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The Use of Noninvasive Brain Stimulation Techniques in Autism Spectrum Disorder

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Abstract

Noninvasive Brain Stimulation (NIBS) techniques, including repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS), have recently emerged as alternative, nonpharmacological interventions for a variety of psychiatric, neurological, and neurodevelopmental conditions. NIBS is beginning to be applied in both research and clinical settings for the treatment of core and associated symptoms of autism spectrum disorder (ASD) including social communication deficits, restricted and repetitive behaviors, irritability, hyperactivity, depression and impairments in executive functioning and sensorimotor integration. Though there is much promise for these targeted device-based interventions, in other disorders (including adult major depressive disorder (MDD) and obsessive compulsive disorder (OCD) where rTMS is FDA cleared), data on the safety and efficacy of these interventions in individuals with ASD is limited especially in younger children when neurodevelopmental interventions typically begin. Most studies are open-label, small scale, and/or focused on a restricted subgroup of individuals with ASD. There is a need for larger, randomized controlled trials that incorporate neuroimaging in order to develop predictive biomarkers of treatment response and optimize treatment parameters. We contend that until such studies are conducted, we do not have adequate estimates of the safety and efficacy of NIBS interventions in children across the spectrum. Thus, broad off-label use of these techniques in this population is not supported by currently available evidence. Here we discuss the existing data on the use of NIBS to treat symptoms related to ASD and discuss future directions for the field.

Lay Summary

Noninvasive Brain Stimulation techniques are currently being studied in research centers and being offered in clinical settings to treat individuals with autism spectrum disorder. In this commentary, we discuss the evidence base for the use of these techniques. We also highlight the limitations and caution against broad expedited translation of these tools to the clinic without properly powered and controlled studies that provide sufficient data to inform their safety and efficacy in this population.

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Keywords

Autism Spectrum Disorder; Transcranial Magnetic Stimulation; Transcranial Direct Current Stimulation; Noninvasive Brain Stimulation; Clinical Translation; Neurodevelopment

Introduction

The mechanisms underlying the behavioral symptoms of autism spectrum disorder (ASD) are thought to be related to aberrant neurodevelopment, affecting functional brain networks, resulting in relatively unique pathophysiology for each individual. Thus, neural circuit-based interventions, such as noninvasive brain stimulation (NIBS) techniques (e.g. transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS)) have recently been put forth as alternative/adjunctive treatment options targeting these putative brain network mechanisms.

There is increasing literature on the use of NIBS techniques across multiple psychiatric and neurological disorders. Consistent with numerous positive randomized controlled trials establishing efficacy, a strong safety record, established safety and efficacy guidelines (Lefaucheur et al., 2020; Rossi et al., 2021) and with industry support, the US Food and Drug Administration (FDA) has now cleared rTMS for treatment-resistant major depressive disorder with and without comorbid anxiety (2021 and 2008 respectively) and obsessive compulsive disorder (2019) in individuals over the age of 21. There is currently no FDA approved indication for tDCS.

Though there is a substantial literature base for the safety and efficacy of NIBS in adult depression, obsessive compulsive disorder (OCD), and anxiety disorders (on the order of hundreds of thousands of patients), the literature base in pediatric and neurodevelopmental disorders is substantially smaller and more limited in scope. As these alternative treatments emerge, it is critical to evaluate their safety and efficacy in the context of a developing (and in the case of ASD, an atypically developing) brain. Interventions may be safe and have a defined therapeutic profile in typically developing individuals or those with other neuropsychiatric or behavioral disorders but may have different or even paradoxical effects in a child or adult with ASD. There is a paucity of rTMS studies in younger children and those with intellectual disabilities. Investigations that do include these pediatric or neurodevelopmentally delayed populations utilize protocols and dosages shown to be effective in adults without consideration for neurodevelopmental stage. Thus, caution is warranted before considering immediate or expedited clinical implementation of alternate interventions, especially those that alter brain function, in children with ASD, until their safety and efficacy for this population has been more fully examined using properly powered randomized controlled trials. Here we summarize the current evidence base for the use of rTMS and tDCS to treat symptoms related to ASD.

