Pediatric Neurology 68 (2017) 3–17

Contents lists available at ScienceDirect

Pediatric Neurology

journal homepage: www.elsevier.com/locate/pnu

Topical Review

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

Corey H. Allen BS [a], Benzi M. Kluger MD, MS [b], Isabelle Buard PhD [b,*]

[a] *Neuroscience Institute, Georgia State University, Atlanta, Georgia*
[b] *Department of Neurology, University of Colorado-Anschutz Medical Campus, Aurora, Colorado*

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

Pediatr Neurol 2017; 68: 3-17

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

Funding Source: All phases of this study were supported by an NIH grant, 1K02NS080885-01A1 (PI: Kluger).

Financial Disclosure: The authors have no financial relationships relevant to this article to disclose.

Conflict of Interest: The authors have no conflicts of interest to disclose.

Article History:
Received July 15, 2016; Accepted in final form December 19, 2016

* Communications should be addressed to: Dr. Buard; Department of Neurology; UCD TMS and MEG Laboratories; University of Colorado Denver-Anschutz Medical Campus; 13001 E. 17th Pl F548; Aurora, CO 80045.

E-mail address: Isabelle.Buard@ucdenver.edu

0887-8994/$ – see front matter © 2017 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.pediatrneurol.2016.12.009

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).

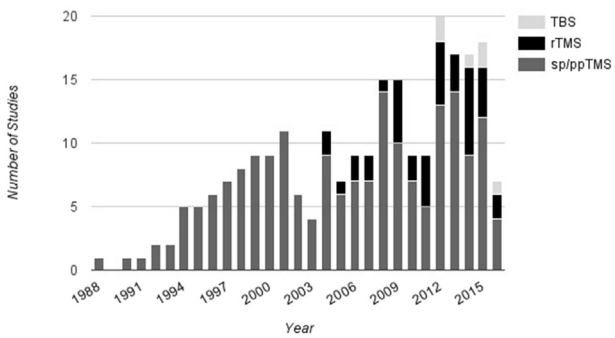

FIGURE 1.
Number of publications each year focusing on sp/ppTMS (dark gray), rTMS (black), and TBS (light gray). TBS, theta-burst stimulation; rTMS, repetitive transcranial magnetic stimulation; sp/ppTMS, single-pulse and paired-pulse transcranial magnetic stimulation.

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

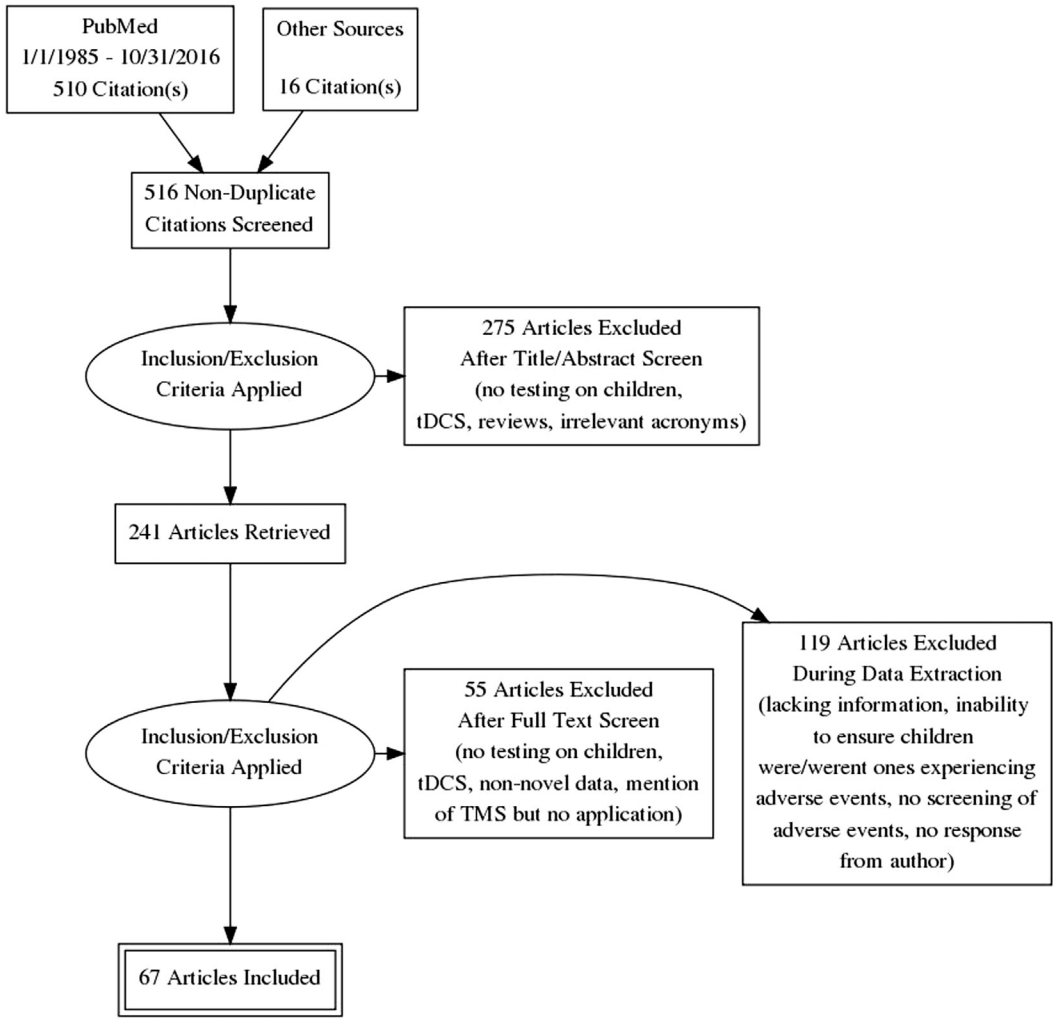

FIGURE 2.
Flowchart using the PRISMA statement for the systematic review. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-analyses; tDCS, transcranial direct current stimulation; TMS, transcranial magnetic stimulation.

stimulation in epileptic children (n = 4),[48] loss of appetite (n = 2),[39] hearing change (n = 1),[39] and other (n = 2).[39,43] Moderate adverse events include headache (n = 1),[39] ringing of the ears (n = 1),[43] and neurocardiogenic syncope (n = 2).[21]

Studies including rTMS

We identified 23 rTMS studies involving child patients[13-15,21,64-70,72-83] including a total of 230 children with CNS disorders and 76 children with epilepsy. There were 81 adverse events that were attributed to rTMS protocols in the CNS disorder population (Table 2). The mild adverse events were as follows: headache (n = 45),[15,21,65-67,69,73,76] dizziness (n = 8),[66,68,69] jaw twitching (n = 4),[68] nausea/vomiting (n = 4),[21,65] anxiety (n = 3),[66] neck stiffness (n = 3),[21] tingling/dullness (n = 3),[65,66] scalp pain (n = 2),[13,74] neck pain (n = 2),[69] restlessness (n = 1),[70] and sleepiness (n = 1).[14] Moderate adverse events include generalized tonic-clonic seizure (n = 3)[64,72,75] and rapid mood swings (n = 1).[70] The only severe adverse event to occur in rTMS stimulation is eight to nine hours of stimulation-induced hypomania (n = 1).[75] The risk of any adverse event during rTMS by population is 0.0378 (95% CI, 0.0301 to 0.0468) per session for individuals with CNS disorders and 0 (95% CI, 0.0000 to 0.0070) per session for patients with epilepsy. Inside this bracket of adverse events, the crude risk of seizure for patients with CNS disorders per session is 0.0014 (95% CI, 0.0003 to 0.0041).

Studies including TBS

We identified three theta-burst studies involving 90 healthy children and 40 children with CNS disorders.[43,63,80] Of these studies, two identified adverse events (Table 2).[43,63] No seizures were reported, thus the crude risk of seizures is 0 (95% CI, 0.0000 to 0.0202). Nine adverse events were reported in healthy children, thus the crude risk per session is 0.0978 (95% CI, 0.0457 to 0.1776). In the population with CNS disorders, nine mild self-limited adverse events were attributed to TBS with a crude risk

