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REVIEW PAPER

Transcranial magnetic stimulation as a new therapeutical approach in autism spectrum disorders and attention deficit hyperactivity disorder – a review

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ABSTRACT

Introduction and aim. Autism spectrum disorders (ASD) and attention deficit hyperactivity disorder (ADHD) neurobiology reveals a complex picture of altered excitation-inhibition balance, aberrant neuronal and neurotransmitter activity, and network disorganization that could be addressed through repetitive transcranial magnetic stimulation (TMS). In this paper, we provide a narrative review of the most recent literature on the use of TMS to treat patients with ASD and ADHD.

Material and methods. Literature search from 2018 up to November 2022 has been conducted on PubMed database. Keywords reflected diagnoses and treatment modalities of interest.

Analysis of the literature. Eleven clinical trials regarding the use of TMS as a therapeutic tool in ASD, and seven studies (of which 3 are case reports) for ADHD have been reported. The dorsolateral prefrontal cortex (DLPFC) is the most frequent area stimulated. Heterogeneity in stimulation parameters, patient age, and outcome measures limited the interpretation of findings.

Conclusion. TMS as a therapeutic tool for neurodevelopmental disorders is still in its infancy. To define the real efficacy of TMS, future studies must be randomized, sham-controlled, and double-blind, and should include a larger sample with adequate inclusion/exclusion criteria, and longitudinal follow-up.

Keywords. ADHD, ASD, autism, neuromodulation, neurodevelopmental disorders, TMS

Introduction

Autism spectrum disorder (ASD) and attention deficit hyperactivity disorder (ADHD) are complex, heterogeneous, neurodevelopmental disorders caused by a strict interplay of genetic vulnerability and environmental factors that typically onset in childhood. Heterogeneity in etiology, phenotype, comorbidities, and outcomes are common hallmarks among these diseases. Treatment options for these neurodevelopmental disorders are limited, mainly focusing on early behavioral interventions. While for ASD there are no specific pharmacological treatments to address the core symptoms, psychostim-

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ulants are considered the most effective therapy for patients with ADHD, with various side effects and the potential for abuse.[1-3]

In this scenario, transcranial magnetic stimulation (TMS) could emerge as a therapeutic option to treat ASD and ADHD in children and adolescents. TMS involves magnetic stimulation of the brain to cause long-term changes in excitability and neurochemical activity, healing the key neurobiological alterations known to be involved in neurodevelopment disorders.[1]

ASD refers to a group of clinical conditions that share the symptomatic core dyad of impaired social communication and interaction, as well as restricted, repetitive patterns of behavior and interests. ADHD is characterized by pervasive symptoms of age-inappropriate inattention, and/or hyperactivity/impulsivity, which interferes with daily functioning and development.[1] In both cases, symptoms persist across the lifespan, with a higher prevalence among males.[1]

Treatment options for these neurodevelopmental disorders are limited, mainly focusing on early behavioral interventions. While for ASD there are no specific pharmacological treatments to address the core symptoms, psychostimulants are considered the most effective therapy for patients with ADHD[3]. Unfortunately, various side effects and the potential for abuse with no reduction in symptom severity in long-term use can restrict its administration.[4]

In this scenario, alternative therapeutic strategies have been explored. Noninvasive brain stimulation, and in particular TMS could emerge as a therapeutic option for the treatment of ASD and ADHD in children and adolescents.[5]

TMS is based on the scientific principle of electromagnetic induction, consisting of the rapid pulse of electrical current in a copper wire coil, which in turn induces a rapidly fluctuating magnetic field. The magnetic field passes through the skull and generates an electric field, able to depolarize and fire brain networks safely and painlessly.[6]

Three TMS paradigms have been extensively used: single-pulse, paired pulses, and repetitive pulses. Among these, repeated TMS (rTMS) pulses protocols show the greatest therapeutic potential and longest-lasting effects.[6,7] By convention, low-frequency rTMS (<5 Hz) plays an inhibitory effect on the underlying cortex, while high-frequency stimulation (>5Hz) typically induces cortical facilitation.[2,6] Besides these classic rTMS procedures, there are other TMS protocols with the potential to modulate cortical activities for therapeutic purposes, such as theta-burst stimulation (TBS).[6,8,9] Continuous theta-burst stimulation (cTBS) shows an inhibitory effect on the cortex, while intermittent theta-burst stimulation (iTBS) is excitatory.