Repetitive Transcranial Magnetic Stimulation (rTMS)

During rTMS, trains of magnetic pulses are applied at various stimulation frequencies (e.g., 1 Hz, 5 Hz, 10 Hz) and patterns (e.g., Intermittent Theta Burst Stimulation (iTBS)

and Continuous Theta Burst Stimulation (cTBS). rTMS modulates excitability in targeted regions of stimulation (Hallett, 2000; Huang et al., 2005; Pascual-Leone et al., 1998) and exerts broader effects across networks connected to those regions (Beynel et al., 2020; Hawco et al., 2018). It was originally thought that stimulation frequencies 1 Hz or lower produce local cortical inhibition while those 5 Hz or higher lead to local cortical excitation (Chen et al., 1997; Pascual-Leone et al., 1994). Similarly, iTBS and cTBS protocols were originally thought to lead to long-lasting facilitation and suppression of cortical excitability, respectively (Huang et al., 2005). However, recent meta-analyses highlight the substantial interindividual variability (Corp et al., 2020). Beyond the various stimulation parameters, an increasingly recognized critical factor is the individual's behavioral and electrophysiological state at the time of stimulation (Sathappan et al., 2019; Silvanto & Pascual-Leone, 2008). Such state-dependency effects can be used to increase the specificity of the rTMS modulatory effects.

Safety of rTMS

The safety of rTMS in clinical practice and research has been evaluated through multiple meta-analyses (e.g. (Janicak et al., 2008; Machii et al., 2006)). Safety guidelines have been disseminated by the International Federation of Clinical Neurophysiology (Rossi et al., 2021). Widespread application of several rTMS protocols, across diverse populations and devices, show a low incidence of adverse events (Lerner et al., 2019).

Compared to the adult literature, data on the safety of rTMS in pediatric populations are relatively lacking. However, existing data suggest a similar safety profile in children and adolescents as compared to adults with adverse event rates ranging from 3.4% to 10.11%. Adverse event (AE) rates vary based on the patient population, the form of TMS, and the number of sessions (Allen et al., 2017). Similar to the adult literature, the most common side effects seen in the pediatric literature are transient headache and neck pain (Zewdie et al., 2020).

More serious adverse events in pediatric studies have been rare (1-2% of participants). Two cases of syncope in children with pediatric stroke and six cases of seizures have been reported (Chiramberro et al., 2013; Cullen et al., 2016; Hu et al., 2011; Kallel & Brunelin, 2020; Purushotham et al., 2018; Wang et al., 2018). The most recent International Federation of Clinical Neurophysiology TMS safety guidelines indicate that the extant pediatric literature "provides reassurance regarding the safety of these techniques" in pediatric populations (Rossi et al., 2021). However, this "reassurance" is based on far less data than in the adult literature. Furthermore, the neurodevelopmental processes ongoing in children and adolescence, compounded by the pathophysiological processes affecting those with neuropsychiatric and neurodevelopmental disorders, require careful consideration (Kirton & Gilbert, 2016; Oberman & Enticott, 2019).

Efficacy of rTMS

The mechanism of action of the therapeutic effect of rTMS is thought to be in the modulation of the functional connectivity of targeted networks. Thus, researchers have taken a "Research Domain Criteria (RDoC)" approach to targeting networks associated

with specific behavioral domains shown to be dysfunctional in individuals with ASD. The literature appears promising at first glance but is limited, composed of underpowered, sometimes open-label trials and case reports from only a handful of labs.

Three relatively small-scale (n=28, 75, and 13 respectively) randomized rTMS trials applied over the dorsomedial prefrontal cortex (dmPFC) (Enticott et al., 2014) and the posterior superior temporal cortex (pSTS) (Ni et al., 2021; Ni et al., 2022) led to improvements in social relating in children and adults with ASD. Additionally, multiple small-scale open-label trials of rTMS over the dorsolateral prefrontal cortex (dlPFC) conducted out of a single lab (Abujadi et al., 2018; Baruth et al., 2010; Casanova et al., 2012; Casanova et al., 2014; Casanova et al., 2020; Sokhadze et al., 2010; Sokhadze et al., 2009; Sokhadze, El-Baz, Sears, et al., 2014; Sokhadze, El-Baz, Tasman, et al., 2014; Sokhadze et al., 2018) and pSTS (Ni et al., 2021) (same study as above) led to a reduction in repetitive behaviors in children and adolescents with ASD.