TABLE 1.
Description of all the Studies Meeting Search Criteria

Hyperlink	Author	Year	Modality
http://www.ncbi.nlm.nih.gov/pubmed/27007257	Pedapati et al.	2016	TBS
http://www.ncbi.nlm.nih.gov/pubmed/26679420	Babajani-Feremi et al.	2016	TMS
http://www.ncbi.nlm.nih.gov/pubmed/27029628	Kirton et al.	2016	rTMS
https://www.ncbi.nlm.nih.gov/pubmed/27447245	Cullen et al.	2016	rTMS
http://www.ncbi.nlm.nih.gov/pubmed/26439103	Baranello et al.	2016	sp/ppTMS
http://www.ncbi.nlm.nih.gov/pubmed/26580570	Lewis et al.	2016	sp/ppTMS
https://www.ncbi.nlm.nih.gov/pubmed/27554347	Glasby et al.	2016	sp/ppTMS
http://www.ncbi.nlm.nih.gov/pubmed/26762952	Tarapore et al.	2015	TMS
http://www.ncbi.nlm.nih.gov/pubmed/26228567	Pedapati et al.	2015	rTMS
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4662165/	Pathak et al.	2015	rTMS
http://www.ncbi.nlm.nih.gov/pubmed/25283350	Gillick et al.	2015	rTMS
http://www.ncbi.nlm.nih.gov/pubmed/26026582	Vitikainen et al.	2015	rTMS
http://www.ncbi.nlm.nih.gov/pubmed/25439485	Narayana et al.	2015	sp/ppTMS
http://www.ncbi.nlm.nih.gov/pubmed/24283505	Draper et al.	2015	sp/ppTMS
http://www.ncbi.nlm.nih.gov/pubmed/24909435	Khedr et al.	2015	sp/ppTMS
http://www.ncbi.nlm.nih.gov/pubmed/25770194	Hyppönen et al.	2015	sp/ppTMS
http://www.ncbi.nlm.nih.gov/pubmed/25792073	Pitcher et al.	2015	sp/ppTMS
http://www.ncbi.nlm.nih.gov/pubmed/26104046	Fiori et al.	2015	sp/ppTMS
https://www.ncbi.nlm.nih.gov/pubmed/26426515	Cassidy et al.	2015	sp/ppTMS
http://www.ncbi.nlm.nih.gov/pubmed/25640772	Damji et al.	2015	sp/ppTMS
http://www.ncbi.nlm.nih.gov/pubmed/25913518	Khedr et al.	2015	sp/ppTMS
http://www.ncbi.nlm.nih.gov/pubmed/26183338	Bleyenheuft et al.	2015	sp/ppTMS
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4340218/	Pedapati et al.	2015	TBS
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4316715/	Hong et al.	2015	TBS and sp/ppTMS
https://www.ncbi.nlm.nih.gov/pubmed/25306083	Parain et al.	2014	rTMS
https://www.ncbi.nlm.nih.gov/pubmed/24522997	Pikho et al.	2014	TMS
https://www.ncbi.nlm.nih.gov/pubmed/23962321	Gillick et al.	2014	rTMS
https://www.ncbi.nlm.nih.gov/pubmed/24979652	Christancho et al.	2014	rTMS
https://www.ncbi.nlm.nih.gov/pubmed/25037768	Gomez et al.	2014	rTMS
http://www.ncbi.nlm.nih.gov/pubmed/25267414	Sokhadze et al.	2014	rTMS
https://www.ncbi.nlm.nih.gov/pubmed/24113340	Panerai et al.	2014	rTMS
https://www.ncbi.nlm.nih.gov/pubmed/24820947	Yang et al.	2014	rTMS
https://www.ncbi.nlm.nih.gov/pubmed/24126573	D'Agati et al.	2014	sp/ppTMS
https://www.ncbi.nlm.nih.gov/pubmed/24341408	Islam et al.	2014	sp/ppTMS
https://www.ncbi.nlm.nih.gov/pubmed/24360599	Croarkin et al.	2014	sp/ppTMS
https://www.ncbi.nlm.nih.gov/pubmed/24574502	Heinrich et al.	2014	sp/ppTMS
https://www.ncbi.nlm.nih.gov/pubmed/24793204	Schneider et al.	2014	sp/ppTMS
https://www.ncbi.nlm.nih.gov/pubmed/24866824	Kronenburg et al.	2014	sp/ppTMS
https://www.ncbi.nlm.nih.gov/pubmed/24907638	Flamand et al.	2014	sp/ppTMS
http://www.ncbi.nlm.nih.gov/pubmed/24413361	Chen et al.	2014	sp/ppTMS
https://www.ncbi.nlm.nih.gov/pubmed/24268723	Wu et al.	2014	TBS
https://www.ncbi.nlm.nih.gov/pubmed/22659020	Makela et al.	2013	TMS
https://www.ncbi.nlm.nih.gov/pubmed/22886323	Coburger et al.	2013	TMS
https://www.ncbi.nlm.nih.gov/pubmed/24376426	Wall et al.	2013	rTMS
https://www.ncbi.nlm.nih.gov/pubmed/23238046	Le et al.	2013	rTMS
https://www.ncbi.nlm.nih.gov/pubmed/23518261	Chiramberro et al.	2013	rTMS
https://www.ncbi.nlm.nih.gov/pubmed/23912578	Galloway et al.	2013	sp/ppTMS
https://www.ncbi.nlm.nih.gov/pubmed/23157428	Jung et al.	2013	sp/ppTMS
https://www.ncbi.nlm.nih.gov/pubmed/22804795	Jackson et al.	2013	sp/ppTMS
https://www.ncbi.nlm.nih.gov/pubmed/23192441	Vijayakumari et al.	2013	sp/ppTMS

TABLE 1. (*continued*)

Hyperlink	Author	Year	Modality
https://www.ncbi.nlm.nih.gov/pubmed/23303429	Croarkin et al.	2013	sp/ppTMS
https://www.ncbi.nlm.nih.gov/pubmed/22766351	Cuppen et al.	2013	sp/ppTMS
https://www.ncbi.nlm.nih.gov/pubmed/23398231	Muralidharan et al.	2013	sp/ppTMS
https://www.ncbi.nlm.nih.gov/pubmed/23646925	Van der aa et al.	2013	sp/ppTMS
https://www.ncbi.nlm.nih.gov/pubmed/23746624	Puri et al.	2013	sp/ppTMS
https://www.ncbi.nlm.nih.gov/pubmed/23937719	Juenger et al.	2013	sp/ppTMS
https://www.ncbi.nlm.nih.gov/pubmed/23973307	Jhunjhunwala et al.	2013	sp/ppTMS
https://www.ncbi.nlm.nih.gov/pubmed/23894067	Carrascosa-Romero et al.	2013	sp/ppTMS
https://www.ncbi.nlm.nih.gov/pubmed/22656259	Coburger et al.	2012	TMS
https://www.ncbi.nlm.nih.gov/pubmed/22311204	Sokhadze et al.	2012	rTMS
https://www.ncbi.nlm.nih.gov/pubmed/23185537	Helfrich et al.	2012	rTMS
https://www.ncbi.nlm.nih.gov/pubmed/22917208	Jardri et al.	2012	rTMS
https://www.ncbi.nlm.nih.gov/pubmed/22257125	Croarkin et al.	2012	rTMS
https://www.ncbi.nlm.nih.gov/pubmed/22037133	Enticott et al.	2012	rTMS
https://www.ncbi.nlm.nih.gov/pubmed/22722631	Reis et al.	2012	sp/ppTMS
https://www.ncbi.nlm.nih.gov/pubmed/22964441	Geerdink et al.	2012	sp/ppTMS
https://www.ncbi.nlm.nih.gov/pubmed/21974786	Enticott et al.	2012	sp/ppTMS
https://www.ncbi.nlm.nih.gov/pubmed/22018705	Flamand et al.	2012	sp/ppTMS
https://www.ncbi.nlm.nih.gov/pubmed/22153667	Kesar et al.	2012	sp/ppTMS
https://www.ncbi.nlm.nih.gov/pubmed/22462681	Zsoter et al.	2012	sp/ppTMS
https://www.ncbi.nlm.nih.gov/pubmed/22491191	Farrar et al.	2012	sp/ppTMS
https://www.ncbi.nlm.nih.gov/pubmed/22494662	Sebastiano et al.	2012	sp/ppTMS
https://www.ncbi.nlm.nih.gov/pubmed/22966161	Pitcher et al.	2012	sp/ppTMS
https://www.ncbi.nlm.nih.gov/pubmed/23049936	Hoegl et al.	2012	sp/ppTMS
https://www.ncbi.nlm.nih.gov/pubmed/22883282	Wu et al.	2012	sp/ppTMS
https://www.ncbi.nlm.nih.gov/pubmed/22492560	Bruckmann et al.	2012	sp/ppTMS
https://www.ncbi.nlm.nih.gov/pubmed/23152623	Pitcher et al.	2012	TBS
https://www.ncbi.nlm.nih.gov/pubmed/22515662	Wu et al.	2012	TBS
https://www.ncbi.nlm.nih.gov/pubmed/21309441	Sun et al.	2011	rTMS
https://www.ncbi.nlm.nih.gov/pubmed/22118010	Hu et al.	2011	rTMS
https://www.ncbi.nlm.nih.gov/pubmed/21256925	Kwon et al.	2011	rTMS
https://www.ncbi.nlm.nih.gov/pubmed/21740832	He et al.	2011	rTMS
https://www.ncbi.nlm.nih.gov/pubmed/21121906	Koerte et al.	2011	sp/ppTMS
https://www.ncbi.nlm.nih.gov/pubmed/21321335	Gilbert et al.	2011	sp/ppTMS
https://www.ncbi.nlm.nih.gov/pubmed/21600814	Van der aa et al.	2011	sp/ppTMS
https://www.ncbi.nlm.nih.gov/pubmed/21707595	McClelland et al.	2011	sp/ppTMS
https://www.ncbi.nlm.nih.gov/pubmed/21664777	Pearl et al.	2011	sp/ppTMS
https://www.ncbi.nlm.nih.gov/pubmed/20479530	Schmidt et al.	2010	TMS
https://www.ncbi.nlm.nih.gov/pubmed/20863666	Säisänen et al.	2010	TMS
https://www.ncbi.nlm.nih.gov/pubmed/20568093	Chastan et al.	2010	rTMS
https://www.ncbi.nlm.nih.gov/pubmed/20537584	Kirton et al.	2010	rTMS
https://www.ncbi.nlm.nih.gov/pubmed/20466521	Koudijs et al.	2010	sp/ppTMS
https://www.ncbi.nlm.nih.gov/pubmed/19807768	Holstrom et al.	2010	sp/ppTMS
https://www.ncbi.nlm.nih.gov/pubmed/20033462	Domenech et al.	2010	sp/ppTMS
https://www.ncbi.nlm.nih.gov/pubmed/20129761	Barba et al.	2010	sp/ppTMS
https://www.ncbi.nlm.nih.gov/pubmed/20370810	Enticott et al.	2010	sp/ppTMS
https://www.ncbi.nlm.nih.gov/pubmed/19560399	Rotenberg et al.	2009	rTMS
https://www.ncbi.nlm.nih.gov/pubmed/19030976	Sokhadze et al.	2009	rTMS
https://www.ncbi.nlm.nih.gov/pubmed/19268844	Mylius et al.	2009	rTMS

