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Therapeutic Applications of Noninvasive Neuromodulation in Children and Adolescents

Deniz Doruk Camsari, MD[a], **Melissa Kirkovski, PhD**[b], and **Paul E. Croarkin, DO, MS**[a,*]

[a]Department of Psychiatry and Psychology, Mayo Clinic, 200 First Street Southwest, Rochester, MN 55905, USA

[b]Deakin Child Study Centre, School of Psychology, Deakin University, Gee-long, VIC 3220, Australia

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INTRODUCTION

Noninvasive brain stimulation (NIBS) techniques have emerged as alternatives to invasive modalities given the ease of application, safety, tolerability, and reversibility. The 2 most well-studied forms of NIBS are transcranial magnetic stimulation (TMS) and transcranial electrical stimulation. Research protocols began applying brain stimulation techniques to children and adolescents in the early 1990s. Progress has been slow due to practical limitations and safety concerns.[1] As of 2017, there is no Food and Drug Administration–approved therapeutic use of NIBS techniques in children. Current evidence suggests potential use of NIBS techniques in children with depression, attention-deficit hyperactivity disorder (ADHD), epilepsy, autism, schizophrenia, dystonia, dyslexia, cerebral palsy, and Tourette syndrome (Table 1).[2–4]

TRANSCRANIAL MAGNETIC STIMULATION

The applications of TMS in children first started in the early 2000s and included both diagnostic and therapeutic approaches. Potential therapeutic applications of TMS in children include epilepsy, ADHD, autism spectrum disorder (ASD), depression, schizophrenia, and Tourette syndrome.[2] Single-pulse TMS is also used for presurgical mapping of the motor cortex and language areas.[5]

Safety and application guidelines for TMS were published in 2009 but focused on adults.[1]

In children and adolescents, recent systematic reviews suggest that both single-pulse and repetitive TMS have similar adverse effect profiles to adult populations.[3,6,7] The most commonly reported side effects are headache (11.5%), scalp discomfort (2.5%), twitching

*Corresponding author. croarkin.paul@mayo.edu.

(1.2%), mood changes (1.2%), fatigue (0.9%), and tinnitus (0.6%).[3] The most serious side effect is seizure and to date there are 3 reported seizures in adolescents receiving TMS. These events occurred in the context of epileptogenic medication use,[8,9] alcohol consumption before the TMS session,[9] and application of deep TMS.[10] There are 2 reported instances of TMS-induced hypomania[8,11] and 2 reported cases of neurocardiogenic syncope, which were associated with preexisting circumstances.[12] No changes in cognitive functioning have been reported (Fig. 1).[13]

Major Depressive Disorder

Major depressive disorder is one of the most common psychiatric illnesses in children and adolescents. Suboptimal outcomes in the treatment of depression in children and adolescents have sparked interest focused on the study of novel, brain-based approaches such as TMS. Prior therapeutic TMS studies included 73 participants between the ages of 7 to 21 years in open trials, case studies, case series, and small sham-controlled trials. In a systematic review, Donaldson and colleagues[14] suggested that TMS may be an effective and well-tolerated treatment for treatment-resistant depression in adolescents. The most common TMS application was high-frequency TMS (10 Hz) over the left dorsolateral prefrontal cortex (L-DLPFC). TMS parameters varied in terms of number of sessions (10–30), session duration (10–37.5 min), and intensity (80%–120% of motor threshold [MT]). Among these studies, 2 open trials by Bloch and colleagues[11] (2008) and Wall and colleagues[15] (2011) showed statistically significant improvement in depressive symptoms measured by CDRS-R as well as the significant improvement in the Clinical Global Impression Severity of Illness Scales (CGI-S) with high-frequency TMS applied over the DLPFC. The study by Wall and colleagues differed from the study by Bloch and colleagues based on MT intensity (120% vs 80%), total number of pulses per session (3000 vs 400) and number of total TMS sessions (30 vs 14). A follow-up study by Bloch and colleagues[11] showed sustained improvement after 3 years.[13] Another open-label study by Wall and colleagues[16] in 2016 (n 5 10) showed significant improvement (60% of participants) in depressive symptoms measured by CDRS-R, the Quick Inventory for Depressive Symptomatology Adolescent Seventeen-Item Self-Report (QIDS-A17-SR) and CGI-S after treatment and at 6-month follow-up. Initial studies suggest that high-frequency TMS treatments may modulate glutamatergic neurotransmission, and this presents an opportunity for precision medicine approaches to TMS.[17,18]

