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Noninvasive Brain Stimulation in Pediatric Attention-Deficit Hyperactivity Disorder (ADHD): A Review

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Abstract

Attention-deficit hyperactivity disorder (ADHD) is one of the most prevalent neurodevelopmental disorders in the pediatric population. The clinical management of ADHD is currently limited by a lack of reliable diagnostic biomarkers and inadequate therapy for a minority of patients who do not respond to standard pharmacotherapy. There is optimism that noninvasive brain stimulation may help to address these limitations. Transcranial magnetic stimulation and transcranial direct current stimulation are 2 methods of noninvasive brain stimulation that modulate cortical excitability and brain network activity. Transcranial magnetic stimulation can be used diagnostically to probe cortical neurophysiology, whereas daily use of repetitive transcranial magnetic stimulation or transcranial direct current stimulation can induce long-lasting and potentially therapeutic changes in targeted networks. In this review, we highlight research showing the potential diagnostic and therapeutic applications of transcranial magnetic stimulation and transcranial direct current stimulation in pediatric ADHD. We also discuss the safety and ethics of using these tools in the pediatric population.

Keywords

ADHD, pediatric, neuromodulation, transcranial magnetic stimulation, transcranial direct current stimulation

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Attention-deficit hyperactivity disorder (ADHD) is one of the most prevalent neurodevelopmental disorders, affecting 2% to 7.5% of school-aged children and often persisting into adulthood.[1-4] It is characterized by 3 core symptoms: inattention, hyperactivity, and impulsivity.[3] Despite intensive study, the pathophysiology of ADHD remains unclear.[5] The clinical management of ADHD is hindered by a lack of widely accepted biomarkers or diagnostic tests. As such, diagnosis is typically made using parent- and teacher-reported behavioral rating scales in combination with a physician's clinical impression, without regard to the neural correlates of the individual's symptoms. Pharmacologic treatments for ADHD are generally effective, and there is strong evidence that treatment improves long-term outcomes in several social and academic domains.[6] Despite the well-established clinical efficacy of available medications,[7,8] a minority of patients do not respond to standard pharmacotherapy, and its use may be limited by side effects and concerns of abuse.[9-11]

Noninvasive brain stimulation may help address some of the aforementioned diagnostic and therapeutic challenges associated with the clinical management of ADHD. Several noninvasive brain stimulation procedures are available to physicians and investigators, and all have in common the capacity to modulate cortical excitability via transcranial electrical stimulation. Of these, the 2 most common procedures are

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transcranial magnetic stimulation and transcranial direct current stimulation, both of which are emerging as realistic clinical tools.

In this review, we will briefly highlight leading theories regarding the neural basis of ADHD. We then discuss transcranial magnetic stimulation and transcranial direct current stimulation, focusing on their mechanism of neuromodulation, their safety profile in the pediatric population, and their application in ADHD. We also briefly discuss newer neuromodulation techniques and ethical considerations in applying noninvasive brain stimulation to the pediatric population.

Neural Correlates of ADHD

The exact pathophysiology of ADHD has been difficult to delineate because of complicating factors such as evolving diagnostic criteria, phenotypic heterogeneity, frequent comorbidities, and environmental variables that may exacerbate or mimic symptoms. The 3 hallmark symptoms of ADHD are each likely to have distinct neural substrates,[12,13] which may obscure attempts to elucidate the pathophysiology from studies that incorporate a variety of clinical presentations. Even well-designed neuroimaging studies in ADHD struggle with a variety of potentially confounding variables, such as maturational changes in the brain and motion artifacts from a population that has trouble complying with prolonged MRI studies.[14] Despite these challenges, there has been some recent headway in understanding the neural correlates of ADHD.