Though these trials did show positive effects, Ni and colleagues noted variability in response rates with certain factors mediating the level of improvement in their studies. Specifically, higher IQ, better baseline social cognitive performance, less severe social-communicative impairments, less severe baseline ASD symptoms, and less attention-deficit hyperactivity disorder (ADHD) severity predicted better response (Ni et al., 2021; Ni et al., 2022). Additionally, those on concurrent psychotropic medication appeared to benefit less from pSTS stimulation in their social relating abilities (Ni et al., 2022). If replicated, these studies suggest that rTMS to pSTS for social relating may only be beneficial for a small subgroup of individuals with ASD (i.e., those without co-occurring ADHD or intellectual disability (common comorbidities), with relatively mild social-communicative impairments, or not taking concomitant medications). However, much larger trials are needed to determine whether these baseline clinical and behavioral variables should be used for patient stratification or as predictive markers of clinical response to rTMS.

Beyond the core ASD symptoms, rTMS has been used in clinical trials to improve associated symptoms of ASD with variable success. First, Ni and colleagues found a single session of active iTBS to the dlPFC led to immediate improvements on executive functioning tasks, effects not seen with sham iTBS (Ni et al., 2017). Shortly after, Abujadi and colleagues reported positive effects on executive functioning tasks following a series of open-label iTBS sessions to dlPFC (Abujadi et al., 2018). However, a randomized controlled trial over the same target resulted in no significant difference between the active and sham groups in improvement of executive functioning following a course of high-frequency rTMS (Ameis et al., 2020).

Ameis and colleagues (Ameis et al., 2020) highlight that baseline adaptive functioning moderated the effect of the stimulation. Specifically, the subgroup of participants with more severe impairment in baseline adaptive functioning experienced significant improvement in the active, but not the sham group compared with no difference in those with relatively higher levels of adaptive functioning at baseline. Interestingly, this is opposite to what was seen in Ni and colleagues' studies (Ni et al., 2021; Ni et al., 2022) where higher levels of functioning and lower levels of symptom severity predicted better response. This

difference may be due to differences in the primary outcome with Ameis and colleagues targeting executive functions and Ni and colleagues focusing on social relating and repetitive behaviors. As above, since this trial had a relatively small sample size (20 participants in each group), the degree to which these subgroup analyses represent a true predictor of response will have to be determined in a larger trial.

rTMS to dlPFC has also led to reduction in irritability in children/adolescents (Baruth et al., 2010; Casanova et al., 2012; Casanova et al., 2020; Sokhadze et al., 2010; Sokhadze et al., 2009; Sokhadze, El-Baz, Sears, et al., 2014), hyperactivity in children/adolescents (Casanova et al., 2020; Sokhadze, El-Baz, Sears, et al., 2014), and co-occurring depression in adults with ASD (Gwynette et al., 2020), in open-label trials of variable rTMS protocols. Given the open-label methodology and variable parameters used, the degree to which any specific protocol may be effective for these symptom domains will require replication in larger-scale, randomized, sham-controlled trials.

To date, four preliminary studies from a single lab have examined the use of rTMS to target impairments in sensorimotor integration in ASD (Panerai et al., 2014). These investigations are also notable for their inclusion of individuals with comorbid intellectual disability. Across the series of four small studies (n = 9, 17, 4, and 13), improved performance on eye-hand integration was seen following high-frequency stimulation to premotor cortex, and further improved when paired with eye-hand integration training.

Transcranial Direct Current Stimulation (tDCS)

Transcranial direct current stimulation (tDCS) is a form of transcranial electrical stimulation (tES) that alters cortical excitability through the application of a weak constant electrical current. The current is delivered via electrodes placed on the scalp. Unlike TMS, the applied current is not strong enough to induce action potentials. The current modulates the electrical field impacting surface neurons, increasing or decreasing the probability of neuronal firing in the affected area. Anodal stimulation depolarizes neurons leading to an increase in the likelihood of firing and cathodal stimulation hyperpolarizes neurons decreasing the likelihood of firing (Auvichayapat & Auvichayapat, 2022; Ciechanski & Kirton, 2017; Moreno-Duarte et al., 2014; Woods et al., 2016).

