multi-session intermittent theta burst stimulation over bilateral posterior superior temporal sulci in adults with autism-a pilot study. *Biomed J*. 2022;45(4):696–707. doi:10.1016/j.bj.2021.07.008
38. Kaokhieo J, Tretriluxana J, Chaiyawat P, et al. Effects of repetitive transcranial magnetic stimulation combined with action-observation-execution on social interaction and communication in autism spectrum disorder: feasibility study. *Brain Res*. 2023;1804:148258. doi:10.1016/j.brainres.2023.148258
39. Ni HC, Chen YL, Chao YP, et al. A lack of efficacy of continuous theta burst stimulation over the left dorsolateral prefrontal cortex in autism: a double blind randomized sham-controlled trial. *Autism Res*. 2023;16(6):1247–1262. doi:10.1002/aur.2954
40. Schneider HD, Hopp JP. The use of the Bilingual Aphasia Test for assessment and transcranial direct current stimulation to modulate language acquisition in minimally verbal children with autism. *Clin. Linguist. Phon*. 2011;25(6–7):640–654. doi:10.3109/02699206.2011.570852
41. Amatachaya A, Jensen MP, Patjanasoontorn N, et al. The short-term effects of transcranial direct current stimulation on electroencephalography in children with autism: a randomized crossover controlled trial. *Behav. Neurol*. 2015;2015:928631. doi:10.1155/2015/928631
42. Gómez L, Vidal B, Maragoto C, et al. Non-invasive brain stimulation for children with autism spectrum disorders: a short-term outcome study. *Behav Sci*. 2017;7(3):63. doi:10.3390/bs7030063
43. Esse Wilson J, Trumbo MC, Wilson JK, Tesche CD. Transcranial direct current stimulation (tDCS) over right temporoparietal junction (rTPJ) for social cognition and social skills in adults with autism spectrum disorder (ASD). *J Neural Transm*. 2018;125(12):1857–1866. doi:10.1007/s00702-018-1938-5
44. Rothärmel M, Moulier V, Vasse M, et al. A prospective open-label pilot study of transcranial direct current stimulation in high-functioning autistic patients with a dysexecutive syndrome. *Neuropsychobiology*. 2019;78(4):189–199. doi:10.1159/000501025
45. Hadoush H, Nazzal M, Almasri NA, Khalil H, Alafeef M. Therapeutic effects of bilateral anodal transcranial direct current stimulation on prefrontal and motor cortical areas in children with autism spectrum disorders: a pilot study. *Autism Res*. 2020;13(5):828–836. doi:10.1002/aur.2290
46. Qiao YX, Hu Q, Xuan RR, et al. High-definition transcranial direct current stimulation facilitates emotional face processing in individuals with high autistic traits: a sham-controlled study. *Neurosci lett*. 2020;738.
47. Parmar D, Enticott PG, Albein-Urios N. Anodal HD-tDCS for cognitive inflexibility in autism spectrum disorder: a pilot study. *Brain Stimulation*. 2021;14(5):1298–1300. doi:10.1016/j.brs.2021.08.020
48. Salehinejad MA, Paknia N, Hosseinpour AH, et al. Contribution of the right temporoparietal junction and ventromedial prefrontal cortex to theory of mind in autism: a randomized, sham-controlled tDCS study. *Autism Res*. 2021;14(8):1572–1584. doi:10.1002/aur.2538
49. Han YMY, Chan MMY, Shea CKS, et al. Neurophysiological and behavioral effects of multisession prefrontal tDCS and concurrent cognitive remediation training in patients with autism spectrum disorder (ASD): a double-blind, randomized controlled fNIRS study. *Brain Stimulation*. 2022;15(2):414–425. doi:10.1016/j.brs.2022.02.004
50. Padrón I, García-Marco E, Moreno I, et al. Multisession Anodal tDCS on the right temporo-parietal junction improves mentalizing processes in adults with autistic traits. *Brain Sciences*. 2022;12(1). doi:10.3390/brainsci12111506.
