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Topical Review

Safety of Transcranial Magnetic Stimulation in Children: A Systematic Review of the Literature

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ABSTRACT

BACKGROUND: Data and best practice recommendations for transcranial magnetic stimulation (TMS) use in adults are largely available. Although there are fewer data in pediatric populations and no published guidelines, its practice in children continues to grow. **METHODS:** We performed a literature search through PubMed to review all TMS studies from 1985 to 2016 involving children and documented any adverse events. Crude risks were calculated per session. **RESULTS:** Following data screening we identified 42 single-pulse and/or paired-pulse TMS studies involving 639 healthy children, 482 children with central nervous system disorders, and 84 children with epilepsy. Adverse events occurred at rates of 3.42%, 5.97%, and 4.55% respective to population and number of sessions. We also report 23 repetitive TMS studies involving 230 central nervous system and 24 children with epilepsy with adverse event rates of 3.78% and 0.0%, respectively. We finally identified three theta-burst stimulation studies involving 90 healthy children, 40 children with central nervous system disorder, and no epileptic children, with adverse event rates of 9.78% and 10.11%, respectively. Three seizures were found to have occurred in central nervous system disorder individuals during repetitive TMS, with a risk of 0.14% per session. There was no significant difference in frequency of adverse events by group ($P = 0.988$) or modality ($P = 0.928$). **CONCLUSIONS:** Available data suggest that risk from TMS/theta-burst stimulation in children is similar to adults. We recommend that TMS users in this population follow the most recent adult safety guidelines until sufficient data are available for pediatric specific guidelines. We also encourage continued surveillance through surveys and assessments on a session basis.

Keywords: transcranial, neurostimulation, pediatric, adverse, seizure

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Introduction

Transcranial magnetic stimulation (TMS) is a noninvasive technique for cortical stimulation that uses electromagnetic induction to generate a strong fluctuating magnetic field, which induces intracranial currents.[1] Single-pulse TMS (spTMS) and paired-pulse TMS (ppTMS) studies have been shown to be safe and effective in studying a variety of measures of motor cortex excitability including resting motor threshold, motor evoked potential amplitude, recruitment curves, cortical silent period, short-interval intracortical inhibition, long-interval intracortical inhibition, and intracortical facilitation.[2] It is now a state-of-the-art technique for studying neurophysiology *in vivo*. Repetitive TMS (rTMS) applies repeated TMS pulses at set frequencies or bursts of stimulation to induce changes in cortical excitability, which last longer than the period of stimulus administration by minutes to hours, with more durable changes in clinical outcomes reported when rTMS is given in daily sessions for one to six weeks.[3] These alterations have generally been observed as a decrease in cortical excitability with low-frequency stimulation ($\leq$1 Hz) and an increase in cortical excitability with high-frequency

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rTMS (≥5 Hz).[3] rTMS demonstrates therapeutic potential for many conditions in adults including depression,[4] eating disorders,[5] epilepsy,[6] schizophrenia,[7] tinnitus,[8,9] migraine,[10] and Parkinson disease.[9,11] In children, possible therapeutic benefits have been reported for motor function and tics.[12-15] Theta-burst stimulation (TBS) is a newer form of rTMS that administers 50 Hz bursts of three pulses every 200 milliseconds either continuously (cTBS) or in intermittent two-second trains every ten seconds (iTBS).[16] TBS may induce longer lasting cortical inhibition (cTBS) or excitation (iTBS) than standard rTMS.[16] In general, benefits when present have been of small to moderate magnitude and short lived. Still, given the potential for clinical benefit and limitations of medical options there is a need for further studies of rTMS/TBS as a therapeutic intervention.[4,8]

The use of TMS in both healthy and clinical adult populations has been associated with several adverse events of varying severity. The most common are transient headaches and scalp discomfort, which are thought to be due to activation of scalp pericranial muscles.[17,18] However, more severe adverse effects may include mood changes and induction of seizures.[17] Seizures during TMS are thought to be a result of cortical pyramidal cell activation, spread of excitation to neighboring neurons, and persistent changes in motor cortical inhibition.[19] Whether TMS can induce seizures is theoretically possible but controversial given the extremely rare occurrence. We wanted to provide a brief but complete review of all published studies where TMS has been used in children and describe adverse events to provide a safety profile of TMS in children for researchers and clinicians as well as safety measures for institutional review boards (IRBs). The procedure's safety is of crucial importance given the increasing number of published studies using these tools in pediatric populations (Fig 1).