One of the most influential theories for the neural basis of ADHD has focused on deficient inhibitory control leading to executive dysfunction,[15,16] which is likely under genetic influence.[17] The neuroanatomic substrate of inhibitory control is believed to involve basal ganglia-thalamocortical circuits.[18,19] Specifically, this network links the prefrontal cortex to the dorsal neostriatum via excitatory glutaminergic cells, the basal ganglia to the dorsomedial thalamus via inhibitory projections, and the thalamus back to the prefrontal cortex via excitatory projections.[20,21] Inhibitory control parallels the maturation of this circuit, and both structural and functional neuroimaging studies reveal differences in this circuit in association with ADHD.[22-24]

A number of other large-scale networks have also been implicated in ADHD. Impulse control deficits have been linked to frontostriatal circuits, specifically underactivity in the ventrolateral prefrontal cortex, dorsolateral prefrontal cortex, and the anterior cingulate.[25-27] Anticipation of reward was shown to correspond with underactivity in the mesolimbic circuit, which includes the ventral striatum and orbitofrontal cortex.[27,28] Spatial working memory deficits are associated with a temporoparietal circuit.[29-31] As noted, the involvement of these networks is likely to vary by ADHD subtype, which is taken into account with recent studies.[12,13]

To add a layer of complexity to the imaging findings in ADHD, abnormal patterns of brain activity may sometimes represent compensatory changes rather than the primary underlying deficits. For instance, there is a compensatory and likely adaptive increase in posterior parietal activity that accompanies underactivation in frontostriatal regions during executive tasks.[23,27,32-34]

There are also a large number of ADHD studies showing regional volumetric changes,[23,24,35-39] abnormal trajectory of brain development,[37,40] abnormal functional connectivity,[41] and abnormal EEG patterns.[42,43] A detailed summary of this work is beyond the scope of this review, but several reviews are available.[12,37]

Structural and functional differences in the ADHD brain are accompanied by abnormalities of the catecholaminergic neurotransmitters, dopamine and norepinephrine, which are believed to be critical in the pathophysiology of ADHD.[44,45] Low levels of dopamine in prefrontal regions are associated with increased hyperactivity and irritability.[46] Stimulant drugs used in the treatment of ADHD increase dopamine and norepinephrine activity in frontostriatal networks with improvement in symptoms.[47,48]

While acknowledging the complexity of ADHD and the significant limitations in our current understanding of the underlying neural processes, we now turn our attention to noninvasive brain stimulation and its potential utility in pediatric ADHD.

Transcranial Magnetic Stimulation Basics

Transcranial magnetic stimulation (TMS) is based on the principle of electromagnetic induction: an electric current in the stimulation coil produces a magnetic field, which induces an electric current in nearby conductors, in this case, in the cerebral cortex. The transcranial magnetic stimulation device components include a charging mechanism, the storage capacitor, the thyristor, and a discharging coil. The coil design impacts the focality of the resulting stimulation. A circular coil activates a broad area, a figure-8 coil provides relatively focal stimulation of approximately 5 mm^3, and an H-coil targets deeper structures, up to 6 cm below the stimulation site.[49,50] The induced electrical current triggers action potentials in the brain via current flowing parallel to the surface of the coil. The magnitude of the stimulation is inversely related to the distance from the coil.[51]

Single-Pulse Transcranial Magnetic Stimulation

The simplest stimulation paradigm for transcranial magnetic stimulation involves applying a single, brief electromagnetic pulse. When a transcranial magnetic stimulation pulse is applied to the motor cortex, it can elicit observable motor output, often in the contralateral hand.[49] The motor evoked potential resulting from the transcranial magnetic stimulation pulse can be recorded using electromyography (EMG). When applied to the visual cortex, a transcranial magnetic stimulation pulse may induce a visual percept, or a phosphene. The effect of a single transcranial magnetic stimulation pulse on other cortical areas outside the motor and visual cortices can be recorded by scalp EEG or other imaging modalities. The effects of a

single transcranial magnetic stimulation pulse are brief, and its safety is well established.[52]

Paired-Pulse Transcranial Magnetic Stimulation

Paired-pulse transcranial magnetic stimulation stimulates the cortex with 2 pulses separated by a variable delay. The main application of this protocol is to measure cortical inhibitory-excitatory balance, which is described in more detail below.