Changes in synaptic strength determine the long-lasting effects of TMS on the brain, which also result in specific structural modifications of dendritic spines and sprouting.[10]

In animal models, rTMS promoted complex neurobiochemical effects such as early genes stimulation, neurotransmitters release modulation, and expression of glutamate AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid)/NMDA (*N*-methyl-D-aspartate) receptors.[11] These molecular effects influence the electrophysiological properties of neurons, leading to synaptic plasticity-related phenomena, including long-term potentiation (LTP) and long-term depression (LTD).[11-13] When TMS is applied repetitively, a number of AMPA receptors (that open quickly and briefly) are recruited with secondary induction of NMDA transmission. NMDA receptors activation increases calcium influx and, therefore, calcium-sensitive signaling pathways. Accordingly, long-term changes in both the presynaptic and postsynaptic neurons lead to increased synaptic strength.[11,14] LTP is enhanced, in part, by retrograde signals that further release glutamate and BDNF. This in turn, activates the BDNF-TrkB pathway, which prompts the NMDA-dependent after-effects on synaptic plasticity.[15] In an *in vitro* model has been demonstrated that rTMS may increase the steady-state current in the presynaptic compartment independently from NMDA postsynaptic transmission. In this way, it is likely that a longer duration of rTMS may strengthen these presynaptic steady-state currents, thus prolonging the TMS-induced sequelae.[11,16]

Since rTMS produces a non-invasive form of brain cells activation, it has been considered for the treatment of several neuropsychiatric conditions, where behavioral disability is associated to altered cortical excitability and plasticity.[2]

In the pediatric population, rTMS has been demonstrated to be safe and tolerable.[17] Krishnan et al. reviewed data from 48 studies involving over 513 children and adolescents (aged 2.5-17.8 years old) and found that TMS side effects were generally mild and transient, such as headache, scalp discomfort, twitching, mood changes, fatigue, tinnitus. Seizures are the most serious side effect, and there have been very few cases in adolescents receiving TMS.[18] Overall, the risk of seizure is considered to be less than 0.01% across all patients and all paradigms.[2]

Aim

Here we provide an overview of the most recent literature on the use of TMS as treatment in patients with ASD and ADHD. We also briefly discuss the biological mechanisms of these disorders and how TMS may modulate them. Then we summarize the current evidence associated with safety, tolerability, and efficacy of rTMS in ASD and ADHD populations.

Material and methods

Although this article is not intended to be a systematic review, to identify all relevant articles a comprehensive search of the PubMed database has been conducted up to November 2022. Search terms reflected the diagnoses of interest (ASD, Autism, Autism Spectrum Disorders, Asperger, ADHD, Attention Deficit Hyperactivity Disorder, Neurodevelopmental disorders) and the interventions of interest (Transcranial magnetic stimulation, TMS, rTMS, TBS, neuromodulation). Only full articles published in English and in peer-review journals were considered.

Analysis of the literature

Neurobiology of ASD and ADHD: the rationale behind TMS treatment

The neurobiology of ASD and ADHD reveals a complex picture of altered excitation-inhibition (E/I) balance, aberrant neuronal activity, neurotransmission, and disorganization of brain networks.[19]

ASD

One of the most recent theories on the etiopathogenesis of ASD suggests that it may depend on the structural disarray of the neocortex's vertical morpho-functional units, otherwise known as mini-columns.[20] Mini-columns have a clearly defined hierarchical structure, with combinations of GABAergic interneurons that control inputs and outputs of pyramidal cells at their periphery, and radially oriented arrays of pyramidal projection neurons in their core.[21]

Minicolumns were both more numerous and smaller than usual in autistic patients' cerebral cortex, and there was less peripheral neuropil compartment. Because this compartment contains the unmyelinated projections of certain interneurons, researchers hypothesize that inhibition is impaired in autism.[20]

In ASD, cortical dysplasia which underlies the hypothesis of an inhibitory deficit appears in overabundance within the prefrontal lobes.[22] Immunocytochemical studies have localized this inhibitory deficit to a subset of interneurons containing the calcium-binding protein parvalbumin (PV). The loss of PV interneurons has been proposed to determine gamma oscillation abnormalities, which are thought to be a neurophysiological biomarker of ASD. Gamma oscillations (typically defined as 30 to 120 Hz with a low amplitude of 10-20V) are generated locally as a result of reciprocal interactions between excitatory pyramidal cells and the rhythmic perisomatic inhibition of PV interneurons.[23] In autism, uninhibited gamma activity suggests that none of the circuits of the brain comes to dominance as many of them are active simultaneously, with the consequent inability to focus attention on relevant, social stimuli. Thus, some researchers point that altered–gamma oscillations could explain the "weak central coherence" theory and its associated deficits in ASD patients.[23-25]

ADHD

One of the most influential theories for the neural basis of ADHD has focused on deficits in key domains of executive functions (EF).[26] The most consistent deficits seem to involve the "cool" EF such as motor response inhibition, working memory, sustained attention, response variability, and cognitive switching.[26-28] However, less severe impairments have also been observed in the so-called "hot" EF, including motivation control and reward-related decision making.[28,29]