The intensity of tDCS is held constant (excluding ramping up and down of the current, usually 10-15 seconds) throughout a session and ranges from 0.5 to 2mA for 5-30 minutes. Often multiple sessions are applied within one day. Current passes from anode (negative pole/−) to cathode (positive pole/+), therefore, anodal versus cathodal (polarity) stimulation is determined by the placement of the negative or positive electrode over the target or region of interest (ROI). This divides conventional tDCS into three montages: anodal, cathodal, and bihemispheric. Anodal stimulation places the anode over the ROI and the cathode at a distant or “inert” location; cathodal stimulation reverses this paradigm. In bihemispheric stimulation both electrodes are placed on ROIs, the anode over the ROI one is seeking to depolarize and the cathode over the location one is seeking to hyperpolarize (Auvichayapat & Auvichayapat, 2022; Ciechanski & Kirton, 2017; Moreno-Duarte et al., 2014; Woods et al., 2016). Beyond electrode placement, polarity, and intensity - the individuals’ brain

state at the time of stimulation is another important factor impacting the effects of tDCS. tDCS paired with a task or behavioural intervention is referred to as an “online” design or “online” tDCS (Thair et al., 2017). This design allows the investigator to observe the impact of stimulation on the task/ behavior and/or the impact of the task or behavior on the brain network response to tDCS (Horvath et al., 2014; Li et al., 2019; Nozari et al., 2014; Parmar et al., 2021).

Safety of tDCS

tDCS has been shown to be both safe and tolerable across the age-span in research settings (Bikson et al., 2016; Buchanan et al., 2021; Zewdie et al., 2020) and at home in recent trials of remotely supervised at-home devices (Cappon et al., 2021; Pilloni et al., 2022; Shaw et al., 2020; Simpson et al., 2022). Common reported side effects of tDCS are all considered mild and include sensations (i.e., tingling, itching, and mild burning) and redness at the stimulation site. Uncommon side effects include headaches, nausea, small blistering at the stimulation site, mood changes, difficulty concentrating, and transient changes in attention and memory (Auvichayapat & Auvichayapat, 2022; Buchanan et al., 2021; Zewdie et al., 2020). The largest tDCS safety data set, composed of >2800 tDCS sessions across ~500 children, was aggregated by Bikson and colleagues (Bikson et al., 2016) and found no serious adverse effects and low dropout rates across the studies. The estimated prevalence and quality of the side effect profile of tDCS, however, is limited by the small sample sizes of the studies. More recently, Zewdie et al (Zewdie et al., 2020) aggregated a decade of brain stimulation data from a single clinic representing 92 children who combined received 612 sessions of tDCS primarily over the primary motor cortex (n=48 typically developing, n=43 with perinatal stroke, n=1 with schizophrenia). Anodal, cathodal, and high-density tDCS (HD-tDCS) approaches were conducted with 1mA median dose of electrical current (range 1-2mA). All sessions were 20 minutes in duration. There were no dropouts or serious adverse effects reported and individuals ranked the experience as highly tolerable, between “attending a birthday party” and a “long car ride”. Itching and burning sensations under the stimulation site was the most reported side effect, followed by tingling. Headache, neck pain, lightheadedness (without altered consciousness), and nausea were also reported at lower rates. Given the minor and transient nature of side effects, tDCS trials often carry a “nonsignificant risk” designation (Fregni et al., 2021).

Efficacy of tDCS

It is hypothesized that tDCS may modulate network activity via processes such as regulation of synaptic plasticity (Hameed et al., 2017), increased synaptogenesis (Auvichayapat et al., 2020), and promotion of cortical meta-plasticity (Monai et al., 2016). Therefore, similar to TMS, tDCS has been investigated as a possible tool in the treatment of ASD by targeting these putative pathophysiological mechanisms. Like TMS, an obstacle to the broad dissemination of tDCS as a clinical treatment is the variability in methodology and response across studies. The heterogeneity of ASD and the small study sample sizes are recognized and established factors. Other contributors include differences in outcome measures, current intensity, electrode placement, stimulation sites, and the state of the targeted network at the time of stimulation.

While current is held steady and the range across investigations is relatively small, 0.5-2mA, utilizing computer modeling to map the electrical field may aid researchers in optimizing current delivery, not only individualized stimulation locations but also current intensity. As current travels from anode to cathode, the path taken can be influenced by the different resistance properties of the skin, bone, and underlying fluid and tissues. Therefore, utilizing E-field modeling programs, such as simNIBS, mapping and/or optimizing the current to the individual can be achieved by taking these physical factors into account (Saturnino et al., 2015; Truong & Bikson, 2018). Additionally, as the current travels the cortical tissue along the path is impacted. One must remember that the sites directly under the electrodes are not the only neurons exposed to current. Therefore, electrode placement is important as it greatly influences the path.