Repetitive Transcranial Magnetic Stimulation

Repetitive transcranial magnetic stimulation uses a rapid sequence of magnetic pulses to induce longer-lasting modulation of the underlying cortex. Low-frequency repetitive transcranial magnetic stimulation (1 Hz or less) generally has an inhibitory effect on the underlying cortex, and high-frequency stimulation will typically increase the excitability of the underlying cortex.[53] For example, when applied to the motor cortex, 1-Hz repetitive transcranial magnetic stimulation will depress the motor evoked potential whereas 20-Hz repetitive transcranial magnetic stimulation will increase it.[54,55] Theta-burst stimulation is a patterned form of repetitive transcranial magnetic stimulation that requires less stimulation time relative to the duration of effect. For example, a single session with 3 minutes of theta-burst stimulation may modulate the underlying cortex for 30 minutes, and the duration of effect is extended with repeated application. Continuous theta-burst stimulation typically has an inhibitory effect on the underlying cortex, whereas intermittent theta-burst stimulation is excitatory.[56] Single sessions of theta-burst stimulation in children appear to be safe and well tolerated.[57]

Transcranial Magnetic Stimulation Measures of Cortical Excitability

There are a few commonly used neurophysiological measures to study cortical excitability, which have relevance as potential diagnostic tests for ADHD. Motor threshold is a proxy of motor cortex excitability,[58,59] and is defined as the minimum intensity of stimulation necessary to elicit a motor evoked potential (>50 μV) in a target muscle 50% of the time.[53]

Paired-pulse transcranial magnetic stimulation protocols are used to assess the intracortical inhibitory-excitatory balance. Varying the interstimulus interval between 2 transcranial magnetic stimulation pulses leads to reliable alterations in the size of the motor evoked potential. The 3 most commonly used paired-pulse protocols include short-interval intracortical inhibition, long-interval intracortical inhibition, and intracortical facilitation. Short-interval intracortical inhibition uses a subthreshold transcranial magnetic stimulation pulse followed by a short interstimulus interval of 1 to 5 milliseconds, then a suprathreshold pulse.[60] The first pulse may activate inhibitory neurons that project to corticospinal neurons, thus lowering the excitability of these corticospinal neurons for the second suprathreshold stimulus.[60] This effect appears to be mediated primarily by $GABA_A$.[61-63] Long-interval intracortical inhibition uses 2 suprathreshold pulses at a longer interstimulus interval of 50 to 100 milliseconds. $GABA_B$ has a role in mediating the inhibitory effect of the first pulse on the second.[63] Intracortical facilitation uses a subthreshold pulse followed by a suprathreshold pulse, separated by an interstimulus interval of 7 to 20 milliseconds.[60] In this case, the initial pulse facilitates the motor evoked potential of the second, possibly mediated by NMDA-receptor excitatory neurotransmission.[60]

In addition to using motor output to assess cortical excitability of the motor cortex, it is also possible to combine transcranial magnetic stimulation with EEG to probe other cortical regions.[64] Transcranial magnetic stimulation pulses can elicit a characteristic EEG response, termed a transcranial magnetic stimulation–evoked potential. This consists of a set of peaks and volleys in the EEG that occurs along a defined temporal sequence. These tend to be consistent among subjects, and the amplitude can be correlated to other measures of cortical excitability, even at intensities below the motor threshold.

Interhemispheric Connectivity

Paired pulse stimulation can also be used to study interhemispheric interactions using 2 transcranial magnetic stimulation coils. The effects of a conditioning stimulus applied to the motor cortex of one hemisphere can affect the motor evoked potential elicited by transcranial magnetic stimulation in the contralateral hemisphere.[65] The motor evoked potential is reduced if the conditioning stimulus in the opposite hemisphere precedes the second stimulus by 7 milliseconds or more.[65] This interhemispheric inhibition appears to occur at the level of motor cortex, and it is mediated by transcallosal motor fibers. The ipsilateral cortical silent period is another protocol for assessing interhemispheric interaction. It involves a single transcranial magnetic stimulation pulse to the motor cortex that induces a transient suppression of voluntary tonic muscle activity in the ipsilateral hand muscles, as assessed with EMG.[65] It may be mediated by excitatory transcallosal neurons projecting to contralateral inhibitory interneurons in the homologous region of the motor cortex, thus reflecting the functional integrity of the transcallosal projections between motor cortices.[65,66]