ADHD patients appear to report multisystemic deficits affecting the front-striate-parietal-cerebellar system, which controls different cognitive functions.[28,29] In neuroimaging studies, during motor inhibitory control and attentional tasks, the right ventrolateral and dorsolateral prefrontal cortices (VLPFC and DLPFC) show consistently lower activation in people with ADHD. This makes the PFC a potential target for rTMS treatment.[30,31] In addition, during "hot" EF tasks (like decision-making tasks involving rewards or tasks requiring temporal discounting), children with ADHD have also demonstrated underactivation in the ventromedial prefrontal cortex (vmPFC), orbitofrontal cortex (OFC), and striate-limbic region.[28]

ADHD patients display also abnormally increased activation in areas of the default mode network, which consists of intercorrelated activation of the ventromedial frontal cortex, posterior cingulate, precuneus, inferior parietal, and temporal regions and is supposed to reflect task-irrelevant thoughts.[30,32] It has been proposed that poor performance on attention-demanding higher-level cognitive tasks in ADHD is caused by a combination of decreased activation of task-relevant regions and decreased deactivation of the default mode network, which reflects more mind-wandering.[29,33]

A large number of ADHD studies have also revealed regional volumetric changes, an abnormal trajectory of brain development, and abnormal functional connectivity.[9] Structural and functional differences in the ADHD brain are accompanied by defects of the catecholaminergic neurotransmitters, dopamine, and norepinephrine, which are believed to be critical in the pathophysiology of ADHD.[9] Low dopamine levels in the prefrontal cortex are linked to increased hyperactivity and irritability.

Interestingly, it has been shown that TMS might produce a similar effect on the dopamine system as D-amphetamine.[34] rTMS over prefrontal regions in animals and humans would alter neurotransmitter systems, including changes in serotonin, striatal dopamine release, and metabolite levels, as well as in striatal glutamate release and concentration.[28] Due to this and the

TMS's known safety profile, it can be considered a secure and efficient therapy option for ADHD.

TMS and ASD

Several trials indicate that specific rTMS protocols target certain regions of the cortex leading to improvement in behavioral deficits.[35]

These results have been also confirmed by recent meta-analyses showing that TMS may improve social abilities, repetitive and stereotyped behaviors, as well as errors in executive function tasks.[36]

In the next section, we will discuss articles on this topic published from 2018 to 2022 (Table 1A and 1B).

Clinical effects of TMS in ASD

A 3-week open-label trial (aged 9-17 years) delivered fifteen sessions of iTBS at 100% motor threshold on the right DLPFC in a population of 10 male children.[37] Improvements were reported in parent report scores on the repetitive behaviors. The iTBS treatments were well tolerated with no serious adverse effects.

In 2018, Kang et al. explored the efficacy of low-frequency rTMS on brain activity and behavior of 32 autistic children with intellectual disabilities (Intelligence Quotient, IQ < 70.[38] The autistic children were divided randomly into an experimental group and a control group. Participants received 18 times rTMS treatment with Fig8 coil, two times per week (9 weeks). The coil was placed over the left DLPFC for the first six times, then over the right DLPFC for the next six times, and finally over the bilateral DLPFC for the remaining six times. Low-frequency rTMS at 1 Hz with 90% MT was used. The Autism Behavior Checklist (ABC) scores revealed positive effects of rTMS on behavior. Furthermore, they recorded electroencephalographic (EEG) data before and after TMS treatment, highlighting an improvement in neurophysiological markers of cognitive function and brain connectivity. Particularly, an augmented peak alpha frequency (PAF) in the frontal, left temporal, right temporal, and occipital regions and alpha coherence between the central and the right temporal regions were reported.

More recently, using a similar stimulation protocol, the same research group published new findings on children with low-functioning autism.[39] Thirty-two children were divided equally into 2 groups: 16 children received a real rTMS treatment, while the other 16 children sham stimulation. Data EEG and ABC scores were collected before and after rTMS. To characterize the deterministic features of cortical activity, three recurrence quantification analysis (QRA) measures were extracted from EEG signals: recursive rate (RR), deterministic (DET), and mean diagonal length (L). Significant differences in RR and DET were observed between the experimental group and the sham group, highlighting a positive outcome for brain activity. They also found an improvement in the ABC score post-rTMS only for the experimental group.

High-frequency rTMS has been used on the left inferior parietal lobule in 11 low-functioning ASD children to improve autism core symptoms.[40] Patients received two rTMS treatment courses six weeks apart. Each treatment course consisted of 5-second trains at 20 Hz, with 10-minute inter-train intervals, on each consecutive weekday for three weeks. Subjects were evaluated five times: before and after the first and second rTMS courses, and six weeks after the second rTMS treatment course. Participants showed a significant and long-lasting reduction in language and social-related symptoms measured by ATEC (Autism Treatment Evaluation Checklist). Furthermore, caregivers referred to some improvements in imitation and cognition.