51. Zemestani M, Hoseinpanahi O, Salehinejad MA, Nitsche MA. The impact of prefrontal transcranial direct current stimulation (tDCS) on theory of mind, emotion regulation and emotional-behavioral functions in children with autism disorder: a randomized, sham-controlled, and parallel-group study. *Autism Res*. 2022;15(10):1985–2003. doi:10.1002/aur.2803
52. Auvichayapat P, Intayot K, Udomchat C, et al. Long-term effects of transcranial direct current stimulation in the treatment of autism spectrum disorder: a randomized controlled trial. *Dev Med Child Neurol*. 2023;65(6):811–820. doi:10.1111/dmcn.15457
53. Chan MMY, Choi CXT, Tsoi TCW, Shea CKS, Yiu KWK, Han YMY. Effects of multisession cathodal transcranial direct current stimulation with cognitive training on sociocognitive functioning and brain dynamics in autism: a double-blind, sham-controlled, randomized EEG study. *Brain Stimulation*. 2023;16(6):1604–1616. doi:10.1016/j.brs.2023.10.012
54. Hadoush H, Hadoush A. Modulation of resting-state brain complexity after bilateral cerebellar anodal transcranial direct current stimulation in children with autism spectrum disorders: a randomized controlled trial study. *Cerebellum*. 2023;22(6):1109–1117. doi:10.1007/s12311-022-01481-6
55. Han YM, Chan MM, Shea CK, et al. Effects of prefrontal transcranial direct current stimulation on social functioning in autism spectrum disorder: a randomized clinical trial. *Autism*. 2023;27(8):2465–2482. doi:10.1177/13623613231169547
56. Kang J, Fan X, Zhong Y, et al. Transcranial direct current stimulation modulates EEG microstates in low-functioning autism: a pilot study. *Bioengineering*. 2023;10(1):98. doi:10.3390/bioengineering10010098

57. Ratsapbhayakul T, Keeratitanont K, Chonprai C, et al. Anodal transcranial direct-current stimulation and non-verbal intelligence in autism spectrum disorder: a randomized controlled trial. *Dev Med Child Neurol*. 2024;66:1244–1254. doi:10.1111/dmcn.15874
58. Zaw FK, Bates GD, Murali V, Bentham P. Catatonia, autism, and ECT. *Dev Med Child Neurol*. 1999;41(12):843–845. doi:10.1111/j.1469-8749.1999.tb00552.x
59. Ghaziuddin M, Quinlan P, Ghaziuddin N. Catatonia in autism: a distinct subtype? *J. Intellect. Disabil. Res*. 2005;49(Pt 1):102–105. doi:10.1111/j.1365-2788.2005.00666.x
60. Wachtel LE, Kahng S, Dhossche DM, Cascella N, Reti IM. ECT for catatonia in an autistic girl. *Am J Psychiatry*. 2008;165(3):329–333. doi:10.1176/appi.ajp.2007.07081246
61. Wachtel LE, Contrucci-Kuhn SA, Griffin M, Thompson A, Dhossche DM, Reti IM. ECT for self-injury in an autistic boy. *Eur Child Adolesc Psychiatry*. 2009;18(7):458–463. doi:10.1007/s00787-009-0754-8
62. Dhossche DM, Reti IM, Shettar SM, Wachtel LE. Tics as signs of catatonia: electroconvulsive therapy response in 2 men. *The Journal of ECT*. 2010;26(4):266–269. doi:10.1097/YCT.0b013e3181cb5f60
63. Ghaziuddin N, Gih D, Barbosa V, Maixner DF, Ghaziuddin M. Onset of catatonia at puberty: electroconvulsive therapy response in two autistic adolescents. *The Journal of ECT*. 2010;26(4):274–277. doi:10.1097/YCT.0b013e3181de332e
64. Wachtel LE, Griffin M, Reti IM. Electroconvulsive therapy in a man with autism experiencing severe depression, catatonia, and self-injury. *The Journal of ECT*. 2010;26(1):70–73. doi:10.1097/YCT.0b013e3181a744ec