(*continued on next page*)

TABLE 1. (*continued*)

Hyperlink	Author	Year	Modality
https://www.ncbi.nlm.nih.gov/pubmed/18832045	Rotenberg et al.	2009	rTMS
https://www.ncbi.nlm.nih.gov/pubmed/18771675	Jardi et al.	2009	rTMS
https://www.ncbi.nlm.nih.gov/pubmed/18286510	Wilke et al.	2009	sp/ppTMS
https://www.ncbi.nlm.nih.gov/pubmed/19200077	Vandermeeren et al.	2009	sp/ppTMS
https://www.ncbi.nlm.nih.gov/pubmed/19329268	Walther et al.	2009	sp/ppTMS
https://www.ncbi.nlm.nih.gov/pubmed/19346962	Koerte et al.	2009	sp/ppTMS
https://www.ncbi.nlm.nih.gov/pubmed/19559057	Sun et al.	2009	sp/ppTMS
https://www.ncbi.nlm.nih.gov/pubmed/19664531	Walther et al.	2009	sp/ppTMS
https://www.ncbi.nlm.nih.gov/pubmed/19740221	Wittenberg et al.	2009	sp/ppTMS
https://www.ncbi.nlm.nih.gov/pubmed/19795964	Juenger et al.	2009	sp/ppTMS
https://www.ncbi.nlm.nih.gov/pubmed/19818945	Juenger et al.	2009	sp/ppTMS
https://www.ncbi.nlm.nih.gov/pubmed/19796876	Siniatchkin et al.	2009	sp/ppTMS
https://www.ncbi.nlm.nih.gov/pubmed/18580562	Bloch et al.	2008	rTMS
https://www.ncbi.nlm.nih.gov/pubmed/18725065	Kirton et al.	2008	sp/ppTMS
https://www.ncbi.nlm.nih.gov/pubmed/18206409	Hufschmidt et al.	2008	sp/ppTMS
https://www.ncbi.nlm.nih.gov/pubmed/18627417	Groppa et al.	2008	sp/ppTMS
https://www.ncbi.nlm.nih.gov/pubmed/18811703	Kuhnke et al.	2008	sp/ppTMS
https://www.ncbi.nlm.nih.gov/pubmed/18295455	Lappchen et al.	2008	sp/ppTMS
https://www.ncbi.nlm.nih.gov/pubmed/18053763	Yayla et al.	2008	sp/ppTMS
https://www.ncbi.nlm.nih.gov/pubmed/18196201	Heise et al.	2008	sp/ppTMS
https://www.ncbi.nlm.nih.gov/pubmed/18759336	Marelli et al.	2008	sp/ppTMS
https://www.ncbi.nlm.nih.gov/pubmed/19294597	Juenger et al.	2008	sp/ppTMS
https://www.ncbi.nlm.nih.gov/pubmed/18684310	Redman et al.	2008	sp/ppTMS
https://www.ncbi.nlm.nih.gov/pubmed/18043504	Berweck et al.	2008	sp/ppTMS
https://www.ncbi.nlm.nih.gov/pubmed/18214452	Vry et al.	2008	sp/ppTMS
https://www.ncbi.nlm.nih.gov/pubmed/18422835	Muralidharan et al.	2008	sp/ppTMS
https://www.ncbi.nlm.nih.gov/pubmed/19086697	Uozumi et al.	2008	sp/ppTMS
https://www.ncbi.nlm.nih.gov/pubmed/17593127	Valle et al.	2007	rTMS
https://www.ncbi.nlm.nih.gov/pubmed/17389898	Jardri et al.	2007	rTMS
https://www.ncbi.nlm.nih.gov/pubmed/17719015	Buchmann et al.	2007	sp/ppTMS
https://www.ncbi.nlm.nih.gov/pubmed/17588810	Gilbert et al.	2007	sp/ppTMS
https://www.ncbi.nlm.nih.gov/pubmed/17382585	Guzzetta et al.	2007	sp/ppTMS
https://www.ncbi.nlm.nih.gov/pubmed/17444535	Eyre et al.	2007	sp/ppTMS
https://www.ncbi.nlm.nih.gov/pubmed/17627085	Kimiskidis et al.	2007	sp/ppTMS
http://www.ncbi.nlm.nih.gov/pubmed/17121743	Siniatchkin et al.	2007	sp/ppTMS
https://www.ncbi.nlm.nih.gov/pubmed/17188003	Kamida et al.	2007	sp/ppTMS
https://www.ncbi.nlm.nih.gov/pubmed/16630205	Loo et al.	2006	rTMS
https://www.ncbi.nlm.nih.gov/pubmed/16644277	Fregni et al.	2006	rTMS
https://www.ncbi.nlm.nih.gov/pubmed/16674759	Rinalduzzi et al.	2006	sp/ppTMS
https://www.ncbi.nlm.nih.gov/pubmed/16690208	Moll et al.	2006	sp/ppTMS
https://www.ncbi.nlm.nih.gov/pubmed/16776434	Anninos et al.	2006	sp/ppTMS
https://www.ncbi.nlm.nih.gov/pubmed/16760197	Gilbert et al.	2006	sp/ppTMS
https://www.ncbi.nlm.nih.gov/pubmed/16815631	Buchmann et al.	2006	sp/ppTMS
https://www.ncbi.nlm.nih.gov/pubmed/16864822	Dueget et al.	2006	sp/ppTMS
https://www.ncbi.nlm.nih.gov/pubmed/15564059	Morales et al.	2005	rTMS
https://www.ncbi.nlm.nih.gov/pubmed/15607602	Staudt et al.	2005	sp/ppTMS
https://www.ncbi.nlm.nih.gov/pubmed/15794178	Perritti et al.	2005	sp/ppTMS
https://www.ncbi.nlm.nih.gov/pubmed/15979402	Garvey et al.	2005	sp/ppTMS
https://www.ncbi.nlm.nih.gov/pubmed/15984026	Bender et al.	2005	sp/ppTMS
https://www.ncbi.nlm.nih.gov/pubmed/15953499	Gilbert et al.	2005	sp/ppTMS
https://www.ncbi.nlm.nih.gov/pubmed/16010059	Sahota et al.	2005	sp/ppTMS

TABLE 1. (*continued*)