In 2020 Gwynette et al. conducted an open-label, single-arm study to evaluate the safety and effects of rTMS on depression and autism symptoms in individuals with both major depressive disorder (MDD) and ASD.[41] Ten participants aged 23–29 years with ASD and MDD (without any medication changes in the last month, with IQ >60) were involved in the study. They underwent 25 sessions of rTMS applied to the left DLPFC. Overall, rTMS was well tolerated with just minor adverse effects. The Hamilton Rating Scale for Depression (HDRS) significantly improved, and 40% of participants achieved depression remission after rTMS treatment. There was no change in self-reported autism questionnaires following treatment, while parents' clinical scales of core symptoms of autism suggested an improvement in the ritualistic, sameness, and restricted behaviors that lasted over the next 3 months.

The Aimes' group published a pilot, double-blind, randomized controlled trial on the use of rTMS as treatment for EF deficits in ASD.[42] Thirty-eight autistic patients (age 16-35 years old) with IQ > 70, were equally randomized into two groups: the active group (n=18) and the sham group (n=20). Participants received TMS stimulation bilaterally on DLPFC for each session. Clinical and cognitive assessments were completed before and 4 weeks later the rTMS cycle. No evidence for the efficacy of active versus sham rTMS on EF was found. However, they found preliminary evidence of EF improvement following active *vs*. sham rTMS in participants with ASD with more severe adaptive functioning deficits. Adverse events experienced across groups were mild or moderate.

From the same lab, Moxon-Emre et al. conducted a randomized double-blind sham-controlled trial designed to investigate the impact of excitatory rTMS on glutamatergic (Glx) and γ-aminobutyric acid (GABA) metabolite brain levels, in ASD patients with EF defi-

Table 1A. Summary of studies on ADS, outcome measures, and results, including use of medication and adverse effects

Study	TMS modality/ Study design	N of patients on TMS	N of controls	Age (Years)	Target	Number of sessions	Frequency	Hz	MT(%)	Pulses/Sessions	Inter-Train Interval	Duration/session (minutes)
Abujadi et. al, 2018	iTBS //case-study (open-label)	10 (males)	/	Age range: 9-17	R DLPFC	15	Daily (5 weekday, over 3 weeks)	50 (x 3 pulse bursts at 5 Hz)	100	900 PPS (300 burst)	8 s On/ 2 s Off	5min
Kang et al., 2018	rTMS // case-study (randomized, sham controlled study)	16 (13 males: 3 females)	Sham group 16 (13 males: 3 females)	Active group= 7.8 ± 2.1; Sham group= 7.2 ± 1.6	L DLPFC & R DLPFC	18 (6 L DLPFC, 6 R DLPFCS, 6 bilaterally)	Twice every week, for 9 weeks	1	90	180PPSx18 (180 for each session)	20 s	Not reported
Kang et al., 2022	rTMS // case-study (randomized, sham controlled study)	16 (13 males: 3 females)	Sham group 16 (13 males: 3 females)	Active group= 7.8 ± 2.1; Sham group= 7.2 ± 1.6	L DLPFC & R DLPFC	18 (6 L DLPFC, 6 R DLPFCS, 6 bilaterally)	Twice every week, for 9 weeks	1	90	180PPSx18 (180PPS for each session)	20s	Not reported
Yang et al., 2019	rTMS/ case series	11 (7males: 4females)	/	7.09 ± 2.88	L inferior parietal lobule	30 (15 sessions for each course)	Daily (5 weekdays over 6 weeks)	20	50	Not reported	10 min	Not reported
Gwynette et al., 2020	rTMS/ case-study (open label)	10 (9males: 1 female)	/	25.5	L DLPFC	25	Daily	10	100-120	3.000 PPS	5 s On/ 10 s Off	Not reported
Ameis et al., 2020	rTMS/case-study (double-blind, randomized, sham controlled study)	20 (14 males: 6 females); 2 withdrew	Sham group 20 (14 males:6 females)	22.58 ± 4.5	L DLPFC & R DLPFC	20	Daily (5 weekdays over 4 weeks)	20	90	1500 PPS= 750 pulses/ hemisphere	30sec	Not reported
Moxon-Emre et. Al, 2021	rTMS/ case-study (Double blind, sham-controlled study)	16 (16 males: 2 females)	Sham group 12 patients(8 males: 4 females)	23.3 ± 4.69	L DLPFC	20	Daily (5 weekday for 4 weeks)	20	90	1500 PPS	30sec	30-45 min
Casanova et al., 2021	rTMS /case-control study	19 (14 males:5 females)	19 healthy controls, who did not receive TMS	14.2 ± 3.61	L DLPFC & R DLPFC	18 (6 left DLPFC, 6 r DLPFCS, 6 bilaterally)	Weekly	1	90	180 PPS (9x20)	20-30s	Not reported
Darwish et al., 2021	rTMS/ randomized control study	15 (11males: 4 females)	15 (9 males: 6females)	Active group (5.13±1.89) Sham group (5.92±2.33) Total range (3-10years)	Broca's area on L IFC	4	Weekly	1	70	1800 PPS per day session	20 s	40 min
Ni et al., 2021	iTBS/ a randomized, single-blind parallel sham-controlled trial, followed by additional 4-week open-label	75 divided into Active group 40 (35males: 5 females)	35 (30 males: 5 females)	Active group (13.0±2.8) Sham group (12.5±2.9) Total range (8 -17years)	Bilateral pSTS	16	Twice per week (2 days/week for 8 weeks)	50	80	2400 PPS/session.	10 s	Not reported
Ni et al., 2021	iTBS/ randomized, single-blinded, sham-controlled crossover trial	13 (11males: 2 females)	12	22.7±1.4	Bilateral pSTS	10	Daily (5weekday for 2 weeks)	50	80	2400 PPS/ session.	10 s	Not reported