65. Wachtel LE, Griffin MM, Dhossche DM, Reti IM. Brief report: electroconvulsive therapy for malignant catatonia in an autistic adolescent. *Autism*. 2010;14(4):349–358. doi:10.1177/1362361309350135
66. Wachtel LE, Hermida A, Dhossche DM. Maintenance electroconvulsive therapy in autistic catatonia: a case series review. *Prog Neuro Psychopharmacol Biol Psychiatry*. 2010;34(4):581–587. doi:10.1016/j.pnpbp.2010.03.012
67. Wachtel LE, Reti IM, Dhossche DM, Slomine BS, Sanz J. Stability of neuropsychological testing during two years of maintenance electroconvulsive therapy in an autistic man. *Prog Neuropsychopharmacol Biol Psychiatry*. 2011;35(1):301–302. doi:10.1016/j.pnpbp.2010.11.013
68. Haq AU, Ghaziuddin N. Maintenance electroconvulsive therapy for aggression and self-injurious behavior in two adolescents with autism and catatonia. *J Neuropsychiatry Clin Neurosci*. 2014;26(1):64–72. doi:10.1176/appi.neuropsych.12110284
69. Sturm V, Fricke O, Bührle CP, et al. DBS in the basolateral amygdala improves symptoms of autism and related self-injurious behavior: a case report and hypothesis on the pathogenesis of the disorder. *Front Hum Neurosci*. 2012;6:341. doi:10.3389/fnhum.2012.00341
70. Stocco A, Baizabal-Carvallo JF. Deep brain stimulation for severe secondary stereotypies. *Parkinsonism Related Disord*. 2014;20(9):1035–1036. doi:10.1016/j.parkreldis.2014.06.019
71. Benedetti-Isaac JC, Torres-Zambrano M, Vargas-Toscano A, et al. Seizure frequency reduction after posteromedial hypothalamus deep brain stimulation in drug-resistant epilepsy associated with intractable aggressive behavior. *Epilepsia*. 2015;56(7):1152–1161. doi:10.1111/epi.13025
72. Segar DJ, Chodakiewitz YG, Torabi R, Cosgrove GR. Deep brain stimulation for the obsessive-compulsive and Tourette-like symptoms of Kleefstra syndrome. *Neurosurgical Focus*. 2015;38(6):E12. doi:10.3171/2015.3.FOCUS1528
73. Park HR, Kim IH, Kang H, et al. Nucleus accumbens deep brain stimulation for a patient with self-injurious behavior and autism spectrum disorder: functional and structural changes of the brain: report of a case and review of literature. *Acta Neurochirurgica*. 2017;159(1):137–143. doi:10.1007/s00701-016-3002-2
74. Doshi PK, Hegde A, Desai A. Nucleus accumbens deep brain stimulation for obsessive-compulsive disorder and aggression in an autistic patient: a case report and hypothesis of the role of nucleus accumbens in autism and comorbid symptoms. *World Neurosurg*. 2019;125:387–391. doi:10.1016/j.wneu.2019.02.021
75. Kakko K, Bjelogrlic-Laakso N, Pihlakoski L, Lehtimäki K, Järventausta K. tardive dyskinesia should not be overlooked. *J Child Adolesc Psychopharmacol*. 2019;29(1):72–74. doi:10.1089/cap.2018.0084
76. Davis RA, Winston H, Gault JM, Kern DS, Mikulich-Gilbertson SK, Abosch A. deep brain stimulation for ocd in a patient with comorbidities: epilepsy, tics, autism, and major depressive disorder. *J Neuropsychiatry Clin Neurosci*. 2021;33(2):167–171. doi:10.1176/appi.neuropsych.20060153
77. Graat I, Balke S, Prinssen J, et al. Effectiveness and safety of deep brain stimulation for patients with refractory obsessive compulsive disorder and comorbid autism spectrum disorder; A case series. *J Affective Disorders*. 2022;299:492–497. doi:10.1016/j.jad.2021.12.089