Hyperlink	Author	Year	Modality
https://www.ncbi.nlm.nih.gov/pubmed/15016013	Graff-Guerrero et al.	2004	rTMS
https://www.ncbi.nlm.nih.gov/pubmed/15122428	Brasil-Neto et al.	2004	rTMS
https://www.ncbi.nlm.nih.gov/pubmed/15003756	Dachy et al.	2004	sp/ppTMS
https://www.ncbi.nlm.nih.gov/pubmed/15036427	Kao et al.	2004	sp/ppTMS
https://www.ncbi.nlm.nih.gov/pubmed/15324826	Tataroglu et al.	2004	sp/ppTMS
https://www.ncbi.nlm.nih.gov/pubmed/15562409	Staudt et al.	2004	sp/ppTMS
https://www.ncbi.nlm.nih.gov/pubmed/15890159	Kimiskidis et al.	2004	sp/ppTMS
https://www.ncbi.nlm.nih.gov/pubmed/16206975	Staudt et al.	2004	sp/ppTMS
https://www.ncbi.nlm.nih.gov/pubmed/15077239	Gilbert et al.	2004	sp/ppTMS
https://www.ncbi.nlm.nih.gov/pubmed/15127311	Mall et al.	2004	sp/ppTMS
https://www.ncbi.nlm.nih.gov/pubmed/15174827	Carlstedt et al.	2004	sp/ppTMS
https://www.ncbi.nlm.nih.gov/pubmed/12689695	Oguro et al.	2003	sp/ppTMS
https://www.ncbi.nlm.nih.gov/pubmed/12948795	Garvey et al.	2003	sp/ppTMS
https://www.ncbi.nlm.nih.gov/pubmed/14499742	Vandermeeren et al.	2003	sp/ppTMS
https://www.ncbi.nlm.nih.gov/pubmed/14580601	Buchmann et al.	2003	sp/ppTMS
http://brain.oxfordjournals.org/content/125/10/2222	Staudt et al.	2002	sp/ppTMS
https://www.ncbi.nlm.nih.gov/pubmed/11897533	Dachy et al.	2002	sp/ppTMS
https://www.ncbi.nlm.nih.gov/pubmed/12088086	Rutten et al.	2002	sp/ppTMS
https://www.ncbi.nlm.nih.gov/pubmed/12395132	Vandermeeren et al.	2002	sp/ppTMS
https://www.ncbi.nlm.nih.gov/pubmed/12455860	Maegaki et al.	2002	sp/ppTMS
https://www.ncbi.nlm.nih.gov/pubmed/11870691	Tshala-Katumbay et al.	2002	sp/ppTMS
http://www.ncbi.nlm.nih.gov/pubmed/11459685	Garvey et al.	2001	sp/ppTMS
http://www.ncbi.nlm.nih.gov/pubmed/11261515	Moll et al.	2001	sp/ppTMS
http://www.ncbi.nlm.nih.gov/pubmed/11408329	Shimizu et al.	2001	sp/ppTMS
http://www.ncbi.nlm.nih.gov/pubmed/11428513	Collado-Corona et al.	2001	sp/ppTMS
http://www.ncbi.nlm.nih.gov/pubmed/11506408	Roricht et al.	2001	sp/ppTMS
https://www.ncbi.nlm.nih.gov/pubmed/11261506	Thickbroom et al.	2001	sp/ppTMS
https://www.ncbi.nlm.nih.gov/pubmed/11303768	Hamzei et al.	2001	sp/ppTMS
https://www.ncbi.nlm.nih.gov/pubmed/11701594	Dobson et al.	2001	sp/ppTMS
https://www.ncbi.nlm.nih.gov/pubmed/11706088	Eyre et al.	2001	sp/ppTMS
https://www.ncbi.nlm.nih.gov/pubmed/11785502	Garvey et al.	2001	sp/ppTMS
https://www.ncbi.nlm.nih.gov/pubmed/11723265	Manganotti et al.	2001	sp/ppTMS
http://www.ncbi.nlm.nih.gov/pubmed/10825702	Manganotti et al.	2000	sp/ppTMS
http://www.ncbi.nlm.nih.gov/pubmed/10825709	Santoro et al.	2000	sp/ppTMS
http://www.ncbi.nlm.nih.gov/pubmed/11043527	Shimizu et al.	2000	sp/ppTMS
http://www.ncbi.nlm.nih.gov/pubmed/11108505	Ucles et al.	2000	sp/ppTMS
http://www.ncbi.nlm.nih.gov/pubmed/11118802	Noguchi et al.	2000	sp/ppTMS
https://www.ncbi.nlm.nih.gov/pubmed/10738920	Dan et al.	2000	sp/ppTMS
https://www.ncbi.nlm.nih.gov/pubmed/10771177	Moll et al.	2000	sp/ppTMS
https://www.ncbi.nlm.nih.gov/pubmed/10795559	Fietzek et al.	2000	sp/ppTMS
http://www.ncbi.nlm.nih.gov/pubmed/11022138	Ertas et al.	2000	sp/ppTMS
https://www.ncbi.nlm.nih.gov/pubmed/10203149	Maegaki et al.	1999	sp/ppTMS
https://www.ncbi.nlm.nih.gov/pubmed/10024139	Heinen et al.	1999	sp/ppTMS
https://www.ncbi.nlm.nih.gov/pubmed/10319880	Mayston et al.	1999	sp/ppTMS
https://www.ncbi.nlm.nih.gov/pubmed/10372901	Nezu et al.	1999	sp/ppTMS
https://www.ncbi.nlm.nih.gov/pubmed/10479033	Nezu et al.	1999	sp/ppTMS
https://www.ncbi.nlm.nih.gov/pubmed/10507537	Moll et al.	1999	sp/ppTMS
https://www.ncbi.nlm.nih.gov/pubmed/10514585	Karak et al.	1999	sp/ppTMS

(*continued on next page*)

TABLE 1. (*continued*)

Hyperlink	Author	Year	Modality
https://www.ncbi.nlm.nih.gov/pubmed/10533116	Yasuhara et al.	1999	sp/ppTMS
https://www.ncbi.nlm.nih.gov/pubmed/10590956	Moll et al.	1999	sp/ppTMS
https://www.ncbi.nlm.nih.gov/pubmed/11003066	Inghilleri et al.	1998	sp/ppTMS
https://www.ncbi.nlm.nih.gov/pubmed/9506553	Meyer et al.	1998	sp/ppTMS
https://www.ncbi.nlm.nih.gov/pubmed/9572251	Di Lazzaro et al.	1998	sp/ppTMS
https://www.ncbi.nlm.nih.gov/pubmed/9585354	Heinen et al.	1998	sp/ppTMS
https://www.ncbi.nlm.nih.gov/pubmed/9743265	Cincotta et al.	1998	sp/ppTMS
https://www.ncbi.nlm.nih.gov/pubmed/9806140	Heinen et al.	1998	sp/ppTMS
https://www.ncbi.nlm.nih.gov/pubmed/9853705	Reitz et al.	1998	sp/ppTMS
https://www.ncbi.nlm.nih.gov/pubmed/9741799	Nezu et al.	1998	sp/ppTMS
https://www.ncbi.nlm.nih.gov/pubmed/9105661	Nezu et al.	1997	sp/ppTMS
https://www.ncbi.nlm.nih.gov/pubmed/9134188	Nezu et al.	1997	sp/ppTMS
https://www.ncbi.nlm.nih.gov/pubmed/9286189	Ziemann et al.	1997	sp/ppTMS
https://www.ncbi.nlm.nih.gov/pubmed/9389236	Tamer et al.	1997	sp/ppTMS
https://www.ncbi.nlm.nih.gov/pubmed/9392569	Muller et al.	1997	sp/ppTMS
https://www.ncbi.nlm.nih.gov/pubmed/10728200	Maegaki et al.	1997	sp/ppTMS
https://www.ncbi.nlm.nih.gov/pubmed/9266555	Maegaki et al.	1997	sp/ppTMS
https://www.ncbi.nlm.nih.gov/pubmed/8648332	Yokota et al.	1996	sp/ppTMS
https://www.ncbi.nlm.nih.gov/pubmed/8879655	Nezu et al.	1996	sp/ppTMS
https://www.ncbi.nlm.nih.gov/pubmed/8880692	Nezu et al.	1996	sp/ppTMS
https://www.ncbi.nlm.nih.gov/pubmed/8902719	Perretti et al.	1996	sp/ppTMS
https://www.ncbi.nlm.nih.gov/pubmed/8739408	Ucles et al.	1996	sp/ppTMS
https://www.ncbi.nlm.nih.gov/pubmed/8997449	Carr et al.	1996	sp/ppTMS
https://www.ncbi.nlm.nih.gov/pubmed/8892376	Heinen et al.	1996	TMS
http://www.ncbi.nlm.nih.gov/pubmed/7625552	Masur et al.	1995	sp/ppTMS
https://www.ncbi.nlm.nih.gov/pubmed/7587914	D'Annunzio et al.	1995	sp/ppTMS
http://www.ncbi.nlm.nih.gov/pubmed/8545718	Kitagawa et al.	1995	sp/ppTMS
http://www.ncbi.nlm.nih.gov/pubmed/8719747	Gacson et al.	1995	sp/ppTMS
http://www.ncbi.nlm.nih.gov/pubmed/8848203	Maegaki et al.	1995	sp/ppTMS
http://www.ncbi.nlm.nih.gov/pubmed/8363351	Reutens et al.	1994	sp/ppTMS
http://www.ncbi.nlm.nih.gov/pubmed/8747423	Imai et al.	1994	sp/ppTMS
http://www.ncbi.nlm.nih.gov/pubmed/7512917	Glocker et al.	1994	sp/ppTMS
http://www.ncbi.nlm.nih.gov/pubmed/7924067	Shizukawa et al.	1994	sp/ppTMS
http://www.ncbi.nlm.nih.gov/pubmed/8190300	Haug et al.	1994	sp/ppTMS
https://www.ncbi.nlm.nih.gov/pubmed/7679632	Caramia et al.	1993	sp/ppTMS
http://www.ncbi.nlm.nih.gov/pubmed/8423883	Reutens et al.	1993	sp/ppTMS
http://www.ncbi.nlm.nih.gov/pubmed/1293281	Hicks et al.	1992	sp/ppTMS
http://www.ncbi.nlm.nih.gov/pubmed/1373370	Muller et al.	1992	sp/ppTMS
http://www.ncbi.nlm.nih.gov/pubmed/2065752	Muller et al.	1991	sp/ppTMS
http://www.ncbi.nlm.nih.gov/pubmed/1773779	Hufnagel et al.	1991	TMS
http://www.ncbi.nlm.nih.gov/pubmed/2273410	Hufnagel et al.	1990	sp/ppTMS
https://www.ncbi.nlm.nih.gov/pubmed/3202641	Koh et al.	1988	sp/ppTMS

Abbreviations:
AE = Adverse event
ppTMS = Paired-pulse TMS
rTMS = Repetitive TMS
spTMS = Single-pulse TMS
TBS = Theta-burst stimulation
TMS = Transcranial magnetic stimulation
Rows' color codes: white, no AE; lightest gray, AE not mentioned; middle gray, no access to screen; dark gray, AE assessed and subjected to analysis.