Noninvasive Brain Stimulation in ADHD

Literature Review Method

The use of noninvasive brain stimulation in the ADHD pediatric population was searched systematically using MEDLINE. Search terms included [(ADHD) OR (comorbidities) OR (neuroplasticity) OR (child psychiatry) OR (child neurology) OR (adolescents)] AND [(transcranial magnetic stimulation) OR (transcranial direct current stimulation) OR (alternating current stimulation) OR (transcranial random noise stimulation)]. Searches were limited to humans under age 18. References of the articles obtained were cross-referenced. The literature review was performed in January of 2015.

Transcranial Magnetic Stimulation as a Diagnostic Tool in ADHD

Behavioral ratings of hyperactivity in ADHD patients have neurophysiological correlates in the motor cortex, which can be probed with single-pulse and paired-pulse transcranial magnetic stimulation protocols (Table 1). These studies have shown an inverse correlation between short-interval intracortical inhibition and hyperactivity, such that low levels of intracortical inhibition are associated with greater hyperactivity. This suggests that short-interval intracortical inhibition may serve as a biomarker of symptom severity.[16,73,76,77] Moreover, these abnormalities in short-interval intracortical inhibition improve with administration of methylphenidate.[73] It is not clear if these deficits in cortical inhibition are due to differences at a microscopic scale or from large-scale network properties, or some combination. It is similarly unclear if differences in cortical excitability in ADHD are present throughout the cortex or limited to the motor cortex.

In addition to differences in short-interval intracortical inhibition, transcallosal-mediated inhibition is also deficient in ADHD.[70-72] Both the latency and duration of the ipsilateral silent period is prolonged in children with ADHD,[70-72] with the duration being correlated with hyperactivity and restlessness.[74] The cause of abnormal transcallosal-mediated inhibition in pediatric ADHD is not clear. The ipsilateral silent period normalizes with a single dose of methylphenidate, suggesting that abnormal motor cortex excitability may have a more important role than structural differences in the corpus callosum. This view is also supported by the inverse correlation of ipsilateral silent period duration and magnitude of the short-interval intracortical inhibition.[54,85]

Interestingly, early results of cortical excitability from adults differ from those reported in the pediatric population. Adults with ADHD have less hyperactivity and relatively normal inhibitory motor circuits.[74] Unlike children with ADHD, adults have a shortened ipsilateral silent period with normal latency.[74] These differences between adults and children may relate to developmental differences in the inhibitory intracortical pathways,[86] but additional study is needed. A neurophysiologic correlate of inattentive symptoms in ADHD has not been identified.

Transcranial magnetic stimulation–evoked EEG potentials have also been used to assess neurophysiology in ADHD cohorts. The negative deflection of EEG at 100 milliseconds after a transcranial magnetic stimulation pulse, termed the N100, is a proxy of cortical inhibitory processes.[87-91] Recent studies have shown N100 abnormalities in association with ADHD.[91-93]

Most of the research to date relevant to transcranial magnetic stimulation–derived neurophysiological measures in ADHD has focused on the motor cortex. Transcranial magnetic stimulation–evoked potentials, as described above, will allow future studies to incorporate physiological measures of sites beyond the motor cortex. As methodologies improve and become easier to integrate, future studies may use transcranial magnetic stimulation–EEG to probe the neurophysiology of individual networks.[94,95] The ultimate diagnostic utility of transcranial magnetic stimulation–derived measures may require an integration of multiple parameters to elucidate a neurophysiological profile to which machine learning algorithms could be applied to identify common profiles among patients with ADHD or even subgroups within ADHD cohorts, a technique currently being explored in neuroimaging research.[13]

