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Review Article

Safety of Noninvasive Brain Stimulation in Children and Adolescents

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ABSTRACT

Background: Noninvasive brain stimulation (NIBS) techniques such as transcranial magnetic stimulation (TMS) and transcranial current stimulation (tCS) have the potential to mitigate a variety of symptoms associated with neurological and psychiatric conditions, including stroke, cerebral palsy, autism, depression, and Tourette syndrome. While the safety of these modalities has been established in adults, there is a paucity of research assessing the safety of NIBS among children.

Objective: To examine the existing literature regarding the safety of NIBS techniques in children and adolescents with neurologic and neuropsychiatric disorders.

Methods: An electronic search was performed on online databases for studies using NIBS in individuals less than 18 years of age. Non-English publications, diagnostic studies, electroconvulsive therapy, single/dual pulse TMS studies, and reviews were excluded. Adverse events reported in the studies were carefully examined and synthesized to understand the safety and tolerability of NIBS among children and adolescents.

Results: The data from 48 studies involving more than 513 children/adolescents (2.5–17.8 years of age) indicate that the side effects of NIBS were, in general, mild and transient [TMS: headache (11.5%), scalp discomfort (2.5%), twitching (1.2%), mood changes (1.2%), fatigue (0.9%), tinnitus (0.6%); tCS: tingling (11.5%), itching (5.8%), redness (4.7%), scalp discomfort (3.1%)] with relatively few serious adverse events.

Conclusion: Our findings indicate that both repetitive TMS and tCS are safe modalities in children and adolescents with various neurological conditions, especially when safety guidelines are followed. The incidence of adverse events appears to be similar to that observed in adults; however, further studies with longer treatment and follow-up periods are needed to better understand the benefits and tolerance of long-term use of NIBS in children.

Introduction

Noninvasive brain stimulation (NIBS) refers to a group of modalities that are used to induce electric currents to and within the brain for diagnostic or therapeutic purposes [1–4]. A growing body of evidence suggests that NIBS techniques may have a promising role in the diagnosis, monitoring, and treatment of a variety of neurological and psychiatric conditions [5–9]. The therapeutic potential of NIBS stems from the capacity to evoke immediate and sustained modulation of neural network activity through alterations in neuronal excitation. The induced neuromodulation can be either excitatory or inhibitory, depending on the polarity, frequency, and duration of the stimulation [2,10]. Moreover, the ability to induce directional modulation further enhances the therapeutic possibilities of NIBS, as the necessary direction of the brain excitability for recovery varies with different disease conditions [10,11].

Two major types of NIBS techniques are currently in use on humans for clinical and research applications: Transcranial Magnetic Stimulation (TMS) and Transcranial Current Stimulation (tCS) [12]. TMS uses a varying magnetic field to induce weak electric currents in the brain. It can be delivered as a single pulse or as a train of pulses. Single-pulse TMS is typically used to study brain physiology and plasticity [3,13–16], whereas repetitive-pulse TMS (rTMS) is commonly used to elicit neuromodulation and neuroplasticity, and can result in prolonged excitability changes that

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outlast the stimulation period [6,15]. Typically, the direction of neuromodulation is driven by the frequency at which the stimulation is performed, such that high-frequency rTMS increases cortical excitability and low-frequency rTMS decreases cortical excitability [17]. However, theta burst stimulation (a variation of high frequency rTMS) can induce either depression or facilitation of cortical excitability, depending on burst-train duration, such that intermittent theta burst stimulation increases cortical excitability and continuous theta burst stimulation decreases cortical excitability [18].

tCS refers to the application of direct or alternating current on a specific region of the brain, transmitted via electrodes attached to the scalp. A wide range of tCS modalities exists, but only a few have been well-studied. Transcranial direct current stimulation (tDCS), (or "Transcranial Micropolarization"), is the most commonly used type of tCS [2,19–25]. It employs a battery-driven stimulator to deliver weak direct currents (0.5–2.0 mA) through contact electrodes over the scalp. The current flow modulates neuronal excitability by altering the resting membrane potential of the neurons and produces aftereffects (i.e., prolonged changes in neuronal excitability) that are thought to be driven by Glutamatergic and GABAergic synapsic plasticity [26]. tDCS can be used to elicit an excitatory (anodal) or inhibitory (cathodal) effect, depending on the polarity of stimulation. Specifically, anodal stimulation has a depolarizing effect, which increases neuronal excitability; whereas, cathodal stimulation has a hyperpolarizing effect, which decreases neuronal excitability [1,19,27,28].