Table 1B. Summary of studies on ADS, outcome measures, and results, including use of medication and adverse effects*

Study	Clinical	Cognitive	Effects	Adverse Effects	Medication
Abujadi et al., 2018	ASD	IQ>50	Yale-Brown Obsessive-Compulsive Scale improvement, reduced perseverative errors on the Wisconsin Card Sorting Test and lower total time for the Stroop test were highlighted.	None	Not reported
Kang et al., 2018	LF ASD	IQ< 70	Significant increases in the Peak Alpha Frequency at the frontal region, the left temporal region, the right temporal region and the occipital region and a significant increase of alpha coherence between the central region and the right temporal region. Improvements or repetitive behaviours	Not reported	Not reported
Kang et al., 2022	LF ASD	IQ< 70	Significant differences in RR and DET were observed between the experimental group and the control group, highlighting a positive outcome for brain activity. They found also, an improvement in the Autism Behavior Checklist (ABC) score post-rTMS only for the experimental	Not reported	Not reported
Yang et al., 2019	LF ASD	IQ <70	Participants showed a significant reduction in language- and social-related symptoms measured by Autism Treatment Evaluation Checklist (ATEC). Moreover, some possible improvements in imitation and cognition were reported by caregivers	1 partecipant showed more Irritability during the first 3 days of each treatment course; 1 patient reported emotional dysregulation and restless after the second course, which recovered in 5 days; 1 patient showed Hyperactivity and irritability during the first 5 days of the first course	None
Gwynette et al., 2020	ASD + MDD	IQ>60	The Hamilton rating scale for depression (HAM-D17) improved, and 40% of participants achieved remission. Clinical scales of core symptoms of autism also suggested improvement, though no change was observed by the participants themselves	1 partecipant had anticipatory anxiety; 1 reported increased irritability; 1 participant had transient muscle spasms. Other adverse events included mild scalp dicomfort, mild headache, and fatigue, were reported within the first week of treatment. 1 partecipant had a seizure due to a programming error	Not reported wich medication
Ameis et al. 2020	ASD	IQ>70	No evidence for efficacy of active versus sham rTMS on EF performance was found. However, we found promising preliminary evidence of EF performance improvement following active versus sham rTMS in participants with ASD with more severe adaptive functioning deficits	Adverse events experienced across groups included: headache, pain, nausea, nose bleed, congestion, laceration. The rate of adverse events in the active group was 1.37 times the rate in the sham group	26/40 partecipants used psychotropic medications. Active group= 16/20; Sham group= 10/20
Moxon-Emre et al., 2021	ASD	IQ>70 (Active group=112+19.5; Sham group=112±16.1)	Normalization of local Glx levels in adults with ASD.	Not reported	Psychotropic medication=12/16 partecipants of Active group; 5/12 partecipants of Sham group
Casanova et al., 2021	ASD	IQ>80	A significant reduction in the time period to reach peak amplitude and an increase in the decay phase (settling time) og gamma oscillations.	Not reported	None
Darwish et al., 2021	ASD	Not reported	There was a statistically significant clinical improvement in the active group comparing baseline Childhood Autism Rating at Scale (CARS) assessment. No significant difference between inter-groups. There was significant difference in improvement between the two groups according to eye contact and in response to examiner. Significant difference between active and sham groups in improvement of the active expressive language. No difference in passive vocabulary.	Not reported	Not reported
Ni et al., 2021	ASD	IQ>70	No therapeutic efficacy on the clinical symptoms and cognitive performance of social impairment	Local pain during iTBS intervention (10% in the Active at both phases and 29% in the Sham group at Phase 2) as well as headache, dizziness, tinnitus, and anxiety	24/75 patients on Methylphenidate; 2/75 on Atomoxetine; 10/75 on Antipsychotics
Ni et al., 2021	ASD	IQ= 102.9 ±17.4	Positive effects on parent-rate autistic symptoms	Not reported	1/13 was os sertraline; 1/13 on Fluoxetine; 1/13 on Methylphenidate; 1/13 on Alprazolam

* LF ASD – low function autism; DLPFC – dorsolateral prefrontal cortex; pSTS – posterior superior temporal sulcus; IFC – inferior frontal cortex; L – left. R – right; iTBS – intermittent theta-burst stimulation; rTMS – repetitive transcranial magnetic stimulation; MT – Motor threshold

cits.[43] Twenty-eight participants aged 16 to 33, underwent two magnetic resonance spectroscopy (MRS) scans of the left DLPFC, before and after randomization to receive active or sham rTMS in the same area. Baseline MRS data was available for 19 typically developing controls, matched for age and sex. Metabolite levels for Glx and GABA+ were compared between ASD and control groups at baseline and post-TMS treatment. Absolute Glx level was greater in the active rTMS group compared to the sham group, on the contrary GABA+ did not differ between groups. There was a significant difference between the rTMS and sham groups in terms of participants' use of psychotropic drugs and comorbidities, particularly depression. These findings highlight excitatory rTMS's ability to modulate local Glx levels and improve depression symptoms in young adults with ASD.