Transcranial Magnetic Stimulation in Guiding Pharmacotherapy in ADHD

To date, the selection of specific medications for ADHD treatment is done empirically, often using trial and error to identify the optimal medication for an individual patient. Current pharmacotherapy is not reliably guided by any disease-specific biomarkers or diagnostic tests, though advances in pharmacogenetics may prove useful with further study.[96] It is possible that neurophysiological abnormalities assessed by transcranial magnetic stimulation could also be used for this purpose.[97] Methylphenidate enhances short-interval intracortical inhibition, which has also been reported with other medications that enhance dopaminergic neurotransmission.[73,80,98-101] Given that short-interval intracortical inhibition is correlated to hyperactivity, and methylphenidate normalizes short-interval intracortical inhibition and improves hyperactivity, it is possible that short-interval intracortical inhibition could be used as an objective and quantitative proxy of the therapeutic effectiveness of methylphenidate. There are a variety of potential uses for this information, such as identifying whether an individual has a greater change in short-interval intracortical inhibition with methylphenidate versus other ADHD medications, or as a way to identify methylphenidate nonresponders without the need for a prolonged medication trial. Short-interval intracortical inhibition could also be monitored as a way to optimize dosing to adjust for increased weight or increased tolerance over time. Short-interval intracortical inhibition could also be tracked when investigating new medications for ADHD. Each of these possibilities would require careful investigation prior to any clinical use. As advances are made in the study of transcranial magnetic stimulation–evoked potentials, it may be possible to assess neurophysiological responses to medications outside of the motor cortex as well.[94]

Therapeutic Transcranial Magnetic Stimulation in ADHD

An ideal therapy for ADHD should address the underlying nervous system dysfunction, be associated with minimal or no adverse effects, and be financially and practically feasible for use in clinical practice. Pharmacologic treatments for ADHD generally meet these goals. However, standard pharmacotherapy is not effective for many ADHD patients, stimulants are sometimes contraindicated, and some patients experience untoward side effects, including cardiovascular, hepatic, growth, or suicidal events.[102,103] New interventions are needed to augment or provide alternatives to pharmacotherapy.

Table 1. Neurophysiological Transcranial Magnetic Stimulation Measurements in Children With ADHD, ADHD With Comorbid Tourette Syndrome or Tics, or Tourette Syndrome and Methylphenidate and Atomoxetine Effects.[a]

	Sample (mean age/range)	MT	CMCT	CSP	ICI	SICI	LICI	iSP- L	iSP-D	ICF	MPH	ATX	Study design
ADHD													
Moll et al 2000[67]	18 (8-12)	Ø			↓				Ø	Ø	↑ICI		Open, non-controlled study
Moll et al 2001[68]	16 (12 ± 1.6)	Ø			↓					Ø			
Ucles et al 2000[69]	27 (4-18)		↑										
Garvey et al 2005[70]	12 (10.7 ± 1.6)	Ø						↓	Ø				
Buchmann et al 2003[71]	13 (10.8 ± 1.7)	Ø						↑	↓				
Buchmann et al 2006[72]	23 (11 ± 2.6)	Ø	Ø					↑	↓		↓iSP-L ↑↑ iSP-D		Open, non-controlled study
Buchmann et al 2007[73]	18 (11 ± 2)	Ø	Ø			↓	↓			↓	↑SICI ↑LICI ↑ICF		Open, non-controlled study
Hoeppner et al 2008[74]	21 (28.9 ± 9.2)	Ø	Ø					Ø	↓		Ø iPS-L ↑iPS-D		Open, non-controlled study
Richter et al 2007[75]	10 (29 ± 3.4)	Ø				↓				Ø			
Gilbert et al 2011[16]	49 (10.5)					↓							Case-control study
ADHD/TS/Tics													
Moll et al 2001[68]	16 (12.5 ± 1.1)	Ø		↓	↓					Ø			
Gilbert et al 2004[76]	36 (13-18)	Ø		Ø		↓				Ø	Ø		Open, non-controlled study
Gilbert et al 2005[77]	28 (9-48)	Ø				↓							
Gilbert et al 2007[78]	14 (8-16)											↓SICI Ø ICF	Open, non-controlled study
Orth et al 2009[79]	6 (18-68)	↑				↓				↑			
Healthy													
Kratz et al 2009[80]	14 (20-40)										Ø MT ↑SICI		Double-blind, placebo-controlled, crossover study
Moll et al 2003[81]	12 (20-40)										ØSICI ↑ICF		Open, non-controlled study
Kirschner et al 2003[82]	12										↑SICI ↑ICF		Placebo controlled, crossover study
Ilic et al 2003[83]	8										Ø MT Ø CSP ↓SICI ↑ICF		Open, non-controlled
Gilbert et al 2006[84]	9 (19-35)										↓SICI ↑ICF	↓SICI ↑ICF	Randomized, double-blinded crossover trial