Autism Spectrum Disorder

ASD is diagnosed behaviorally by social impairments and the presence of restricted and repetitive patterns of behavior and interests. Early studies focused on ASD used conventional low-frequency (1 Hz) repetitive TMS applied to the prefrontal cortex daily over a period of time and demonstrated positive effects on behavioral and electrophysiological outcomes in children with ASD.[19,20] More recently, high-frequency theta-burst stimulation protocols applied to the motor cortex have also been investigated experimentally in this population.[21]

Tourette Disorder

TD is thought to involve hyperexcitability of the basal ganglia and motor cortex.[22,23] Among the few studies conducted in children with TD, low-frequency TMS (1 Hz, 110% MT, 10–20 sessions) applied over supplementary motor area has been shown to improve symptoms up to 6 months and was associated with increase in resting MT in children younger than 16 years.[24,25]

Attention-Deficit Hyperactivity Disorder

ADHD affects up to 12% of the population.[26] Initial treatment strategies include pharmacotherapy; yet, because of the unwanted side effects and risk for potential abuse, alternative treatments have emerged. In a study of 9 subjects (age 15–20 years), high-frequency TMS applied to the right prefrontal cortex (100% MT, 10 sessions) showed no difference between active and sham groups.[27]

Schizophrenia

Childhood onset schizophrenia is a rare disorder with an incidence less than 0.04%.[28] In adults, TMS inhibition of left temporoparietal region reduced auditory hallucinations in double-blind, randomized trials.[29,30] In children and young adults (age 18) limited studies showed improvement in positive and negative symptoms of schizophrenia with both high-frequency TMS delivered to the right frontal cortex (10 daily sessions of 20 Hz TMS) and low-frequency TMS applied to the left temporoparietal cortex (10 sessions of 1 Hz TMS).[31,32]

Neurologic Disorders

Inhibitory TMS (1 Hz for 20 minutes) applied over contralesional primary cortex showed improvement in hand functioning in patients aged 6 to 18 years with pediatric stroke,[33] especially when combined with constraint-induced movement therapy (CIMT) in a larger study.[34] In epilepsy, there are only a few case reports in children with intractable epilepsy that shows that low-frequency TMS (1 Hz) can lead to temporary reduction of epileptic activity.[35]

TRANSCRANIAL ELECTRICAL STIMULATION

Transcranial Direct Current Stimulation

In adults, tDCS has shown promise as an intervention for multiple neuropsychiatric disorders.[36] Experience in children and adolescents is limited to small randomized controlled trials (RCTs) and pilot studies,[4,37,38] but tDCS has potential as a tool to modulate cortical activity and promote neuroplasticity. It is appealing because it may prove more portable, safe, and accessible as compared with other techniques such as TMS (Fig. 2).[39]

Electroconvulsive therapy (ECT) is safely used in adults with mood disorders with catatonia, psychotic features, and refractory to antidepressant therapy as well as in patients who refuse food and water intake or are acutely suicidal.[40] In children and adolescents it is often considered as a last resort likely due to factors such as stigma, lack of clinical experience, concerns about long-term side effects, and legal restrictions.[41,42]

Major Depressive Disorder

In adults, prior studies demonstrate that depressed patients who underwent tDCS had greater response and remission rates,[43] but no prior studies have examined the effects of tDCS on depression in children and adolescents. Prior retrospective reviews suggest that electroconvulsive therapy can be effective in treating depression in children and adolescents with the rate of improvements up to 80% in unipolar depression and up to 90% in treatment-resistant depression.[41,42,44] Unfortunately, the dearth of RCTs and safety studies in children limits the use of ECT in younger patients.