During the past two decades, a large number of studies have evaluated the therapeutic benefits of NIBS modalities in a wide range of patient populations, including children with neurological disorders. These studies have demonstrated that NIBS modalities may provide therapeutic benefits for a wide variety of disease-specific symptoms, such as aphasia [29–32], dystonia [33–35], depression [36–41], epilepsy [10,42–47], migraine [48,49], motor dysfunction [11,50–53], neurocognitive impairments [54], and pain [55–57], and are generally safe when the safety guidelines are observed [3,20,58–61]. The majority of the NIBS safety studies have been conducted in adults, and there is a paucity of research specifically devoted to examining the safety of NIBS in children. The few studies that have reviewed the safety of NIBS in children were limited to reporting on single-pulse and paired-pulse TMS protocols [59,62]. A 2010 review on the safety of rTMS for children and adolescents indicated that rTMS was a feasible technique to facilitate recovery in adolescents with neurological and neuropsychiatric conditions with no major adverse events reported [63]. However, that review did not include any studies that examined children less than seven years old, and only three subjects were less than 16 years of age. In light of the growing interest of research directives and clinical applications of NIBS for children and adolescents, it is imperative to better understand the safety of these techniques for this population.

Therefore, the purpose of this review was to collect evidence related to the safety of NIBS application in children and adolescents, and to expand upon the D'agati study [63] by including younger subjects, subsequent studies published after 2009, as well as studies pertaining to the use of tCS in these populations.

Methods

We performed an electronic search of MEDLINE, EMBASE, PubMed, Web of Science, SPORTDiscus™, Evidence Based Medicine Reviews, and Multifile (EBMR) databases from their inception to September 2014. Permutations of the text keyword combinations for topic or study interventions included the following: "transcranial direct current stimulation", "transcranial current stimulation", "micropolarization", "transcranial magnetic stimulation", "rapid transcranial magnetic stimulation", "repetitive transcranial magnetic brain stimulation", "deep transcranial magnetic stimulation", and their respective abbreviations along with search terms "children", "pediatric", and "adolescent." These terms were then combined with CNS diseases or disorders, such as cerebral palsy, stroke, autism, Tourette syndrome, epilepsy, depression, and delayed neuropsychological development. The references of the papers retrieved through this electronic search were manually inspected to find other potential studies that fit our inclusion criteria.

Inclusion criteria were limited to studies on children and adolescents less than 18 years of age that incorporated NIBS. Non-English language publications, diagnostic studies, retrospective studies, electroconvulsive therapy, single/dual pulse TMS studies, and reviews were excluded. Due to the limited number of papers regarding the application of NIBS in pediatric populations, we included both single-session and intervention studies. We did not impose any inclusion criteria based on quality of the study (i.e., study design), as this would have resulted in the exclusion of case reports, case series, and letters to the editors. Since serious adverse events were often communicated through such studies or reports, the use of qualitative assessment and subsequent exclusion of these studies would artificially lower the apparent incidence of such side effects, and thus lead to a misrepresentation of the safety of NIBS in children.

Studies were examined by the authors to determine the eligibility criteria. When there was insufficient information from the abstract, we read the full-length paper to ensure that each potential study was eligible to be included in our review. A data extraction sheet was developed to summarize the following variables: (1) sample size, (2) age, (3) diagnosis, (4) adverse effects, (5) treatment parameters, and (6) stimulation parameters. When there was insufficient information on subject demographics, treatment parameters, and/or adverse events, the corresponding authors of studies were contacted. We also cross-referenced the ClinicalTrials.gov website to retrieve additional information related to adverse events, when the reports were not clearly described in the manuscript and/or in the event that corresponding authors failed to reply. Extracted data were coded and evaluated using descriptive statistics. Adverse effects data were pooled among studies to calculate the incidence (i.e., frequency) of each event. This was performed by dividing the total number of subjects that had reported an adverse event (n), by the total sample size of the pooled data (N), and expressing it as a percentage $\left[\%\mathrm{AE} = \left(n/N\right) \times 100\right]$. There were several studies that included both children and adults. In those instances, and when the exact number of children versus adults reporting an adverse event couldn't be determined (i.e., from the study or by contacting the authors), we made an assumption that all the adverse events occurred in children/adolescents. This was done in order to obtain a more conservative estimate of the incidence of an adverse event.

Results

Our search retrieved 51 studies that met inclusion criteria (Table 1). Of these, eight published manuscripts were case reports [44,64–70]. Three publications, one on tDCS [23] and two on TMS [66,71], did not report the adverse effects of NIBS modalities, nor was the information available from the corresponding authors or ClinicalTrials.gov. The remaining 48 studies addressed the adverse effects of tCS and TMS in more than 513 children and adolescents between 2.5 and 17.8 years of age (Table 1). A total of 23 studies reported the absence of side effects and/or tolerability of TMS/tCS. The longest follow-up period was 1.5 years [72]. Among the variety