Abbreviations: ADHD, attention-deficit hyperactivity disorder; ATX, atomoxetine; CMCT, central motor conduction time; CSP, cortical silent period; ICF, intracortical facilitation; ICI, intracortical inhibition; iSP-D, ipsilateral silent period, duration; iSP-L, ipsilateral silent period, latency; LICI, long-interval intracortical inhibition; MPH, methylphenidate; MT, rest motor threshold; SICI, short-interval intracortical inhibition.
[a]Symbols: Ø, no differences between clinical versus normal group; ↓, decreased parameter value between clinical versus normal group; ↑, increased parameter value between clinical versus normal group. In MPH and ATX columns: ↑, enhanced parameter value after the drug intake; ↓, diminished parameter value after the drug intake.

Repetitive transcranial magnetic stimulation, when used on a daily basis, can induce long-lasting changes in the excitability of the stimulated site. These functional changes can be leveraged for therapeutic effect, as has been shown for medication-refractory depression in adults.[104] Although there are no current US Food and Drug Administration (FDA)–approved therapeutic uses of transcranial magnetic stimulation in the pediatric population, a multicenter trial is currently underway investigating its role in treating medication-refractory depression.[105,106] With regards to ADHD, there have only been a small number of pilot trials exploring the use of therapeutic transcranial magnetic stimulation in the pediatric population.

In 2012, Weaver et al performed a pilot trial of 9 adolescents and young adults, aged 15 to 20 years, using 10-Hz repetitive transcranial magnetic stimulation to the right dorsolateral prefrontal cortex.[107] Subjects underwent 10 sessions over 2 weeks, and each subject was crossed over to receive sham. The objective of the study was to assess safety and the conclusion was that repetitive transcranial magnetic stimulation was safe in this cohort, but the study was underpowered to show efficacy. Although the authors reported an improvement in core ADHD symptoms in the treatment group, the effect did not differ significantly from the sham condition.

There have been a few studies of therapeutic repetitive transcranial magnetic stimulation in adults with ADHD, reviewed in Zaman.[108] In 2010, Bloch et al performed a double-blind, randomized, sham controlled crossover pilot study with positive effects in 13 patients.[109] Niederhofer reported improved ADHD symptoms in a case study that involved motor cortex stimulation using 1-Hz repetitive transcranial magnetic stimulation at 1200 pulses per day for 5 days.[110]

To date, however, there are no published large, randomized, sham-controlled trials of therapeutic repetitive transcranial magnetic stimulation in ADHD, though several trials are ongoing (see clinicaltrials.gov for details). Moreover, the optimal target, frequency, and duration are all unknown. It is likely that the target will vary depending on the symptom being treated, as studies have shown distinct neural substrates for distinct ADHD subtypes.[12,13]

Safety in Pediatric Transcranial Magnetic Stimulation

The majority of the safety data in transcranial magnetic stimulation is derived from adults. Common side effects of transcranial magnetic stimulation include headache and scalp discomfort, which is experienced by up to 40% of participants.[111] Rare, but more concerning, effects include hearing loss[112,113] or the induction of a seizure with repetitive transcranial magnetic stimulation.[52] The risk of hearing loss can be minimized by using earplugs, and the risk of seizure is estimated at less than 1 in 10 000 when appropriate safety guidelines are adhered to.[52,114]