TABLE 2.
Description of Adverse Events

Author	Year	No. of Individuals	Age (Years)	Phenotype	TMS Mode	Paradigm and Target	AEs
Sp/ppTMS							
Hong et al.[43]	2015	89	6-18	19 Tourette's 70 Control	sp/ppTMS Figure-8 coil	MEP, RMT (60% and 120%, AMT, CSP Approximately 200 pulses per part Target: motor cortex	Mild: headache (6), scalp pain (4), arm/hand/other pain (2), numbness/tingling (5), other sensations (1), nausea/vomiting (1), other (1). Moderate: ringing in ears (1)
Damji et al.[33]	2015	28	6-18	Healthy	spTMS Figure-8 coil	100%-150% RMT, 0.2 Hz, 7.5 minutes Target: motor cortex	Mild: neck pain (1), headache (3), transient nausea (2)
Wu et al.[62]	2012	114	8-12	64 Control 50 ADHD	sp/ppTMS Figure-8 coil	20 sp trials set at 15%-30% over RMT. ppTMS of 70% RMT Target: motor cortex	Mild: discomfort (15)
Geerdink et al.[37]	2012	78	6-15	36 Control 42 Spina Bifida	sp/ppTMS Double cone coil	100% Stimulation intensity MEP Target: motor cortex	Mild: discomfort (12) in control subjects and an undisclosed number in Spina Bifida population
Koudijs et al.[48]	2010	34	3-18	Epileptic	sp/ppTMS Round coil and figure-8 coil	Intensity was titrated until MEP—up to max of 4T Target: L/R motor cortex	Increase in seizure frequency that subsided after three days with no intervention (4)
Kirton et al.[21]	2010	4	10-16	Arterial Ischemic stroke Lesions	spTMS ppTMS Figure-8 coil rTMS	110% to 150% RMT or 100% MSO when no RMT six stimuli per level, 36 stimuli per side Target: contralateral motor cortex 100% RMT 8 days, 1 Hz 20 minutes	Mild: headache (2), neck stiffness (3), nausea (3). Moderate: neurocardiogenic syncope (2)
Gilbert et al.[39]	2006	16	8-17	ADHD	sp/ppTMS Circular coil	RMT, AMT, SICI, ICF. All TMS sessions took approximately 30 minutes Target: motor cortex	Mild: numbness/tingling (2), loss of appetite (2), scalp pain (1), nausea (2), stomach pain (1), headache (5), arm/other pain (2), abdominal pain (1), hearing change (1). Moderate: headache (1)
Bender et al.[23]	2005	17	6-10	Healthy	sp/ppTMS Circular coil	105% RMT for MEPs, when RMT > MSO intensity was set to 100%. Target: right motor cortex	Mild: discomfort (1)
Gilbert et al.[38]	2005	28*	<18	Tourette's syndrome (w/ADHD/OCD in some cases)	sp/ppTMS Circular coil	MEP, SICI, at 130% AMT Target: motor cortex	Mild: discomfort (3), scalp pain (5), tiredness (4), hand or leg tingling (3), hand weakness (2), headache (1), and neck pain (1)
Shizukawa et al.[58]	1994	1	16	Hirayama disease	spTMS	MEP Target: motor cortex	Mild: dullness (1)
TBS							
Hong et al.[43]	2015	76	6-18	52 Control 24 Tourette's syndrome	TBS MagStim Rapid 2	60%-90% RMT. Three pulses at 30-50 Hz frequency, 5 Hz burst frequency w/total stimuli 300-600	Mild: headache (5), numbness/tingling (2), other sensations (2), weakness (1), arm/hand/other pain (1), other (1). Moderate: arm/hand/other pain (1)

(*continued on next page*)

TABLE 2. (*continued*)

Author	Year	No. of Individuals	Age (Years)	Phenotype	TMS Mode	Paradigm and Target	AEs
Wu et al.[63]	2012	40	11-18	24 Control 16 Tourette's syndrome	iTBS and cTBS Figure-8 coil	50 Hz, 80% active MT or 90% RMT 32 Sessions Target: left motor cortex	Mild: finger twitching (1), neck stiffness (1), headache (3)
rTMS							
Cullen et al.[64]	2016	1	17	Treatment resistant depression	Deep TMS H-1 coil	18 Hz, 120% MT, 55 trains, 1980 pulses total	Moderate: generalized, tonic-clonic seizure that lasted 90 seconds and resolved spontaneously (1)
Kirton et al.[65]	2016	45	6-19	Hemiparesis	rTMS	1 Hz, 20 minutes 1200 stimuli, 1200 stimuli per session, once a day, 5 days/week, 2 weeks total Target: contralesional M1	Mild: headache (4), nausea (1), tingling (1)
Gillick et al.[66]	2015	10	8-17	Congenital hemiparesis	rTMS Figure-8 coil	6 Hz, 90% RMT, two 5-second trains/minute (total 600 pulses). Followed by 10 minutes of 1 Hz, 90% RMT (600 pulses) Target: contralesional motor cortex	Mild: headache (5), anxiety (3), dizziness (2), tingling (2)
Pathak et al.[67]	2015	13	12-17	Bipolar mood disorder	rTMS Figure-8 coil	20 Hz, 110% MT 800 daily pulses, 10 days Target: right prefrontal cortex	Mild: headache (2)
Cristancho et al.[68]	2014	1	15	Autism	rTMS	90% of the RMT, 1 Hz, 10 seconds on, and 10-30 seconds off. 30 sessions in total. Target: L/R DLPFC	Mild headaches during half of the sessions. Dizziness and jaw twitching also occurred
Gomez et al.[69]	2014	10	7-12	ADHD	rTMS Butterfly coil	90% RMT, 1 Hz. 1500 stimuli/session. 1 session/day. 5 days Target: L-DLPFC	Mild: headache (7), neck pain (2), dizziness (2)
Panerai et al.[70]	2014	35	11-18	Autism	rTMS Figure-8 coil	90% RMT, 1 Hz train (900 pulses), and 30 8 Hz trains of 30 stimuli Target: L/R premotor cortex	Mild: restlessness (1). Moderate: rapid mood swings (1)
Gillick et al.[15]	2014	10	8-17	Congenital hemiparesis	rTMS Figure-8 coil	6 Hz, 90% RMT, two 5-second trains/minute (total 600 pulses). Followed by 10 minutes of 1 Hz, 90% RMT (600 pulses) Target: contralesional motor cortex	Mild: headache
Yang et al.[71]	2014	6	15-21	Major depressive disorder	rTMS Figure-8 coil	120% RMT, 10 Hz, 75 trains (3000 pulses) Target: left DLPFC	Mild: scalp discomfort, sleepiness
Chiramberro et al.[72]	2013	1	16	Major depressive disorder	rTMS Figure-8 coil	10 Hz, 120% RMT 3000 daily pulses 4 weeks of 60 trains of 5 seconds, 5 days/week Target: left DLPFC	Moderate: tonic-clonic seizure of 30 seconds on 12th day of rTMS Patient was taking sertraline and olanzapine, and also had a high blood alcohol content
Le et al.[14]	2013	25	7-16	Tourette's syndrome	rTMS Figure-8 coil	110% RMT, 1 Hz, 20 daily sessions (1200 stimuli daily) Target: supplementary motor area	Mild: sleepiness (1)
Helfrich et al.[73]	2012	25	8-14	ADHD	rTMS Figure-8 coil	80% RMT, 1 Hz (900 stimuli) Target: left motor cortex	Mild: headache (3)

TABLE 2. (*continued*)

Author	Year	No. of Individuals	Age (Years)	Phenotype	TMS Mode	Paradigm and Target	AEs
Croarkin et al.[74]	2012	8	14-17	Major depressive disorder	rTMS	120% MT, 10 Hz, 4-second trains (3000 stimuli per session) Target: motor cortex	Mild: scalp pain (1)
Hu et al.[75]	2011	1	15	Adolescent onset Depressive disorder	rTMS Figure-8 coil	10 Hz, 80% RMT 800 Daily pulses Target: left DLPFC	Moderate/severe: tonic-clonic seizure of 1 minute on first day of rTMS and hypomanic episode the night after the seizure Patient follow-up indicated no further seizure Patient was taking sertraline
Kwon et al.[13]	2011	10	9-14	Tourette's syndrome	rTMS Figure-8 coil	100% RMT, 1 Hz (1200 stimuli daily for 10 days) Target: supplementary motor area	Mild: scalp pain (1)
Bloch et al.[76]	2008	9	16-18	Severe resistant depression	rTMS Circular coil	80% MT, 10-Hz, 2-second trains were given for 20 minutes/day over the course of 14 working days	Mild: headache (5)