A majority of tDCS studies in ASD target the dlPFC. As reviewed in Garcia-Gonzalez et al. and Khaleghi et al (Garcia-Gonzalez et al., 2021; Khaleghi et al., 2020) anodal stimulation of dlPFC was successfully investigated in language (improved syntax acquisition in minimally verbal children with ASD)(Schneider & Hopp, 2011), working memory (increase in performance) (van Steenburgh et al., 2017), and autistic symptoms and behaviors(Amatachaya et al., 2014; Amatachaya et al., 2015; Gomez et al., 2017; Hadoush et al., 2020). In more recent investigations of dlPFC stimulation, Qiu et al. (Qiu et al., 2021) conducted a randomized, parallel-group, sham-controlled investigation of multi-session (15 sessions over 3 weeks) anodal left dlPFC tDCS stimulation in young children (2-6 years old) with ASD (n=20 per group). They noted no difference in improvements in ASD symptom severity between groups. However, in the within group analysis significant decreases ($p < 0.05$) in symptom severity were observed in the active group, but not in the sham group. Improvements in sleep habits were also observed. In 2022, Auvichayapat and colleagues investigated the efficacy of anodal tDCS of the left dlPFC in young children with ASD (up to 2 years 11 months). They randomized the participants to receive sham, five, or 20 tDCS sessions concurrent with a behavioral intervention. They observed superior effects of five and 20 sessions versus sham with the concurrent behavioral intervention, with no difference between 5 and 20 sessions (Auvichayapat & Auvichayapat, 2022). Zemestani et al. (Zemestani et al., 2022) conducted a randomized, sham-controlled, and parallel-group study of children 7-12 years old with ASD (n=17 and 15 in active and sham groups respectively). Participants received ten sessions (15 minutes) of active or sham bilateral dlPFC (left anodal/right cathodal) stimulation over five weeks. Significant improvements were noted in the active tDCS group as compared to the sham in ASD symptom severity, theory of mind (ToM), and emotion regulation following treatment. Additionally, in 2023, a larger tDCS study with 105 (87 completed entire protocol) ASD individuals (14-21 years) was conducted by Han and colleagues (Han et al., 2023). This was a triple-arm (active, sham, waitlist control), double-blind RCT investigating 10 sessions of left cathodal dlPFC online tDCS. Concurrent with stimulation, individuals completed a cognitive training package that included games targeting cognitive flexibility, interference control, visual information processing, and working memory. Improvements were noted in the active tDCS group in social functioning and RRBs with medium and large effect sizes respectively.

Social cognition and information processing, including ToM, have also been targeted via stimulation of right temporoparietal junction (rTPJ) (Esse Wilson, Trumbo, et al., 2018) and

the ventromedial prefrontal cortex (vmPFC) (Salehinejad et al., 2021). Indeed, Salehinejad and colleagues found that a single online (ToM Test) session (20 minutes) of anodal vmPFC stimulation had better outcomes as compared to anodal rTPJ stimulation or sham in children with ASD (n=16) in a randomized, sham-controlled crossover study. Parmar et al (Parmar et al., 2021) recently reported a null finding in a recent randomized, sham-controlled, crossover trial of multiple sessions (20 minutes over four consecutive days) of online (Stop Task) anodal tDCS over the right ventrolateral prefrontal cortex (vlPFC) targeting cognitive inflexibility in adolescents and young adults with ASD (n=12). These two small-sample studies differed in their target (rTPJ versus vlPFC), behavioral domain (ToM versus cognitive inflexibility). Thus, the source of the variability in outcome is unclear.

Future Directions

There are currently numerous gaps in the literature. Properly designed and powered, randomized, controlled, and blinded investigations are lacking and are the gold standard for establishing safety and efficacy of a novel treatment. Such trials are needed for the FDA to expand (rTMS) or establish (tDCS) labels to include ASD and to support broad off-label use. The regulatory pathway to FDA clearance often takes years to accumulate sufficient data for safety and efficacy and can be a costly process. Thus, advising against expedited clinical implementation of NIBS interventions before these trials have been conducted is admittedly difficult in the context of accumulating pressure from parents and clinicians for additional therapeutic options. A cursory google search conducted on April 10, 2023, resulted in dozens of clinics offering “off-label” NIBS interventions for ASD. However, as this is off-label, insurance will likely not cover these treatments, which can cost approximately $6,000-$12,000 per treatment course.