In 2021, the Casanova group conducted a control-trial study involving 19 ASD patients and 19 healthy controls, matched for age and sex.[44] Both groups received rTMS weekly (2 sessions/week for 9 weeks in total). The initial six rTMS sessions were administered over the left DLPC, followed by 6 sessions targeting the right DLPC, and an additional 6 treatments were done bilaterally (over the left and right DLPFC). Gamma frequency oscillations were also analyzed in response to a visual classification task (Kanizsa figures). Besides the normalization of time to peak amplitude and ringing decay of autistic subjects after TMS therapy (considered an index of E/I normalization), and a reduction of total error percentage at the visual task, the ABC and RBS-R (The Repetitive Behavior Scale-Revised) parental behavioral checklists rating changes showed statistically significant improvements, especially in repetitive and restricted behaviors.[44]

In a randomized control study, Darwish et al. evaluated the impact on language of rTMS on Broca's area in a sample of 30 autistic children aged between 3 and 10 years.[45] Patients were randomly divided into active (n=15) and sham (n=15) groups. The rTMS was administered weekly for 4 weeks over the left inferior frontal cortex (IFC), at 1.0 Hz and 70% of MT. CARS (Childhood *Autism* Rating Scale) showed significant improvement in the active group compared to baseline evaluation, though no significant difference between the two groups was highlighted. Moreover, there was a significant difference in the improvement of eye contact and active expressive language.

More recently, Ni et al. assessed the efficacy of iTBS over the bilateral posterior superior temporal sulcus (pSTS) in ASD, in a 4-week randomized, single-blind parallel sham-controlled trial, followed by a 4-week open-label intervention.[46] Seventy-eight children and adolescents (aged 8-17 years) were randomly assigned to one of two groups: active or sham. During the first 4 weeks, the active group received two-session/week of iTBS, whereas the control group received the same number of sham stimulation. After unblinding, both groups received eight-session of real stimulation over the additional 4 weeks. The within-group analysis revealed that 8 weeks of iTBS achieved greater efficacy than 4-week interventions. Participants with higher intelligence and better social cognitive abilities, as well as less severe attention-deficit hyperactivity disorder at baseline, were more likely to respond. However, the clinical efficacy of iTBS of pSTS was insignificant.

In a single-blinded, randomized, crossover, and sham-controlled pilot study, the same research group investigated the effects of 5-day multiple sessions of iTBS over the bilateral pSTS in 13 adults with ASD.[47] Each TBS train was comprised of a burst of 3 pulses at 50 Hz, given 1 every 200 ms for 10 times. The TBS train was given every 10 s for 20 times to have 600 pulses in total for each iTBS course. In this study, two iTBS courses, which were separated by a 5-min break, were first applied to the left and then to the right pSTS. The stimulus intensity of iTBS over the pSTS was 80 % of MT. For the sham control, iTBS sessions were given to the inion. The results revealed significantly immediate effects of multi-session iTBS over the bilateral pSTS on parent-rate autistic symptoms, but also that baseline social impairment and cognitive performance impacted iTBS efficacy.

The prefrontal cortex (PFC), especially DLPFC, is the main stimulation target region in ASD patients. Although most of these studies have reported positive effects of rTMS there is high heterogeneity and variability associated with patient characteristics, study designs, and stimulation parameters. Furthermore, it is still difficult to establish the real impact of variables such as age, sex, severity of the disorder, medications on TMS outcomes.

TMS stimulation in ADHD

There is a limited number of clinical trials on the use of TMS in ADHD population. A recent review reported 6 studies conducted principally in adults (four out of six) over 45 years, highlighting relatively little evidence for rTMS efficacy on ADHD symptoms or cognition.[28]

Here we report the latest trials published, including case reports as well (Table 2A and 2B).

