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Perspective

Pediatric Neuromodulation Comes of Age

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Abstract

This special issue surveys recent work and underscores the challenges of psychiatric brain stimulation research with child and adolescent populations. The field of child and adolescent psychopharmacology is replete with examples of potential pitfalls in the assumption that ''children are little adults.'' Arguably, younger age portends more neurobiological and descriptive heterogeneity in research pursuits and clinical practice. For existing brain stimulation modalities, there are a paucity of translational models to design studies for youth and no well-studied dosing schemes. The long-term positive and negative effects of neuromodulation interventions in youth are unknown. Inherent pragmatic and ethical limitations often present barriers for participant recruitment and will necessitate innovative approaches to study design and team efforts. These challenges are not insurmountable, and sustained efforts will advance the growing field of pediatric neuromodulation.

Neuromodulation is a rapidly evolving field that recognizes electricity as the primary currency of the brain. Collectively, neuromodulation includes a wide range of modalities such as transcranial direct current stimulation (tDCS), transcranial magnetic stimulation (TMS), vagal nerve stimulation, electroconvulsive therapy (ECT), magnetic seizure therapy (MST), and deep brain stimulation (George and Aston-Jones 2010). Treatments stimulating relevant neurocircuitry in psychiatric disorders present unique research opportunities and much needed therapeutic advances for patients with limited options (McClelland et al. 2016). Advances in brain stimulation have already changed the practice of psychiatry and composition of multidisciplinary treatment teams. For example, TMS is no longer considered investigational in adult major depressive disorder and has increasing accessibility (Dunner et al. 2014).

Work with child and adolescent populations is nascent but promising (Croarkin et al. 2011; Rubio et al. 2016). Understandably, there is much excitement as neuromodulatory tools could catalyze mechanistic and therapeutic work related to recent National Institute of Mental Health initiatives (Insel and Cuthbert 2015). Specifically, timely intervention with brain stimulation modalities could address aberrant neurocircuitry early in life, thereby altering the trajectory of neurodevelopment (Bourac 2016). One day, this may thwart years of morbidity, save patients from repeated trials of ineffective treatments, and potentially reduce societal burdens. However, in work with youth, this enthusiasm must be tempered with caution, further research, and an ethical approach to adopting these technologies in clinical practice (Davis 2014; Geddes 2015). While large longitudinal safety studies are lacking, current work suggests that tDCS and TMS in particular may be well tolerated and relatively safe for use in children and adolescents (Krishnan et al. 2015).

Research focused on tDCS has flourished recently due to its low cost, accessibility, tolerability, and presumed safety. Variable tDCS montages with anodal (excitatory) and cathodal (inhibitory) stimulation produce divergent neurophysiological effects. In general, prior research suggests that stimulation with tDCS modifies neuronal resting membrane potential and excitability with resultant alterations in GABAergic and glutamatergic synapses. The neurophysiological, cognitive, and behavioral effects of single tDCS sessions are short lived. Repeated sessions and interleaving tDCS with other modalities may produce more long-lasting changes in neuroplasticity and psychiatric symptoms (Kekic et al. 2016). Further mechanistic understanding, refinements in dosing, and longitudinal safety studies are imperative to nurture prospects of integrating tDCS into clinical practice (Brunoni et al. 2013). Aside from its therapeutic potential, tDCS is already an important tool for clinical neurophysiology and cognitive neuroscience research efforts (Bourac 2016).

Repetitive TMS (rTMS) is an established clinical treatment for major depressive disorder in adults. This indication was first cleared by the US FDA in 2008, and at present, four different types of magnetic stimulators are approved for the treatment of major depressive disorder (MDD) (O'Reardon et al. 2007; George et al. 2010). Initially, therapeutic rTMS research focused on low-frequency (1 Hz) or high-frequency (5–20 Hz) stimulation targeting the dorsolateral prefrontal cortex. Recent work with theta burst stimulation (TBS) dosing