Building upon early promising results and recognition of the benefits of collaboration, in 2014, an international consensus group for TMS in ASD was convened composed of leaders in the field of neuromodulation and neurodevelopmental disorders and sponsored by the Clearly Present Foundation (https://clearlypresent.org/) of which the co-authors (LO and SF) are members. The importance of forming research groups and establishing collaborations are noted by three published consensus statements that call for definitive studies of the safety and efficacy of rTMS in ASD, and careful consideration of stimulation sites, outcome measures, reporter bias, and clinical heterogeneity when designing rTMS trials (Cole et al., 2019; Oberman et al., 2014; Oberman et al., 2016).

Since convening the international consensus group, one large-scale, multisite, randomized trial has been initiated (Enticott et al., 2021). Results are expected in early 2025. This trial will evaluate the safety and efficacy of 20 daily sessions of iTBS to the rTPJ in an effort to improve social communication deficits in 150 adolescents and adults with ASD. Similar large-scale rTMS or tDCS studies for other behavioral domains await further clarification on the pathophysiology underlying other symptom domains, biomarkers of clinical severity and response variability, and commitment of substantial funding from either private or public sources.

Computational models and analysis techniques applied to both rTMS and tDCS (e.g., (Antonenko et al., 2021; Bestmann, 2015; Minhas et al., 2012)) and “big data” meta-analyses (e.g., (Corp et al., 2020; Medaglia et al., 2020) as has begun to be done in rTMS) may be useful to inform the selection of stimulation parameters and target sites for future trials. Additionally, establishing valid and reproducible biomarkers that can predict likely responders to NIBS could help to stratify and enrich samples for those who will most benefit (e.g., (D'Urso et al., 2017; Fidalgo et al., 2014; Garnaat et al., 2019).

Understanding the impact and controlling for ongoing brain state and dynamics on stimulation is also critical in reducing response variability. Guerra et al. (Guerra et al., 2020) and Zrenner et al. (Zrenner et al., 2018) showed that stimulating “at the right time” when the targeted network is most likely to respond enhances neuromodulation effects. Pairing neuroimaging techniques, such as EEG or fMRI, with brain stimulation can assist in timing stimulation to an optimal brain state. TMS or tDCS (Leite et al., 2017; Martens et al., 2021) paired with electroencephalography (EEG), which measures ongoing neural activity at a millisecond timescale, can also synchronize stimulation to an optimal brain state (Zrenner et al., 2018). In both TMS and tDCS a targeted network can be excited or inhibited by an ongoing task or intervention concurrent with the NIBS intervention (Esse Wilson, Quinn, et al., 2018; Esse Wilson, Trumbo, et al., 2018; Li et al., 2019; Parmar et al., 2021; Salehinejad et al., 2021; Sathappan et al., 2019).

Given the varied presentation of ASD, investigators are expanding potential target sites to address different deficits and domains across phenotypic groups. An excitatory/inhibitory imbalance has been observed in ASD individuals (Rubenstein & Merzenich, 2003), including reduced numbers of Purkinje cells, the inhibitory neurons of the cerebellum (Arin et al., 1991). Recently, D’Urso and colleagues (D'Urso et al., 2021) targeted the cerebellum in an open-label pilot study in six children with ASD (20 min, 1.0mA cathodal stimulation to the right cerebellar hemisphere, 20 daily sessions over four weeks). They noted improvements in ASD symptoms, including social withdrawal and irritability. Additionally, in an individual comorbid for Tics, they noted a decrease in tic severity and in the individual with comorbid epilepsy, a reduction in seizures. These findings justify further investigation into this region as a possible treatment target. As mentioned above, computational investigations can aid in identification of new targets streamlining the investigative process. In addition to the future directions above, specific to tDCS and touched upon earlier, further investigations into the use of at-home devices should be conducted. Mandated temporary holds on “nonessential” medical procedures and appointments during the early months of the novel coronavirus disease 2019 (COVID-19) pandemic in spring of 2020, magnified the need to increase accessibility (e.g., city versus rural, outside of clinic and school hours) and alternative options to certain in-clinic treatment procedures. This event accelerated investigations into the use of at-home tDCS devices (Charvet et al., 2015; Charvet et al., 2020). The use of these devices has proven feasible and safe in both adults and children (Cappon et al., 2021; Pilloni et al., 2022; Simpson et al., 2022).

As research groups and clinics around the world increase their acceptance of NIBS techniques as promising scientific and therapeutic tools, it is important to be cognizant

of not only their potential, but also the limitations of the existing literature on the safety and efficacy of various NIBS protocols. More research aimed at the discovery and optimization of parameters for modulating the brain that has an altered developmental trajectory is needed to address these gaps.

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