Transcranial magnetic stimulation has been used in more than 800 normal children and more than 300 neurologically abnormal children, with a good tolerability and safety profile.[115,116] No change in auditory function has been reported in the pediatric population to date.[115] Single- or paired-pulse transcranial magnetic stimulation has not been shown to cause seizures in children, including those with epilepsy or with conditions like cerebral palsy that are associated with increased risk of seizures.[111,117-123] One case of repetitive transcranial magnetic stimulation–induced seizure was reported in an adolescent patient being treated for depression,[124] though other risk factors for seizure were also present, including alcohol use the night before the induced seizure.[105] In 2009, a consensus conference issued recommendations for the safe use of transcranial magnetic stimulation in the pediatric population. They concluded that single-pulse and paired-pulse transcranial magnetic stimulation was safe for children 2 years and older. In the absence of an appreciable volume of data on the potential for adverse effects with repetitive transcranial magnetic stimulation, they recommended that children should not be used as subjects for repetitive transcranial magnetic stimulation without compelling clinical reasons, such as the treatment of particular psychiatric conditions.[52]

Transcranial Direct Current Stimulation in ADHD

Transcranial direct current stimulation is a noninvasive brain stimulation technique that has received a surge of interest in the last decade. With transcranial direct current stimulation, a low-amplitude direct current (0.5-2 mA) is applied to the scalp via electrodes. Electric current flows from the negatively charged cathode to the positively charged anode, penetrating the skull and modifying neuronal transmembrane potentials in the current path. The effect is to modulate the excitability of a given region, but unlike transcranial magnetic stimulation, transcranial direct current stimulation does not deliver suprathreshold currents to induce action potentials.[125-128] The cortex underlying the anode typically becomes more excitable whereas the cathode site has decreased excitability. The efficacy of transcranial direct current stimulation depends on the location, intensity, and duration of the current applied to the brain, which is affected by electrode size and the orientation of the electric field.[128-130] Transcranial direct current stimulation is a much more diffuse form of stimulation than transcranial magnetic stimulation, though smaller electrodes and multielectrode arrays can be used to improve the spatial resolution.

Enduring changes in brain function after transcranial direct current stimulation are documented in the same manner as transcranial magnetic stimulation. When several sessions are applied, the effects can last for several weeks.[131,132] Because transcranial direct current stimulation is subthreshold for inducing action potentials, the greatest therapeutic benefit may be realized by coupling transcranial direct current stimulation sessions with cognitive training. This effect has been leveraged to induce therapeutic effects in disorders such as depression and pain.[133-136]

An ongoing study is investigating the use of transcranial direct current stimulation in adult patients with ADHD, which uses anodal transcranial direct current stimulation over the left dorsolateral prefrontal cortex at 1 mA.[137] The aim of this

parallel, randomized, double-blind, sham-controlled trial is to study the modulation of inhibitory control in this population. Although the results of transcranial direct current stimulation in ADHD are not yet available there is a burgeoning literature suggesting that transcranial direct current stimulation may be used to improve cognitive performance. These studies have shown that transcranial direct current stimulation can improve behavioral inhibition, memory, and attention in healthy subjects,[138,139] and these findings extend to clinical populations.[137,140] There is reason to be optimistic that similar stimulation paradigms may have a beneficial effect for ADHD patients, though it will be critical that future studies be sufficiently powered and include a sham-controlled experimental design.