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suggests that further enhancements in pulse sequences may yield more durable and practical treatment approaches (Chung et al. 2015). TBS approximates *in vitro* protocols for modulating excitatory synaptic strength and is based on delivery of three high-frequency pulses at 50 Hz at 200 ms (5 Hz) intertrain intervals. Continuous TBS (cTBS) has an inhibitory effect on cortical activity as it delivers uninterrupted stimulation typically for 20–40 seconds. Conversely, intermittent TBS (iTBS) likely enhances cortical excitability with 2-second trains of TBS and 10-second intertrain intervals (Huang et al. 2005; Chung et al. 2015). Given that the field is only beginning to understand neurophysiologic and cellular effects of TMS, ongoing, clinical, and preclinical research will continue to refine this treatment for adults (Grehl et al. 2015). Meaningful work will require the navigation of substantial challenges, given the number of variables involved, such as localization of treatment, stimulation parameters, frequency of treatments, duration of treatment, state-dependent factors, and the personalization of stimulation to a patient's distinctive neurobiology. These challenges are magnified in the context of neurodevelopment. However, as brain stimulation technologies rapidly become more accessible to youth outside of research settings, an enhanced understanding of neurobiologic mechanisms, optimum delivery, and long-term safety is an ethical mandate (Krishnan et al. 2015).

This special issue surveys recent work and challenges while underscoring the importance of psychiatric brain stimulation research with child and adolescent populations. The field of child and adolescent psychopharmacology is replete with examples of the potential pitfalls in assuming ''children are little adults.'' Arguably, younger age portends more neurobiological and descriptive heterogeneity in research pursuits and clinical practice (March and Fegert 2012). There are few translational models to design studies for youth or established dosing schemes for brain stimulation. The long-term positive and negative effect of neuromodulation interventions in youth is undetermined and understudied. Inherent pragmatic and ethical limitations often limit recruitment and will necessitate innovative approaches to study design and team efforts. These challenges are not insurmountable, and measured sustained efforts will advance the growing field of pediatric neuromodulation (Croarkin et al. 2011; Rubio et al. 2016).

Prior research has examined the utility of tDCS for adult neuropsychiatric disorders such as major depressive disorder. This noninvasive technique applies weak electrical current over the scalp to modulate cortical excitability. As tDCS may be tolerable, inexpensive, and accessible, it is an appealing modality to consider for the treatment of early-onset psychiatric disorders. Muszkat et al. report on a review of existing literature focused on the application of tDCS in child and adolescent psychiatric disorders. There are three prior randomized trials, but, to date, no study has extended beyond 10 sessions of tDCS. This prior work has focused on childhood-onset schizophrenia, autism spectrum disorders (ASDs), learning disabilities, and attention-deficit/hyperactivity disorder. Evidence for decisive conclusions is lacking, but these preliminary data are encouraging as tDCS appeared to be relatively safe and tolerable on a short-term basis (Muszkat et al. 2016).

In recent years, neurologists, physical therapists, and rehabilitative treatment teams have spearheaded fascinating studies of rTMS interventions for pediatric stroke. These studies have arguably outpaced child and adolescent psychiatry TMS research (Kirton et al. 2010; Damji et al. 2015). Notably, there is much for our field to garner while reviewing this work. Rich et al. review a recent study of long-term outcomes of rTMS applied to the motor cortex with and without concurrent constraint-induced movement therapy. The majority of patients in both groups improved, and 6 of 14 patients reported new-onset conditions at 21–57 months. This study is laudable as it collected long-term follow up data, which are rare in pediatric brain stimulation studies (Rich et al. 2016). This line of research will also inform the development of more sophisticated psychiatric studies. Specifically, future efforts may include concurrent psychotherapeutic techniques or cognitive remediation before, during, or immediately after TMS sessions. Currently, it is not known what sequence of these interventions will provide optimum outcomes in mood disorders, addictive disorders, and neurobehavioral disorders.

The neurobiology of ASD is poorly understood. There is a pronounced unmet need for brained-based therapeutic interventions for impairing target symptoms such as irritability and to optimize trajectories of neurodevelopment. TMS and brain stimulation technologies may prove to be important tools for the study and treatment of ASD. Three studies in this special issue illustrate the importance of a measured approach to this line of research. These studies underscore the unique position of TMS in the neurostimulation device space as a method with robust diagnostic and therapeutic capacity. Kirkovski et al. present recent work with novel concurrent TMS and electroencephalogram (TMS-EEG) paradigms. Twenty-two adult participants with ASD and 20 adult healthy control participants underwent TMS-EEG testing at the dorsolateral prefrontal cortex, primary motor cortex, and temporoparietal junction. While there were no differences between ASD and healthy control participants, phase synchrony data demonstrated relationships with clinical dimensions of ASD (Kirkovski et al. 2016).