Abbreviations:
ADHD = Attention-deficit/hyperactivity disorder
AE = Adverse event
AMT = Active motor threshold
CSP = Cortical silent period
DLPFC = Dorsolateral prefrontal cortex
MEP = Motor evoked potential
MSO = Maximal stimulator output
OCD = Obsessive-compulsive disorder
ppTMS = Paired-pulse TMS
RMT = Resting motor threshold
SICI = Short intracortical inhibition
TBS = Theta-burst stimulation
TMS = Transcranial magnetic stimulation
Rows' color codes: lightest gray, mild AEs (or grade 1); middle gray, moderate AEs (or grade 2); dark gray, severe AEs (or grade 3).
* Number of adolescent participants is exact, whereas the number of AEs is from the entire population of the study (n = 36).

per session of 0.1011 (95% CI, 0.0473 to 0.1833). The mild adverse events are as follows, and all were resolved without medical intervention: headache (n = 8),[43,63] tingling/dullness (n = 2),[43] other sensations (n = 2),[43] finger twitching (n = 1),[63] weakness (n = 1),[43] other pain (n = 1),[43] neck stiffness (n = 1),[63] and other (n = 1).[43] There was only one moderate adverse event: arm/other pain (n = 1).[43]

Comparing populations and modalities

Frequency of adverse events was similar for groups ($F(6,150) = 0.156$, $P = 0.988$) and modalities ($F(6,150) = 0.316$, $P = 0.928$). Frequencies per grade of adverse event, per modality, and per population are represented in Fig 3. As shown, adverse events deemed grade 1 (mild) in healthy populations, occurred at rates of 3.42% and 9.78% per session in sp/ppTMS and TBS, respectively. In CNS populations, grade 1 events occurred at rates of 5.62%, 3.55%, and 8.99% per session in sp/ppTMS, rTMS, and TBS, respectively. Grade 2 (moderate) events occurred at rates of 0.36%, 0.19%, and 1.12% per session in sp/ppTMS, rTMS, and TBS, respectively. Grade 3 (severe) events occurred at a rate of 0.05% in rTMS sessions. For epileptic populations, grade 1 adverse events occurred at a rate of 4.55% per session in sp/ppTMS stimulation.

Discussion

This systematic review focused on the use of magnetic currents as tools to investigate plasticity in the developing brain or to explore their therapeutic potential in children with CNS disorders or epilepsy.

While many people have worries regarding the safety of TMS in the child population, our literature review adds to previous ones showing that most adverse events are mild and overall uncommon.[84,85] However, we did find three reports of new onset seizures[64,72,75] that are lacking in similar recent reviews. Two patients were diagnosed and treated for depression with sertraline, which has been associated with seizures, albeit rarely.[86,87] The first of these patients also exhibited prolonged hypomania. Hypomania is the worst grade level for adverse events in this review. Although this is a unique situation, hypomania is more likely an side effect of selective serotonin reuptake inhibitor-type antidepressants such as sertraline.[88] In the second individual,[72] atypical antipsychotic olanzapine was also taken by the patient on a daily basis. While antipsychotics decrease seizure threshold to varying degrees, olanzapine is known to be safer than other atypical antipsychotics considering adverse effects.[89] Still, isolated examples of olanzapine-

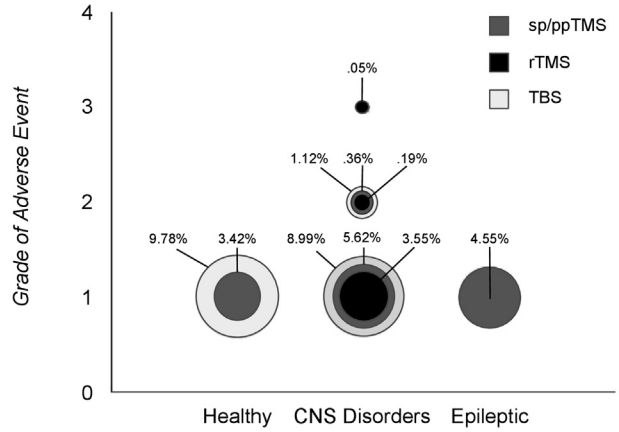

FIGURE 3.
Frequencies per grade of adverse event, per modality, and per population. Circle size is representative of adverse event frequency per session for sp/ppTMS (dark gray), rTMS (black), and TBS (light gray). CNS, central nervous system; TBS, theta-burst stimulation; rTMS, repetitive transcranial magnetic stimulation; sp/ppTMS, single-pulse and paired-pulse transcranial magnetic stimulation.

induced clinical seizure have been reported.[90,91] With multiple seizure risk factors, it is of crucial importance that TMS investigators carefully screen for medications and other potential seizure precipitants. The most recent case was an unmedicated youth with major depressive disorder treated with deep TMS.[64] Deep TMS uses H-coils that induce an effective field at a wider depth l compared with standard figure-8 TMS coils.[92] Generalized seizures in adults and typical mild adverse events have been reported during deep TMS simulation similarly as figure-8 coil stimulation.[93] However, deep TMS technology is new and continuous surveillance is needed because of its particular mode of action.

In regards to other moderate adverse events, neurocardiogenic syncope was associated with pre-existing circumstances that would induce syncope in two individuals. One of these two children failed to eat before the application and had a prior history of syncope with venipuncture; the other had a history of early morning presyncope with micturition and anxiety attacks.[21,94] Noted as the most common adverse event related to either TMS or TBS in our literature search, mild transient headaches have been shown to be a relatively frequent side effect of TMS and are easily quelled with acetaminophen or nonsteroidal anti-inflammatory medications.[95] Finally, local discomfort as well as neck or arm stiffness or pain, tingling, nausea/dizziness, anxiety and discomfort are also common transient mild adverse effect of TMS.[96]

We included one study of children with epilepsy in whom TMS induced an increase in seizure frequency up to three days after TMS in four children based on a phone questionnaire administered to the parents.[48] Epilepsy is a chronic brain disorder characterized by recurrent seizures. Current seizure frequency scales are based on continuous electroencephalography monitoring during hospital stay. Patient or parent report questionnaires have raised concerns about their accuracy.[97] In the aforementioned study, children were experiencing baseline seizures at frequencies ranking from continuous to three per month. How accurate is a self-report of a transient increase in seizure frequency in individuals with continuous seizures or those with baseline seizures occurring less than once a week? The use and report of standardized scales for seizure frequency (and possibly severity) would help weighing the real adverse effect of TMS in epileptic populations.

In this review, we demonstrated that both children and adults seem to experience similar adverse events during TMS experiments. Nonetheless, because neuronal networks are the targets of the resulting electrical currents induced during the TMS, the effects on a developing brain should be monitored carefully; the safety of TMS in child populations may thus be contemplated independently of the safety considerations in adult populations. A good example is the motor evoked potential threshold, directly related to the degree of myelination of the corticospinal tracts (i.e., the less myelinated the tracts, the higher the threshold), which decreases with age.[98] So, with higher motor thresholds, rTMS trials on children may be conducted at much higher output power than in adults. Adult safety guidelines on the maximum intensity may then not be appropriate for children. We suggest safety measures for children to be established through brain measures of activation and connectivity at different exposure levels (i.e., single sessions versus repetitive stimulations) as previously done in adults.[99,100] Because of the temporal resolution required to assess the immediate brain changes associated with TMS or TBS, only a few modalities are able to investigate this simultaneously. Those include functional magnetic resonance imaging, electroencephalography, magnetoencephalography, or functional near infrared spectroscopy. While it is not expected to include these measures in every TMS/TBS study involving children, it may be possible to monitor short- and long-term effects through cognitive and behavioral assessments. Although local IRBs may impose yearly reports for adverse events, other changes might not be monitored by investigators yet. We suggest systematic surveys/reports to be filled out on a session basis to monitor potential changes in behavior, health, quality of life and adverse events. These mainly include children-oriented evaluations such as The Child Behavior Checklist,[101] the Child Health and Illness Profile,[102] and the Pediatric Adverse Event Rating Scale.[103] Children with epilepsy may also add the Hague Seizure Severity Scale.[104]

Pitfalls from conducting an exhaustive safety review for TMS use in children

First, safety data are not reported in a systematic manner, which may lead to diverse biases. Under the Food and Drug Administration (FDA)'s revised reporting requirements in 21 Code of Federal Regulations (CFR) § 882.5805/8, investigators must immediately report any serious adverse events, but mild to moderate adverse events are reportable to the local IRB depending on local guidelines. This results in a lack of adverse event assessment and retrieval as well as incomplete data in some instances. Second, we report and grade adverse events according to the most current guidelines (Common Terminology Criteria for Adverse Events, v4.0[20]), which was originally designed for cancer drug trials.