Schizophrenia

In a double-blind sham-controlled trial, Mattai and colleagues[45] investigated the tolerability of bilateral anodal DLPFC (targeting cognitive difficulties) and bilateral cathodal and superior temporal (targeting auditory hallucinations) (2 mA for 20 min, 10 days) tDCS in 12 children with childhood-onset schizophrenia (age: 10–17 years). They found no difference between groups in terms of adverse effects or clinical measures suggesting that tDCS was well tolerated.

With regard to ECT trials, in a study with 13 participants with schizophrenia spectrum disorder (n 5 13), Baeza and colleagues[46] showed that ECT lead to significant improvements in PANSS scores and CGI scores after acute phase of ECT and at 6 months. In a retrospective study of ECT, Puffer and colleagues[42] found significant improvement in CGI-I and CGI-S scores in 9 adolescents with psychotic disorder.

Autism Spectrum Disorders

Andrade and colleagues[47] targeted language problems in a sample of 14 children with 4 of the subjects with ASD. Across the sample, self-report measures indicate considerable variability in the perceived improvement in symptoms, ranging from “no change” to “very much better.” One pilot study suggested that tDCS may improve syntax acquisition in children and adolescents with ASD.[48]

Other studies found improvement in the childhood autism rating scale and the Autism Treatment Evaluation Checklist with anodal tDCS applied over F3 (1 mA, 5 days).[49] Amatachaya and colleagues[50] found significant association between the electroencephalogram alpha activity and improvement in ASD symptoms with anodal tDCS applied over F3 (DLPFC) (2 mA, 20 min).

There are a small number of case reports supporting the safe and efficacious application of electroconvulsive therapy (ECT) to treat catatonia[51] and self-injurious behaviors[52] in children and adolescents with ASD. Moreover, ECT may also have had positive outcomes for some other characteristics of ASD in these cases, such as eye contact, verbal conversation,[53] and engagement in family activities.[52]

Attention-Deficit Hyperactivity Disorder

The neural basis of ADHD is thought to involve deficient inhibitory mechanisms that could be a potential target for tDCS.[54,55] In children, several studies showed improvement in

inhibitory control with the stimulation of L-DLPFC.[56,57] For example, in a randomized crossover study (n 5 20) anodal tDCS applied over the L-DLPFC improved the accuracy to responses in a Go-No-Go task, whereas cathodal tDCS improved No-Go accuracy suggesting improved inhibitory control.[57] Other studies looked at the effects of the slow oscillating tDCS on modulating cortical activity during non–rapid eye movement sleep phase 2. Participants had improved reaction time and memory performance after slow oscillating tDCS.[58,59]

Epilepsy

Several case series with tDCS revealed reductions in epileptiform discharges in children with continuous spike and Wave during slow-wave sleep and Landau-Kleffner syndrome.[60] Initial pilot work in children suggested that tDCS reduced seizure frequency and severity in patients with generalized seizures due to cerebral palsy and other brain lesions,[61] Rasmussen encephalitis,[62] and focal cortical dysplasia.[63] In a randomized sham-controlled trial, Auvichayapat and colleagues[64] found a reduction in epileptiform discharges at 24 hours, 48 hours, and 4 weeks posttreatment following a single session of tDCS. In contrast, another study found no reduction in epileptiform activity.[65] Overall, tDCS has been well tolerated in patients with epilepsy except that a single case of seizure was reported during a course of tDCS.[66]

Cerebral Palsy/Dystonia

Dystonia is one of the most common movement disorders in children and does not always respond to classical pharmacologic interventions.[67] TDCS studies in dystonia have focused on combination of different therapeutic approaches with tDCS, including CIMT, visual reality, and treadmill. In a randomized clinical study of 20 patients with spastic cerebral palsy, anodal tDCS (1 mA, 20 min, 10 sessions total) applied over C3 combined with virtual reality mobility training improved velocity and cadence, mobility, and gross motor function.[68] Other studies showed similar results, including increase of body sway velocity,[69] decreased spasticity,[70] and improved static balance.[71] In contrast to aforementioned findings, Bhanpuri and colleagues[72] showed that anodal tDCS placed contralateral to the most affected limb worsened motor performance in patients with dystonia.