78. Wagner T, Valero-Cabre A, Pascual-Leone A. Noninvasive human brain stimulation. *Annu. Rev. Biomed. Eng*. 2007;9:527–565. doi:10.1146/annurev.bioeng.9.061206.133100
79. Pascual-Leone A, Tormos JM, Keenan J, Tarazona F, Cañete C, Catalá MD. Study and modulation of human cortical excitability with transcranial magnetic stimulation. *J Clin Neurophysiol*. 1998;15(4):333–343. doi:10.1097/00004691-199807000-00005
80. Suppa A, Huang YZ, Funke K, et al. Ten years of theta burst stimulation in humans: established knowledge, unknowns and prospects. *Brain Stimulation*. 2016;9(3):323–335. doi:10.1016/j.brs.2016.01.006
81. Pedapati EV, Gilbert DL, Erickson CA, et al. Abnormal cortical plasticity in youth with autism spectrum disorder: a transcranial magnetic stimulation case-control pilot study. *J Child Adolesc Psychopharmacol*. 2016;26(7):625–631. doi:10.1089/cap.2015.0183
82. Wang Y, Hensley MK, Tasman A, Sears L, Casanova MF, Sokhadze EM. Heart rate variability and skin conductance during repetitive tms course in children with autism. *Applied Psychophysiology and Biofeedback*. 2016;41(1):47–60. doi:10.1007/s10484-015-9311-z
83. Noda Y, Fujii K, Mimura Y, Taniguchi K, Nakajima S, Kitahata R. A case series of intermittent theta burst stimulation treatment for depressive symptoms in individuals with autistic spectrum disorder: real world tms study in the tokyo metropolitan area. *J. Pers. Med*. 2023;13(1).
84. Sousa B, Martins J, Castelo-Branco M, Gonçalves J. Transcranial Direct Current Stimulation as an Approach to Mitigate Neurodevelopmental Disorders Affecting excitation/inhibition balance: focus on autism spectrum disorder, schizophrenia, and attention deficit/hyperactivity disorder. *J Clin Med*. 2022;11(10):2839. doi:10.3390/jcm11102839
85. Nitsche MA, Cohen LG, Wassermann EM, et al. Transcranial direct current stimulation: state of the art 2008. *Brain Stimul*. 2008;1(3):206–223. doi:10.1016/j.brs.2008.06.004
86. Dmochowski JP, Datta A, Bikson M, Su Y, Parra LC. Optimized multi-electrode stimulation increases focality and intensity at target. *J. Neural Eng*. 2011;8(4):046011. doi:10.1088/1741-2560/8/4/046011
87. Vaquerizo-Serrano J, Salazar De Pablo G, Singh J, Santosh P. Catatonia in autism spectrum disorders: a systematic review and meta-analysis. *European Psychiatry*. 2021;65(1):e4. doi:10.1192/j.eurpsy.2021.2259

88. Fink M, Taylor MA, Ghaziuddin N. Catatonia in autistic spectrum disorders: a medical treatment algorithm. *Int. Rev. Neurobiol*. 2006;72:233–244.
89. Smith JR, Hopkins CE, Xiong J, Luccarelli J, Shultz E, Vandekar S. Use of ECT in Autism spectrum disorder and/or intellectual disability: a single site retrospective analysis. *J Autism Dev Disord*. 2024;54(3):963–982. doi:10.1007/s10803-022-05868-6
90. Amiet C, Gourfinkel-An I, Fau - Bouzamondo A, et al. Epilepsy in autism is associated with intellectual disability and gender: evidence from a meta-analysis. (1873-2402 (Electronic).
91. Dhossche DM, Shah A, Wing L. Blueprints for the assessment, treatment, and future study of catatonia in autism spectrum disorders. *Int. Rev. Neurobiol*. 2006;72:267–284.