Other novel work presented in this issue examines the application of cTBS and iTBS. Oberman et al. examined two 40-second (600 pulses) sessions of cTBS applied to the motor cortex to index cortical synaptic plasticity in 10 participants with ASD, six individuals with Fragile X Syndrome (FXS), and 12 healthy control participants. After the first cTBS session, the ASD participants exhibited a greater period of cortical inhibition compared to controls, while FXS participants had a diminutive period of inhibition. After the second cTBS session 24 hours later, the length of cortical inhibition in the ASD group was no different from controls, while the FXS participants had an increase in cortical excitability. These data suggest distinct plasticity and metaplasticity signatures among ASD and FXS. Further work will provide neurophysiologically informed therapeutic interventions (Oberman et al. 2016). Other work by Pedapati et al. examined the effects of iTBS applied to the motor cortex (300 pulses) in nine adolescents with ASD and nine healthy control participants. The iTBS was tolerable, and the ASD group displayed decreased motor-evoked potential amplitude at 20 minutes, suggesting again that TBS coupled with measures of synaptic plasticity may prove useful in identifying endophenotypes of ASD and crafting future therapeutic interventions with TMS (Pedapati et al. 2016).

Biomarker and therapeutic work in adolescent MDD also continues to progress. Building on prior research (Wall et al. 2011). Wall et al. present new data from an open-label trial of high-frequency rTMS for adolescent MDD. This study was designed to explore the feasibility and utility of a MRI-guided localization approach for coil placement during rTMS sessions. Participants received up to 30 sessions off 10 Hz rTMS at 120% motor threshold targeted to the left dorsolateral prefrontal cortex. Data on scalp location for treatment were compared to standard 5 cm rule and Beam F3 techniques. Treatment with rTMS was tolerable and effective in the majority of participants. Standard localization techniques may identify variable locations for coil placement, but the clinical significance of this in unknown (Wall et al. 2016).

Cullen et al. (2016) also present a case history of a deep TMS-induced generalized tonic-clonic seizure in an adolescent. This underscores the necessity of further safety and dose finding research in adolescents with major depressive disorder.

Finally, Puffer et al. review outcome data on 51 adolescents treated with ECT at a large academic center from 1991 to 2013. While ECT has demonstrated safety and efficacy for severe neuropsychiatric disorders in adults, data on use in children and adolescents are lacking. Although practice guidelines for the use of ECT in adolescent populations exist, there is a concern it may be underutilized for severely impaired adolescent patients (Ghaziuddin et al. 2004). Ethical and pragmatic barriers present significant challenges for conducing randomized clinical trials. Clinical reviews and naturalistic studies are rare. Dr. Puffer's practice review represents one of the largest such reviews to date. In this sample, adolescents were diagnosed with recalcitrant mood disorders, psychosis, or catatonia. The majority of adolescents demonstrated clinical improvement with ECT (Puffer et al. 2016). Future contemporary work may refine dosing strategies as with MST (Noda et al. 2014; Sun et al. 2016), refine practice guidelines for adolescents, and catalyze practice registries focused on ECT practices in adolescents.

In summary, noninvasive brain stimulation research in children and adolescents is rapidly evolving. These powerful tools hold substantial promise as neurophysiologic probes and therapeutic interventions for dysfunctional neurocircuitry. Current literature should elicit both excitement and skepticism. Study design and ethical concerns will need to be carefully balanced in pursuing reliable protocols with large well-characterized samples. One quandary is the inclusion of healthy children in brain stimulation protocols as while essential for scientific motives may be problematic in some instances as control participants are unlikely to receive any direct benefit.

Future therapeutic trial design should consider neurodevelopment, systematic adverse event monitoring, and longitudinal monitoring. Such research should also include systematic testing of the interactions of brain stimulation techniques and pharmacotherapy to identify which pharmaceuticals may enhance neuromodulation efficacy and which agents may interfere with it. Successful efforts will require innovative, multidisciplinary large collaborations. Clinical practice registries, preclinical work, and computational modeling studies would likely assist in bridging current knowledge gaps. Ongoing research is essential, as most likely the clinical application of brain stimulation modalities for child and adolescent psychiatric disorders will soon outpace research efforts and translational understanding.

Disclosures

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