Although pediatric oncologists raise the flag on its deficiencies,[105] pediatric clinicians and researchers outside the field of cancer may find it inappropriate. Third, efficacy and safety guidelines were addressed and published in a single article a couple of decades ago.[17] This included statements that indeed were revised such as "Children should not be used as subjects for rTMS without compelling clinical reasons, such as the treatment of refractory epilepsy or depression." There is an urgent need of criteria and guidelines applicable to children with or without epilepsy, neurological disorders, and other medical conditions, as well as a systematic reporting system of adverse events occurring in TMS laboratories. In this systematic review, we focused on accuracy and hope that biases from all the aforementioned issues did not deviate our main findings. In addition, we hope that this review combined with the most recent ones will help establishing appropriate guidelines for the use of TMS in children.

Conclusions

Over the past 30 years, more than 4000 children with or without neuropsychiatric diseases have been involved in different TMS paradigms. The induction of seizures appears to be quite rare and most reported adverse events are benign. Experiments including children with epilepsy or psychiatric disorders may still require additional clinical guidance, especially screening for at-risk medications and potential seizure precipitants. Overall, the risk of TMS appears to be similar to that in adults but as the number of children tested increases, there is a strong need for establishing reliable guidelines applicable to pediatric populations.

Author Contributions: C.A. carried out the literature search and analyses, wrote and revised the manuscript, and approved the final manuscript. B.K. conceptualized the study, critically reviewed the manuscript, and approved the final manuscript. I.B. supervised literature search, analyses, and writing process, reviewed and revised the manuscript, and approved the final manuscript.

References

1. Kobayashi M, Pascual-Leone A. Transcranial magnetic stimulation in neurology. *Lancet Neurol*. 2003;2:145-156.
2. Wassermann EM, Epstein C, Ziemann U, et al. *Oxford Handbook of Transcranial Stimulation*. Oxford, UK: Oxford Library of Psychology; 2008.
3. Pascual-Leone A, Amedi A, Fregni F, Merabet LB. The plastic human brain cortex. *Annu Rev Neurosci*. 2005;28:377-401.
4. Howland RH, Shutt LS, Berman SR, Spotts CR, Denko T. The emerging use of technology for the treatment of depression and other neuropsychiatric disorders. *Ann Clin Psychiatry*. 2011;23:48-62.
5. McClelland J, Bozhilova N, Campbell I, Schmidt U. A systematic review of the effects of neuromodulation on eating and body weight: evidence from human and animal studies. *Eur Eat Disord Rev*. 2013;21:436-455.
6. Bae EH, Schrader LM, Machii K, et al. Safety and tolerability of repetitive transcranial magnetic stimulation in patients with epilepsy: a review of the literature. *Epilepsy Behav*. 2007;10:521-528.
7. Daskalakis ZJ, Christensen BK, Fitzgerald PB, Fountain SI, Chen R. Reduced cerebellar inhibition in schizophrenia: a preliminary study. *Am J Psychiatry*. 2005;162:1203-1205.
8. Lefaucheur JP, Andre-Obadia N, Antal A, et al. Evidence-based guidelines on the therapeutic use of repetitive transcranial magnetic stimulation (rTMS). *Clin Neurophysiol*. 2014;125:2150-2206.
9. Vonloh M, Chen R, Kluger B. Safety of transcranial magnetic stimulation in Parkinson's disease: a review of the literature. *Parkinsonism Relat Disord*. 2013;19:573-585.
10. Lipton RB, Pearlman SH. Transcranial magnetic simulation in the treatment of migraine. *Neurotherapeutics*. 2010;7:204-212.
11. Fregni F, Simon DK, Wu A, Pascual-Leone A. Non-invasive brain stimulation for Parkinson's disease: a systematic review and meta-analysis of the literature. *J Neurol Neurosurg Psychiatry*. 2005;76:1614-1623.
12. Mylius V, Engau I, Teepker M, et al. Pain sensitivity and descending inhibition of pain in Parkinson's disease. *J Neurol Neurosurg Psychiatry*. 2009;80:24-28.
13. Kwon HJ, Lim WS, Lim MH, et al. 1-Hz low frequency repetitive transcranial magnetic stimulation in children with Tourette's syndrome. *Neurosci Lett*. 2011;492:1-4.
14. Le K, Liu L, Sun M, Hu L, Xiao N. Transcranial magnetic stimulation at 1 Hertz improves clinical symptoms in children with Tourette syndrome for at least 6 months. *J Clin Neurosci*. 2013;20:257-262.
15. Gillick BT, Krach LE, Feyma T, et al. Primed low-frequency repetitive transcranial magnetic stimulation and constraint-induced movement therapy in pediatric hemiparesis: a randomized controlled trial. *Dev Med Child Neurol*. 2014;56:44-52.
16. Huang YZ, Edwards MJ, Rounis E, Bhatia KP, Rothwell JC. Theta burst stimulation of the human motor cortex. *Neuron*. 2005;45:201-206.
17. Wassermann EM. Risk and safety of repetitive transcranial magnetic stimulation: report and suggested guidelines from the International Workshop on the Safety of Repetitive Transcranial Magnetic Stimulation, June 5-7, 1996. *Electroencephalogr Clin Neurophysiol*. 1998;108:1-16.
18. Wassermann EM, Blaxton TA, Hoffman EA, et al. Repetitive transcranial magnetic stimulation of the dominant hemisphere can disrupt visual naming in temporal lobe epilepsy patients. *Neuropsychologia*. 1999;37:537-544.
19. Takano B, Drzezga A, Peller M, et al. Short-term modulation of regional excitability and blood flow in human motor cortex following rapid-rate transcranial magnetic stimulation. *Neuroimage*. 2004;23:849-859.
20. Institute NC. Common Terminology Criteria for Adverse Events v4. 0. NCI, NIH, DHHS. 2009;NIH Publication # 09–7473.
21. Kirton A, Deveber G, Gunraj C, Chen R. Cortical excitability and interhemispheric inhibition after subcortical pediatric stroke: plastic organization and effects of rTMS. Clinical neurophysiology. *Clin Neurophysiol*. 2010;121:1922-1929.
22. Babajani-Feremi A, Narayana S, Rezaie R, et al. Language mapping using high gamma electrocorticography, fMRI, and TMS versus electrocortical stimulation. *Clin Neurophysiol*. 2016;127:1822-1836.
23. Bender S, Basseler K, Sebastian I, et al. Electroencephalographic response to transcranial magnetic stimulation in children: evidence for giant inhibitory potentials. *Ann Neurol*. 2005;58:58-67.
24. Berweck S, Walther M, Brodbeck V, et al. Abnormal motor cortex excitability in congenital stroke. *Pediatr Res*. 2008;63:84-88.
25. Bleyenheuft Y, Dricot L, Gilis N, et al. Capturing neuroplastic changes after bimanual intensive rehabilitation in children with unilateral spastic cerebral palsy: a combined DTI, TMS and fMRI pilot study. *Res Dev Disabil*. 2015;43-44:136-149.
26. Bruckmann S, Hauk D, Roessner V, et al. Cortical inhibition in attention deficit hyperactivity disorder: new insights from the electroencephalographic response to transcranial magnetic stimulation. *Brain*. 2012;135:2215-2230.
27. Buchmann J, Gierow W, Weber S, et al. Restoration of disturbed intracortical motor inhibition and facilitation in attention deficit hyperactivity disorder children by methylphenidate. *Biol Psychiatry*. 2007;62:963-969.
28. Buchmann J, Gierow W, Weber S, et al. Modulation of transcallosally mediated motor inhibition in children with attention deficit hyperactivity disorder (ADHD) by medication with methylphenidate (MPH). *Neurosci Lett*. 2006;405:14-18.
29. Caramia MD, Desiato MT, Cicinelli P, Iani C, Rossini PM. Latency jump of "relaxed" versus "contracted" motor evoked potentials as a marker of cortico-spinal maturation. *Electroencephalogr Clin Neurophysiol*. 1993;89:61-66.
30. Cassidy JM, Carey JR, Lu C, et al. Ipsilesional motor-evoked potential absence in pediatric hemiparesis impacts tracking accuracy of the less affected hand. *Res Dev Disabil*. 2015;47:154-164.