92. Park YD. The effects of vagus nerve stimulation therapy on patients with intractable seizures and either Landau-Kleffner syndrome or autism. *Epilepsy Behav*. 2003;4(3):286–290. doi:10.1016/S1525-5050(03)00080-5
93. Levy ML, Levy KM, Hoff D, et al. Vagus nerve stimulation therapy in patients with autism spectrum disorder and intractable epilepsy: results from the vagus nerve stimulation therapy patient outcome registry. *J Neurosurg Pediatr*. 2010;5(6):595–602. doi:10.3171/2010.3.PEDS09153
94. Wang Z, Yuan X, Zhang Q, et al. Effects of stable vagus nerve stimulation efficacy on autistic behaviors in ten pediatric patients with drug resistant epilepsy: an observational study. *Front. Pediatr*. 2022;10:846301. doi:10.3389/fped.2022.846301
95. Danielsson S, Viggedal G, Gillberg C, Olsson I. Lack of effects of vagus nerve stimulation on drug-resistant epilepsy in eight pediatric patients with autism spectrum disorders: a prospective 2-year follow-up study. *Epilepsy Behav*. 2008;12(2):298–304. doi:10.1016/j.yebeh.2007.10.007
96. Abrams R. *Electroconvulsive Therapy*. Oxford University Press; 2002.
97. Espinoza RT, Kellner CH. Electroconvulsive Therapy. *New Engl J Med*. 2022;386(7):667–672. doi:10.1056/NEJMra2034954
98. Luccarelli J, McCoy TH Jr, Seiner SJ, Henry ME. Real-world evidence of age-independent electroconvulsive therapy efficacy: a retrospective cohort study. *Acta Psychiatrica Scandinavica*. 2022;145(1):100–108. doi:10.1111/acps.13378
99. Zamponi N, Rychlicki F, Corpaci L, Cesaroni E, Trignani R. Vagus nerve stimulation (VNS) is effective in treating catastrophic 1 epilepsy in very young children. *Neurosurg. Rev*. 2008;31(3):291–297. doi:10.1007/s10143-008-0134-8
100. Hauptman JS, Mathern GW. Vagal nerve stimulation for pharmacoresistant epilepsy in children. *Surg. Neurol. Int*. 2012;3(Suppl 4):S269–274. doi:10.4103/2152-7806.103017
101. Orosz I, McCormick D, Zamponi N, et al. Vagus nerve stimulation for drug-resistant epilepsy: a European long-term study up to 24 months in 347 children. *Epilepsia*. 2014;55(10):1576–1584. doi:10.1111/epi.12762
102. Hull MM, Madhavan D, Zaroff CM. Autistic spectrum disorder, epilepsy, and vagus nerve stimulation. *Child's Nervous System*. 2015;31(8):1377–1385. doi:10.1007/s00381-015-2720-8
103. Grossman N, Bono D, Dedic N, et al. Noninvasive deep brain stimulation via temporally interfering electric fields. *Cell*. 2017;169(6):1029–1041.e1016. doi:10.1016/j.cell.2017.05.024
104. Müller R-A, Fishman I. Brain connectivity and neuroimaging of social networks in autism. *Trends Cogn Sci*. 2018;22(12):1103–1116. doi:10.1016/j.tics.2018.09.008
105. Sato M, Nakai N, Fujima S, Choe KY, Takumi T. Social circuits and their dysfunction in autism spectrum disorder. *Mol Psychiatry*. 2023;28(8):3194–3206. doi:10.1038/s41380-023-02201-0
106. Supekar K, Kochalka J, Schaer M, et al. Deficits in mesolimbic reward pathway underlie social interaction impairments in children with autism. *Brain*. 2018;141(9):2795–2805. doi:10.1093/brain/awy191
107. Griff JR, Langlie J, Bencie NB, et al. Recent advancements in noninvasive brain modulation for individuals with autism spectrum disorder. *Neural Regen Res*. 2023;18(6):1191–1195. doi:10.4103/1673-5374.360163
108. Wing L, Shah A. Catatonia in autistic spectrum disorders. *Br J Psychiatry*. 2000;176:357–362. doi:10.1192/bjp.176.4.357