Dyslexia

Two studies explored the effects of tDCS in the treatment of dyslexia in children. In a sham-controlled study, Costanzo and colleagues[73] showed that anodal tDCS (1 mA, 20 min, 18 sessions) applied over the left parietotemporal region, with the cathode placed over the right homologue region, led to improved reading when combined with reading training. In a subsequent study, the investigators showed that cathodal tDCS applied over the left parietotemporal region increased the number of errors, whereas the anodal tDCS over the same region decreased the number of errors.[74]

FRONTIERS AND EMERGING TECHNOLOGIES

Trigeminal Nerve Stimulation and Magnetic Seizure Therapy

External stimulation of the trigeminal nerve (eTNS) and magnetic seizure therapy (MST) are emerging neuromodulatory techniques that have been shown to have therapeutic effects in adults. In an 8-week open-label pilot trial including 24 participants (between ages 7 and14 years) with ADHD, eTNS administered at night time led to significant improvement in ADHD-IV Rating Scale and Conners Global Index.[75] There is a single case report in which the investigators reported full remission of depressive symptoms in an 18-year-old boy with refractory depression in the context of bipolar II disorder following 18 sessions of 100 Hz MST.[76]

DEVELOPMENTAL AND SAFETY CONSIDERATIONS

A recent systematic review that examined 48 studies with 513 children younger than 18 years supported the safety and feasibility of TMS and tDCS in children and adolescents.[3] Yet, in a recent commentary, Davis identified the potential gaps in translating brain stimulation techniques to children.[77] These include the unknown effects of stimulation in developing brains due to differences in anatomy and physiology, unknown side effects, limited translational data, and inherent ethical challenges in work with vulnerable populations.[77]

One of the most serious possible side effects of NIBS is seizure. MTs are typically higher in young children and reach adult levels by the age of 16 to 18 years.[78] As a result, higher stimulus intensities required in younger children might be associated with increased risk for adverse effects.[1] Moreover, infants and young children are thought to be especially prone to seizures due to increased glutamate sensitivity, reduced glutamate clearance, and incomplete GABA-mediated inhibition in the developing brain.[37] Therefore, further shift toward the excitatory activity induced by TMS could theoretically increase the seizure risk. Moreover, computational modeling studies suggest that typical intensities of tDCS results in higher densities and peak electrical fields in the cortex of children compared with that in adults.[79,80] Given the conductivity of the underlying biological tissues plays an important role in determining the maximum intensity and the distribution of the current that reaches to the cortex,[79] differences in skull size and composition can result in variability in the amount of the current delivered to the cortex, introducing not only safety concerns but also intersubject variability in dosing, making standardization more difficult. In addition, the relative size of the external auditory canal is smaller in young children resulting in higher resonance frequency,[81] which can increase the risk of acoustic injury during the delivery of TMS pulses.[1]

NEUROETHICS

Early guidelines regarding recruitment of children in TMS trials conclude that, unless there is compelling evidence for treatment of refractory cases, children should not be included in TMS trials due to concerns for interfering with normal neurodevelopment.[82]

Another important aspect to consider is potential applications of NIBS as a tool for neuroenhancement. It has been demonstrated that brain stimulation can enhance cognitive functions.[83] However, it is still unknown if improvement in one domain hinders the functioning of other domains.[84] Other concerns include emergence of unexpected effects such as unintentional behavioral responses or the discovery of incidental but clinically nonsignificant findings.[85]

In addition, tDCS or similar devices can be easily purchased online or constructed at home by simply watching online videos. Advertisement of these techniques without proper regulatory approvals could lead to inappropriate use of these techniques resulting in significant health issues.

SUMMARY

NIBS techniques have emerged as novel tools to promote plasticity and alleviate symptoms in neuropsychiatric disorders. Despite the intrinsic challenges in work with children and adolescents, the growing evidence suggests that brain stimulation will offer powerful and alternative tools to treat early onset neuropsychiatric disorders.