If transcranial direct current stimulation is effective for certain symptoms of ADHD, it may offer many advantages over repetitive transcranial magnetic stimulation as a therapy. For example, the stimulators are relatively inexpensive compared to transcranial magnetic stimulation equipment, and application requires less cooperation from the patient relative to repetitive transcranial magnetic stimulation, which may be important for hyperactive children. Moreover, the safety profile of transcranial direct current stimulation is excellent and the main recognized side effects include an itching sensation and skin redness under the electrode.[116,129]

Newer Noninvasive Brain Stimulation Tools

Two new promising neuromodulation techniques include transcranial alternating current stimulation and transcranial random noise stimulation (tRNS). Transcranial alternating current stimulation is similar to transcranial direct current stimulation, but the current alternates at a specific frequency. This can alter the oscillatory frequencies in regions being stimulated. A recent study of 12 children with ADHD showed that 0.75-Hz transcranial alternating current stimulation during slow-wave sleep improved declarative memory consolidation to normal levels.[140] Given prior research highlighting abnormal oscillatory activity in the ADHD brain, such as an elevated theta-to-beta ratio in frontocentral leads,[141] it is possible that normalizing these patterns via transcranial alternating current stimulation may be therapeutic. Transcranial random noise stimulation is similar to transcranial alternating current stimulation, except instead of a defined frequency the alternating current is random, resembling noise.[142] It may act by introducing noise into a system to increase the signal-to-noise ratio.[143] Although transcranial random noise stimulation has not been used in ADHD to date, it has improved cognitive parameters for healthy controls.[144]

Ethics of Noninvasive Brain Stimulation in Pediatric ADHD

There are major questions raised by the prospect of inducing functional changes in a child's brain through exogenous stimulation. This includes, but is not limited to, possible long-term effects, access to this technology, and cognitive domain performance trade-offs. In fact, there is evidence that while therapeutic brain stimulation can result in benefits in certain domains, others can become impaired.[145,146] Given the availability of transcranial electrical stimulation devices and direct-to-consumer marketing, one major ethical concern is the proliferation of nonmedical use. If a company markets transcranial direct current stimulation equipment using nonmedical terms (eg, to enhance focus) it may bypass the regulatory processes in place for medical devices, potentially making transcranial stimulation available to consumers prior to carefully monitored clinical trials that are needed to rigorously establish the optimal parameters of use, efficacy and side effect profile. In addition, there is no guarantee that safety data derived from adult trials will carry-over to the pediatric population. As such, we must proceed forward with great caution and foresight. For excellent discussions of the ethics of pediatric brain stimulation, see Davis[147] and Maslen.[148]

Conclusion

This review highlights studies that build early support for the cautious extension of research into the diagnostic and therapeutic use of noninvasive brain stimulation in pediatric ADHD. While the current evidence is admittedly limited, there is reason to be optimistic. With respect to therapy, the developing brain is believed to be more plastic than its adult counterpart, and thus is likely to be more easily influenced by neuromodulation. Supportive of this concept, one of the predictors of better response to repetitive transcranial magnetic stimulation therapy in adult depression is younger age,[149,150] and early results of therapeutic neuromodulation in the pediatric population are encouraging. However, increased plasticity in the pediatric brain may also correspond to increased vulnerability to unintended changes induced by neuromodulation. Researchers must proceed cautiously with a high level of vigilance for side effects. Exactly how noninvasive brain stimulation can be optimally integrated with current clinical management of ADHD will require years of intensive study, but the pervasiveness of ADHD and the need for improved management should make this endeavor a high priority.

Author Contributions

BR conceived of the review, performed the literature review, and wrote the manuscript. ADB also wrote the manuscript and reviewed the literature. SL, AR, DJ, and APL all contributed significantly to editing the manuscript and each contributed important ideas to the final product.

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The authors declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: APL serves on the scientific advisory boards for Nexstim, Neuronix, Starlab Neuroscience, Neuroelectrics, Neosync, and Novavision, and is listed as inventor in issued patents and patent applications on the real-time integration of transcranial magnetic stimulation (TMS) with electroencephalography (EEG) and magnetic resonance imaging

(MRI). In the last 12 months AR has served as an advisor for Cyberonics, and NeuroRex Inc. and has joint grants with Brainsway Inc. and Vivonics Inc. He is a founder, equity holder, and consultant to Neuro'motion Labs and is an inventor on a patent that combines EEG and TMS for purposes of seizure treatments, and a patent pending for technologies to enhance the development of emotional regulation.

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