109. Billstedt E, Gillberg C, Gillberg C. Autism after adolescence: population-based 13- to 22-year follow-up study of 120 individuals with autism diagnosed in childhood. *J Autism Dev Disor*. 2005;35(3):351–360. doi:10.1007/s10803-005-3302-5
110. Withane N, Dhossche DM. Electroconvulsive treatment for catatonia in autism spectrum disorders. *Child Adolesc Psychiatr Clin N Am*. 2019;28(1):101–110. doi:10.1016/j.chc.2018.07.006
111. Grob GN. Endocrine psychiatry: solving the riddle of melancholia. *J. Hist. Med. Allied Sci*. 2011;66(2):272–274. doi:10.1093/jhmas/jrq070
112. Madsen TM, Treschow A, Bengzon J, Bolwig TG, Lindvall O, Tingström A. Increased neurogenesis in a model of electroconvulsive therapy. *Biol. Psychiatry*. 2000;47(12):1043–1049. doi:10.1016/S0006-3223(00)00228-6
113. Lozano AM, Lipsman N. Probing and regulating dysfunctional circuits using deep brain stimulation. *Neuron*. 2013;77(3):406–424. doi:10.1016/j.neuron.2013.01.020
114. Lipsman N, Woodside DB, Giacobbe P, et al. Subcallosal cingulate deep brain stimulation for treatment-refractory anorexia nervosa: a Phase 1 pilot trial. *Lancet*. 2013;381(9875):1361–1370. doi:10.1016/S0140-6736(12)62188-6
115. Ballanger B, Lozano AM, Moro E, et al. Cerebral blood flow changes induced by pedunculopontine nucleus stimulation in patients with advanced Parkinson's disease: a [(15)O] H2O PET study. *Human Brain Mapp*. 2009;30(12):3901–3909. doi:10.1002/hbm.20815
116. Yan H, Elkaim LM, Venetucci Gouveia F, et al. Deep brain stimulation for extreme behaviors associated with autism spectrum disorder converges on a common pathway: a systematic review and connectomic analysis. *J Neurosurg*. 2022;137(3):699–708. doi:10.3171/2021.11.JNS21928
117. Hughes JR, Melyn M. EEG and seizures in autistic children and adolescents: further findings with therapeutic implications. *Clin EEG Neurosci*. 2005;36(1):15–20. doi:10.1177/155005940503600105
118. Matsuo M, Maeda T, Sasaki K, Ishii K, Hamasaki Y. Frequent association of autism spectrum disorder in patients with childhood onset epilepsy. *Brain Dev*. 2010;32(9):759–763. doi:10.1016/j.braindev.2010.05.005
119. Hashimoto T, Sasaki M, Sugai K, Hanaoka S, Fukumizu M, Kato T. Paroxysmal discharges on EEG in young autistic patients are frequent in frontal regions. *J. Med. Invest*. 2001;48(3–4):175–180.
120. Holmes GL, Tian C, Hernan AE, Flynn S, Camp D, Barry J. Alterations in sociability and functional brain connectivity caused by early-life seizures are prevented by bumetanide. *Neurobiol Dis*. 2015;77:204–219. doi:10.1016/j.nbd.2015.02.015
121. Hernan AE, Holmes GL, Isaev D, Scott RC, Isaeva E. Altered short-term plasticity in the prefrontal cortex after early life seizures. *Neurobiol Dis*. 2013;50:120–126. doi:10.1016/j.nbd.2012.10.007

122. van Steenburgh JJ, Varvaris M, Schretlen DJ, Vannorsdall TD, Gordon B. Balanced bifrontal transcranial direct current stimulation enhances working memory in adults with high-functioning autism: a sham-controlled crossover study. *Molecular Autism*. 2017;8. doi:10.1186/s13229-017-0152-x
123. Engineer CT, Hays SA, Kilgard MP. Vagus nerve stimulation as a potential adjuvant to behavioral therapy for autism and other neurodevelopmental disorders. *J. Neurodev. Disord*. 2017;9(1):20. doi:10.1186/s11689-017-9203-z