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KEY POINTS

- Neuromodulation is a rapidly developing field that will provide opportunities to develop new therapeutic modalities in child and adolescent psychiatry.
- Recent research has examined the feasibility and safety of transcranial direct current stimulation and transcranial magnetic stimulation in child and adolescent neuropsychiatric disorders.
- Enthusiasm for applying neuromodulatory tools in childhood and adolescent neuropsychiatric disorders must be moderated with systematic study, neurodevelopmental considerations, and rigorous ethical analyses.

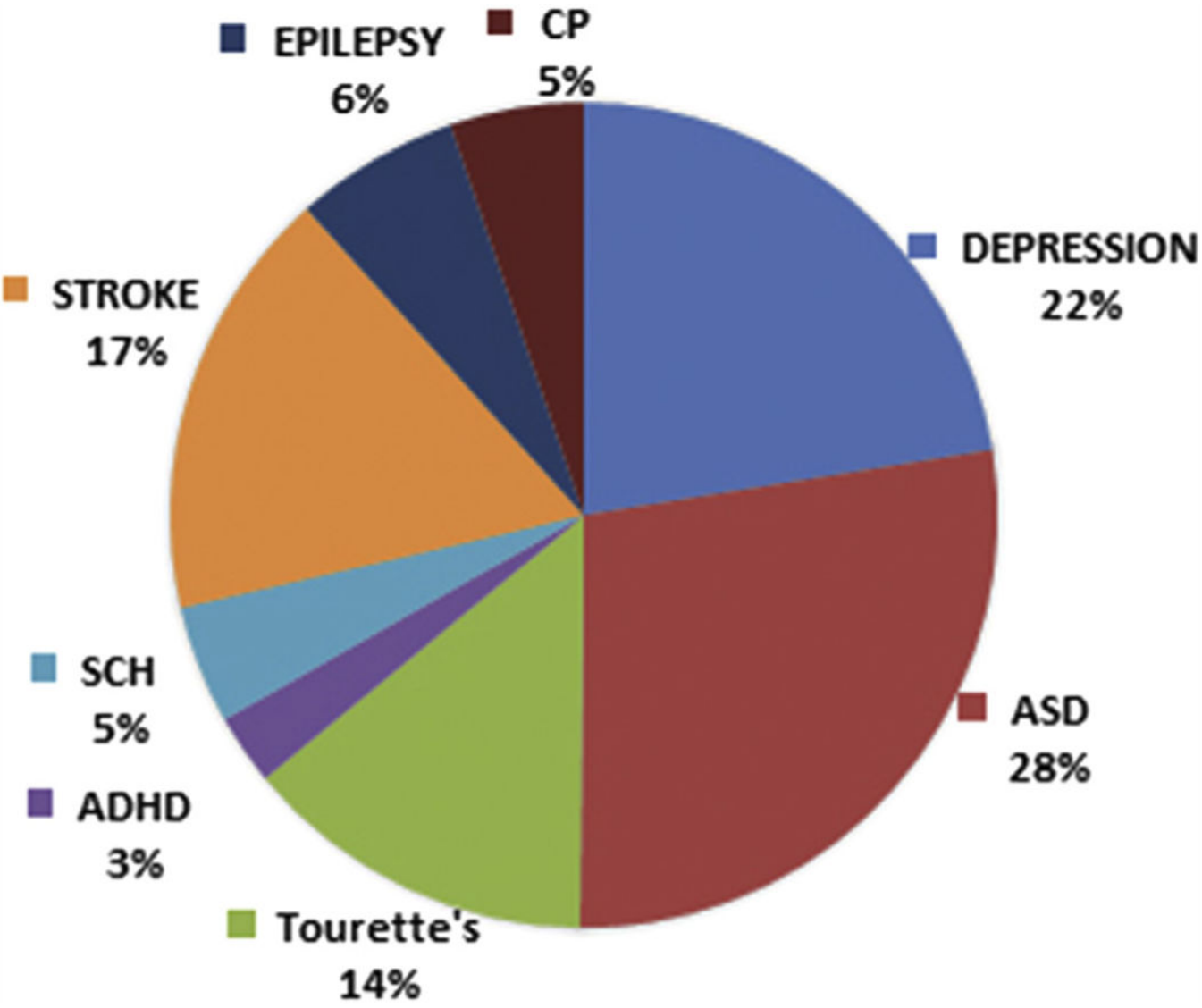

Fig. 1.