Methods

We followed the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines for the conduct and reporting of this review. The different phases of this systematic review are displayed in the PRISMA flowchart (Fig 2).

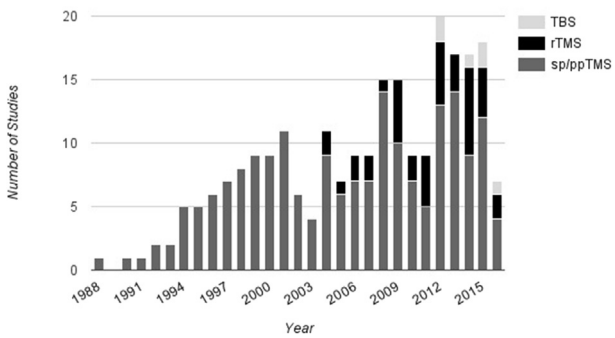

FIGURE 1.
Number of publications each year focusing on sp/ppTMS (dark gray), rTMS (black), and TBS (light gray). TBS, theta-burst stimulation; rTMS, repetitive transcranial magnetic stimulation; sp/ppTMS, single-pulse and paired-pulse transcranial magnetic stimulation.

Literature review

An extensive literature search for English language studies on TMS use in children was conducted through PubMed and links from publications from January 1, 1985 through October 31, 2016. Review articles were excluded except when presenting novel data. The searches used included the following key words: transcranial magnetic stimulation, TMS, TBS, Children, Child, and Pediatric. Dealing with missing data: although our searches were comprehensive, there is a possibility that we may have missed relevant studies; however, we believe this to be unlikely. We sought missing data from study authors, yet many failed to respond. We intended to present all studies in the main report (Table 1). All applicable articles were reviewed for patient demographics (gender, age, and patient phenotype), TMS protocol used (TMS modality and stimuli intensity), and adverse events reported.

Grading adverse events

Adverse events were graded in accordance with the Common Terminology Criteria for Adverse Events (v4.0).[20] This commonly accepted grading scale divides adverse events into five different categories (grades 1 to 5) depending on their severity. Only grades 1 to 3 are present in this report. Grade 1 is a mild event that needs no intervention, grade 2 is a moderate event with noninvasive intervention needed, and grade 3 is a severe event, but not life-threatening, that calls for hospitalization.

Statistical analysis

We extracted all adverse events reported in each TMS and/or TBS study. We computed the proportion estimate of crude risk per session, population, and modality. We also separated single pulse/paired pulse, rTMS, and TBS studies and tested for group differences. Risks were calculated as per-session risk. Confidence intervals (CIs) were calculated using the Clopper-Pearson method in SPSS software version 23, and group differences were calculated via multivariate analysis of variance with weighted least square (WLS) weighting per session.

Results

Studies including spTMS and ppTMS

We identified 42 studies using single- or paired-pulse techniques in child patients.[21-62] This included 639 healthy children, 482 children with central nervous system (CNS) disorders, and separately 84 children with epilepsy. Of these studies, ten reported adverse events (Table 2),[21,23,33,37-39,43,48,58,62] and nine were included in our calculations.[21,23,33,37,39,43,48,58,62] Adverse events by population were distributed as follows: 25 events in the healthy participants group, 50 events in CNS disorder participants group, and four events in the epileptic population. Parents of four epileptic children of total 34 reported a small increase in the frequency of seizures after TMS, with no episode of status epilepticus.[48] Within 3 days after TMS, parents confirmed that seizures resumed to initial frequency ranging from three times per month to continuous. The risk of any adverse event during spTMS or ppTMS in healthy populations is 0.0342 (95% CI, 0.0223 to 0.0501) per session, 0.0597 (95% CI, 0.0447 to 0.0780) per session for patients with a CNS disorder, and 0.0455 (95% CI, 0.0125 to 0.1123) per session for those with epilepsy.

Mild adverse events reported included local discomfort (n = 28),[23,37,62] headache (n = 14),[33,39,43] tingling/dullness (n = 8),[39,43,58] other pain (n = 7),[33,39,43] scalp pain (n = 5),[39,43] nausea/vomiting (n = 4),[33,39,43] self-reported increase in seizure frequency for up to three days after