Clinical effects of TMS in ADHD

In 2008 Niederhofern described a case of a 42-year-old female with ADHD resistant to methylphenidate, stopped 2 months before the trial.[48] A 5-day rTMS over the motor area with B65 coil had been administered at a frequency of 1 Hz, for 1200 pulses per day. Sham stimulation was also administered four months after the active rTMS. Conner's rating scale (CSRS) for adults

Table 2A. Summary of studies on ADHD, outcome measures, and results, including use of medication and adverse effects

Study	TMS modality/ Study design	N of patients	N of controls	Age (Years)	Target	Number of sessions	Frequency	Hz	MT(%)	Pulses/Sessions	Inter-Train Interval	Duration/session (minutes)
Niederhofer et al., 2008	rTMS//case-report	1 (female)	/	42	Motor Area	5	Daily	1	Not reported	1200 PPS/die	Not reported	60 min
Niederhofer et al., 2012	rTMS//case-report	1(female)	/	42	Additional Motor Area	21	Daily	1	Not reported	1200 PPS/die	Not reported	60 min
Ustohal et al., 2012	rTMS//case-report, sham controlled-study	1 (male)	patient received also sham treatment	36	L + R DLPFC	10 (5 for each emisphere)	Not reported	10	120%	1500 PPSfor session	10sec	Not reported
Shahar et al., 2015	Deep rTMS//Double-blind radomized control study	5	5 (sham group)	Not reported (Adults)	Right PFC	15	Not reported	Not reported (High frequency)	Not reported	Not reported	Not reported	Not reported
Harmelech et al. 2018	r TMS// Blinded sham-controlled trial	34 (divided in Active group and sham group)	Not reported	Not reported (Adults)	Bilateral DLPFC	15	Daily (5 weekdays over 3 Weeks)	Not reported (High frequency)	Not reported	Not reported	Not reported	Not reported
Cao et al., 2019	rTMS// Double-Blind sham-controlled study	22= rTMS group; 21 = rTM+ ATX group	the ATX group (n = 16) and the placebo group (n = 16); + Control group (18 healthy children)	< 18	Right DLPFC	30	Daily (5 weekdays over 6 weeks)	10	100%	2400 PPS for session	26sec	30 min
Cardullo et al., 2021	rTMS// retrospective, open- label, no sham control study	22 (21 males: 1 female)= (Cocaine Abuse+ ADHD and 208 (203 males: 5 females)= (Cocaine Abuse)	/ (everyone received TMS)	22-59. ADHD +Coc A(37.91± 8.71); Coc A (37.67± 7.05)	Left DLPFC	30	Twice-daily rTMS sessions for the first 5 consecutive days, followed by twice-daily rTMS sessions once a week over 11 weeks	15	100 % (MT)	2400 PPS(60x40)	60 impulses per stimulation train, inter-train interval 15 s, and 40 total trains, for a session duration of 13 min	13 min

Table 2B. Summary of studies on ADHD, outcome measures, and results, including use of medication and adverse effects

Study	Clinical	Cognitive	Effects	Adverse Effects	Medication
Niederhofer et al., 2008	ADHD resistant to methylphenidate	Not reported	Self-reported improvement (Hyperactive symptoms domain)	None	Methylphenidate interrupted 2 months before TMS
Niederhofer et al., 2012	ADHD combined type with MPH (20 mg)	Not reported	After 3 week reduction in dosage of MPH to 10 mg + Self-reported improvement (Hyperactivity domain)	None	Methylphenidate
Ustohal et al., 2012	ADHD and Depression resistant to atomoxetine	Not reported	Improvement in attention after L DLPFC stimulation	After R DLPFC stimulation, patient reported dysphoria, hypobulia, tension and also inattention	Not reported (previously treated treated with venlafaxine, milnacipran,mirtazapine and tianeptine)
Shahar et al., 2015	ADHD	Not reported	Attention improvement	Not reported	Not reported
Paz et al., 2018	ADHD	Not reported	No difference between Active and Sham group	None	None
Harmelech et al., 2018	ADHD	Not reported	Significant improvements were observed in CAARS inattention sub-scale and in the attention and execu- tive function scores on the Mindstreams battery in the real stimulation groups mainly in the right DLPFC group	Not reported	Not reported
Cao et al., 2019	ADHD	IQ ≥80	Improvement in all ADHD core symptoms on the SNAP-IV scale. Downregulation of miRNA-let-7d expression level only at post- rTMS or at post-ATX treatment	1 patient reported headache.	None
Cardullo et al., 2021	ADHD + Cocaine Abuse	Not reported	Improvements on cocaine use, craving, and other negative affect symptoms. No differences were observed between groups	None	9/22 of ADHD patients were on Atomoxetine

showed an improvement in the hyperactive symptoms only after TMS stimulation with a duration of 4 weeks.[48] Lately, Niederhofer administered rTMS (with the same stimulation paradigm) for 21 days over the right motor area in a patient on methylphenidate.[49] A clinical improvement in hyperactivity was seen after the first 5 days of stimulation, with a 3 weeks long-lasting.[49] Both studies did not show any difference in the inattention domain.