Distribution of subjects in therapeutic TMS studies. SCH, schizophrenia; ASD, autism spectrum disorder; ADHD, attention-deficit hyperactivity disorder; CP, cerebral palsy.

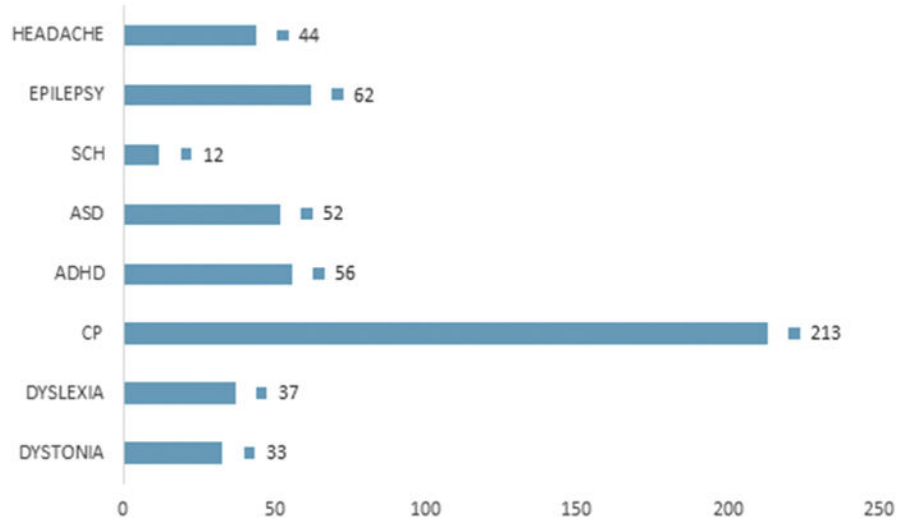

Fig. 2.

Total number of subjects for each condition in TDCS studies. SCH, schizophrenia; ASD, autism spectrum disorder; ADHD, attention-deficit hyperactivity disorder; CP, cerebral palsy. (*Data from* Palm U, Segmiller FM, Epple AN, et al. Transcranial direct current stimulation in children and adolescents: a comprehensive review. J Neural Transm 2016;123(10):1219–34; and Muszkat D, Polanczyk GV, Dias TG, et al. Transcranial direct current stimulation in child and adolescent psychiatry. J Child Adolesc Psychopharmacol 2016;26(7):590–7.)

Table 1

Neuropsychiatric diseases included in neuromodulation trials in children and adolescents

	Depression	OCD	ADHD	Autism	Tourette Syndrome	Schizophrenia	Addiction	Dyslexia	Migraine	Cerebral Palsy	Dystonia	Epilepsy	Stroke	Headache
rTMS	X	—	X	X	X	X	—	—	—	X	—	X	X	—
TBS	—	—	—	X	X	—	—	—	—	—	—	—	—	—
tDCS	—	—	X	X	—	X	—	X	—	X	X	X	—	X
ECT	X	—	—	X	—	X	—	—	—	—	—	—	—	—
MST	X	—	—	—	—	—	—	—	—	—	—	—	—	—
eTNS	—	—	X	—	—	—	—	—	—	—	—	—	—	—

Abbreviations: ECT, electroconvulsive therapy; eTNS, external trigeminal nerve stimulation; MST, magnetic seizure therapy; OCD, obsessive-compulsive disorder; rTMS, repetitive transcranial magnetic stimulation; TBS, theta burst stimulation; tDCS, transcranial direct current stimulation.

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