A 36-year-old man with ADHD and depression, resistant to atomoxetine received 5 sessions of 10 Hz rTMS on the left and right DLPFC at 120% MT. The patient showed improvement in attention at d2Attention test when treated on the left DLPFC, and reported an improvement even after sham stimulation. Neurostimulation on the right DLPFC showed adverse effects of dysphoria, inability to respond emotionally, hypobulia, tension, and impaired attention.[50]

Shahar et al. conducted a double-blind, randomized, control study on 20 adults with ADHD, in which 15 sessions of high-frequency rTMS using either deep, Fig8, or sham coils over the right PFC were administered.[51] Conner's Adult ADHD Rating Scales (CAARS) established improvements in the attention measures and the Stop Signal Reaction Time (SSRT) test showed a better response inhibition.[51]

Thirty-four adults with ADHD were involved in a blinded sham-controlled trial, in which they received H-coil rTMS over bilateral DLPFC after cognitive training, for 15 sessions spread over 3 weeks.[52] Improvements were seen in the CAARS inattention subscale and the attention and executive function scores of the Mindstreams cognitive assessment battery for the group with right DLPFC stimulation, with increased activation of that area during a working memory task, as measured via fMRI.[52]

More recently, Cao analyzed the impact of rTMS on serologic-microRNA-let-7d (miRNA-let-7d) and miRNA-107, as diagnostic and therapeutic biomarkers of ADHD.[53] Seventy-five ADHD patients under 18 years of age, were randomly divided to receive 6 weeks of either rTMS (using a Fig 8 coil, 5 sessions per week, of 30-minute sessions of 60 cycles of 4 s of 10 Hz stimulation followed by 26 s intertrain interval at 100% MT, totaling to 2400 pulses per session of the right DLPFC), sham rTMS, atomoxetine,-or placebo. Improvement in all ADHD core symptoms on the SNAP-IV (the Swanson, Nolan, and Pelham Rating scale) was observed. On the contrary, sham rTMS or placebo failed to produce any improvements. Compared with pre-rTMS or pre-ATX treatment in ADHD patients, the serum miRNA-let-7d expression level was downregulated only at post- rTMS or at post-ATX treatment. This suggested that serum miRNA-let-7d may serve as a potential biomarker for clinical diagnosis and therapeutic assessment of ADHD.[53]

In 2021, Cardullo et colleagues conducted an interesting study on 22 adults with ADHD and CocUD (Cocaine Use Disorder) in comorbidity, compared to 208 CocUD-only subjects, which received a high-frequency (15Hz) rTMS treatment over the left-DLPFC (intensity 100% of the motor threshold, 60 impulses per stimulation train, inter-strain interval 15s, and 40 total trains, for a 13 minutes session)(54). Twice-daily rTMS sessions for the first 5 consecutive days of treatment, followed by twice-daily rTMS sessions once a week over 11 weeks were administrated. The time interval between the two sessions each day was 45–60 min. ADHD/CocUD patients, of whom 19/22 were pharmacologically treated with atomoxetine, received an rTMS treatment in addition to conventional psychosocial intervention. Significant reduction of inattentive and hyperactive symptoms, in addition to decreased cocaine use, craving, and other negative affect symptoms were reported. No differences were observed between groups.[54]

Even for ADHD population, the majority of studies focused on the stimulation of the DLPFC, with some investigating the effect on different areas, including and the motor areas. In general, it could be assumed that stimulation with high-frequency over the right DLPFC and low frequency in the left DLPFC improve ADHD symptoms.

Clinical effect of TMS

Although evidence of TMS potentiality in the treatment of ASD and ADHD, there are still critical challenges that may limit its use in clinical practice.[55]

In most existing studies, lack of blindness and randomization, and self-report evaluation are critical design issues that may significantly impact observed outcomes.[8,35,55]

No adequate amount of data exists on the TMS clinical efficacy depending on patients' age, gender, or cognitive impairment.[36] There are also ongoing concerns about safety, tolerability, and ethical questions. Over half of the existing studies did not report side effects, and the others often did not use standardized questionnaires to evaluate them. In addition, many studies enrolled patients on psychotropic drugs (such as stabilizers, antiepileptics, psychostimulants, antidepressants, and neuroleptics), which may induce long-term changes in the synaptic and excitatory balance, and consequentially may affect rTMS outcomes.[55]

Finally, another crucial weakness is the lack of longitudinal follow-up. This prevents critical questions regarding possible predictors of outcome (e.g., genetic profiling), duration of benefits, and utility of booster session.[23,56] As suggested by Oberman et al., the "one size fits all" approach may not be ideal for this application.[8,35]

Conclusion

Given the phenotypic, endophenotypic, and etiological heterogeneity of ASD and ADHD, it is not surprising to note a parallel heterogenicity in the results of TMS trials. With the spread of the concept of "personalized medicine", a more targeted approach, based on preliminary, individual measures of cortical plasticity and excitability, functional state of target networks, in combination with other behavioral or pharmacological interventions is an urgent need.

Declarations

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Author contributions

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Conflicts of interest

The authors declare no competing interests.

Data availability

No datasets were generated or analyzed during the current study.

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