31. Chen TH, Wu SW, Welge JA, et al. Reduced short interval cortical inhibition correlates with atomoxetine response in children with attention-deficit hyperactivity disorder (ADHD). *J Child Neurol*. 2014;29:1672-1679.
32. Coburger J, Musahl C, Henkes H, et al. Comparison of navigated transcranial magnetic stimulation and functional magnetic resonance imaging for preoperative mapping in rolandic tumor surgery. *Neurosurg Rev*. 2013;36:65-75. discussion 75-66.
33. Damji O, Keess J, Kirton A. Evaluating developmental motor plasticity with paired afferent stimulation. *Dev Med Child Neurol*. 2015; 57:548-555.
34. Galloway GM, Dias BR, Brown JL, Henry CM, Brooks 2nd DA, Buggie EW. Transcranial magnetic stimulation—may be useful as a preoperative screen of motor tract function. *J Clin Neurophysiol*. 2013;30:386-389.
35. Garvey MA, Kaczynski KJ, Becker DA, Bartko JJ. Subjective reactions of children to single-pulse transcranial magnetic stimulation. *J Child Neurol*. 2001;16:891-894.
36. Garvey MA, Ziemann U, Becker DA, Barker CA, Bartko JJ. New graphical method to measure silent periods evoked by transcranial magnetic stimulation. *Clin Neurophysiol*. 2001;112:1451-1460.
37. Geerdink N, Cuppen I, Rotteveel J, Mullaart R, Roeleveld N, Pasman J. Contribution of the corticospinal tract to motor impairment in spina bifida. *Pediatr Neurol*. 2012;47:270-278.
38. Gilbert DL, Sallee FR, Zhang J, Lipps TD, Wassermann EM. Transcranial magnetic stimulation-evoked cortical inhibition: a consistent marker of attention-deficit/hyperactivity disorder scores in Tourette syndrome. *Biol Psychiatry*. 2005;57:1597-1600.
39. Gilbert DL, Wang Z, Sallee FR, et al. Dopamine transporter genotype influences the physiological response to medication in ADHD. *Brain*. 2006;129:2038-2046.
40. Gilbert DL, Zhang J, Lipps TD, et al. Atomoxetine treatment of ADHD in Tourette syndrome: reduction in motor cortex inhibition correlates with clinical improvement. *Clin Neurophysiol*. 2007;118: 1835-1841.
41. Glasby MA, Tsirikos AI, Henderson L, et al. Transcranial magnetic stimulation in the semi-quantitative, pre-operative assessment of patients undergoing spinal deformity surgery. *Eur Spine J*. 2016. http://dx.doi.org/10.1007/s00586-016-4737-4.
42. Groppa S, Siebner HR, Kurth C, Stephani U, Siniatchkin M. Abnormal response of motor cortex to photic stimulation in idiopathic generalized epilepsy. *Epilepsia*. 2008;49:2022-2029.
43. Hong YH, Wu SW, Pedapati EV, et al. Safety and tolerability of theta burst stimulation vs. single and paired pulse transcranial magnetic stimulation: a comparative study of 165 pediatric subjects. *Front Hum Neurosci*. 2015;9:29.
44. Hufschmidt A, Muller-Felber W, Tzitiridou M, Fietzek UM, Haberl C, Heinen F. Canalicular magnetic stimulation lacks specificity to differentiate idiopathic facial palsy from borreliosis in children. *Eur J Paediatr Neurol*. 2008;12:366-370.
45. Jung NH, Janzarik WG, Delvendahl I, et al. Impaired induction of long-term potentiation-like plasticity in patients with high-functioning autism and Asperger syndrome. *Dev Med Child Neurol*. 2013;55:83-89.
46. Kamida T, Fujiki M, Baba H, Ono T, Abe T, Kobayashi H. The relationship between paired pulse magnetic MEP and surgical prognosis in patients with intractable epilepsy. *Seizure*. 2007;16: 113-119.
47. Koh TH, Eyre JA. Maturation of corticospinal tracts assessed by electromagnetic stimulation of the motor cortex. *Arch Dis Child*. 1988;63:1347-1352.
48. Koudijs SM, Leijten FS, Ramsey NF, van Nieuwenhuizen O, Braun KP. Lateralization of motor innervation in children with intractable focal epilepsy—a TMS and fMRI study. *Epilepsy Res*. 2010;90:140-150.
49. Kuhnke N, Juenger H, Walther M, Berweck S, Mall V, Staudt M. Do patients with congenital hemiparesis and ipsilateral corticospinal projections respond differently to constraint-induced movement therapy? *Dev Med Child Neurol*. 2008;50:898-903.
50. Maegaki Y, Maeoka Y, Ishii S, et al. Central motor reorganization in cerebral palsy patients with bilateral cerebral lesions. *Pediatr Res*. 1999;45:559-567.
51. Maegaki Y, Maeoka Y, Ishii S, et al. Mechanisms of central motor reorganization in pediatric hemiplegic patients. *Neuropediatrics*. 1997;28:168-174.
52. Narayana S, Rezaie R, McAfee SS, et al. Assessing motor function in young children with transcranial magnetic stimulation. *Pediatr Neurol*. 2015;52:94-103.
53. Nezu A, Kimura S, Uehara S, Kobayashi T, Tanaka M, Saito K. Magnetic stimulation of motor cortex in children: maturity of corticospinal pathway and problem of clinical application. *Brain Dev*. 1997;19:176-180.
54. Redman TA, Gibson N, Finn JC, Bremner AP, Valentine J, Thickbroom GW. Upper limb corticomotor projections and physiological changes that occur with botulinum toxin-A therapy in children with hemiplegic cerebral palsy. *Eur J Neurol*. 2008;15:787-791.
55. Reis J, Cohen LG, Pearl PL, et al. GABAB-ergic motor cortex dysfunction in SSADH deficiency. *Neurology*. 2012;79:47-54.
56. Rinalduzzi S, Valeriani M, Vigevano F. Brainstem dysfunction in alternating hemiplegia of childhood: a neurophysiological study. *Cephalalgia*. 2006;26:511-519.
57. Saisanen L, Kononen M, Julkunen P, et al. Non-invasive preoperative localization of primary motor cortex in epilepsy surgery by navigated transcranial magnetic stimulation. *Epilepsy Res*. 2010; 92:134-144.
58. Shizukawa H, Imai T, Kobayashi N, Chiba S, Matsumoto H. Cervical flexion-induced changes of motor evoked potentials by transcranial magnetic stimulation in a patient with Hirayama disease—juvenile muscular atrophy of unilateral upper extremity. *Rinsho Shinkeigaku*. 1994;34:500-503.
59. Siniatchkin M, Reich AL, Shepherd AJ, van Baalen A, Siebner HR, Stephani U. Peri-ictal changes of cortical excitability in children suffering from migraine without aura. *Pain*. 2009;147:132-140.
60. Staudt M, Krageloh-Mann I, Holthausen H, Gerloff C, Grodd W. Searching for motor functions in dysgenic cortex: a clinical transcranial magnetic stimulation and functional magnetic resonance imaging study. *J Neurosurg*. 2004;101:69-77.
61. Vry J, Linder-Lucht M, Berweck S, et al. Altered cortical inhibitory function in children with spastic diplegia: a TMS study. *Exp Brain Res*. 2008;186:611-618.
62. Wu SW, Gilbert DL, Shahana N, Huddleston DA, Mostofsky SH. Transcranial magnetic stimulation measures in attention-deficit/hyperactivity disorder. *Pediatr Neurol*. 2012;47:177-185.
63. Wu SW, Shahana N, Huddleston DA, Lewis AN, Gilbert DL. Safety and tolerability of theta-burst transcranial magnetic stimulation in children. *Dev Med Child Neurol*. 2012;54:636-639.
64. Cullen KR, Jasberg S, Nelson B, Klimes-Dougan B, Lim KO, Croarkin PE. Seizure induced by deep transcranial magnetic stimulation in an adolescent with depression. *J Child Adolesc Psychopharmacol*. 2016;26:637-641.
65. Kirton A, Andersen J, Herrero M, et al. Brain stimulation and constraint for perinatal stroke hemiparesis: The Plastic Champs Trial. *Neurology*. 2016;86:1659-1667.
66. Gillick BT, Krach LE, Feyma T, et al. Safety of primed repetitive transcranial magnetic stimulation and modified constraint-induced movement therapy in a randomized controlled trial in pediatric hemiparesis. *Arch Phys Med Rehabil*. 2015;96:S104-S113.
67. Pathak V, Sinha VK, Praharaj SK. Efficacy of adjunctive high frequency repetitive transcranial magnetic stimulation of right prefrontal cortex in adolescent mania: a Randomized Sham-Controlled Study. *Clin Psychopharmacol Neurosci*. 2015;13: 245-249.
68. Cristancho P, Akkineni K, Constantino JN, Carter AR, O'Reardon JP. Transcranial magnetic stimulation in a 15-year-old patient with autism and comorbid depression. *J ECT*. 2014;30:e46-e47.
69. Gomez L, Vidal B, Morales L, et al. Low frequency repetitive transcranial magnetic stimulation in children with attention deficit/hyperactivity disorder. Preliminary results. *Brain Stimul*. 2014;7:760-762.
70. Panerai S, Tasca D, Lanuzza B, et al. Effects of repetitive transcranial magnetic stimulation in performing eye-hand integration tasks: four preliminary studies with children showing low-functioning autism. *Autism*. 2014;18:638-650.
71. Yang XR, Kirton A, Wilkes TC, et al. Glutamate alterations associated with transcranial magnetic stimulation in youth depression: a case series. *J ECT*. 2014;30:242-247.
72. Chiramberro M, Lindberg N, Isometsa E, Kahkonen S, Appelberg B. Repetitive transcranial magnetic stimulation induced seizures in an adolescent patient with major depression: a case report. *Brain Stimul*. 2013;6:830-831.

73. Helfrich C, Pierau SS, Freitag CM, Roeper J, Ziemann U, Bender S. Monitoring cortical excitability during repetitive transcranial magnetic stimulation in children with ADHD: a single-blind, sham-controlled TMS-EEG study. *PLoS One*. 2012;7:e50073.
74. Croarkin PE, Wall CA, Nakonezny PA, et al. Increased cortical excitability with prefrontal high-frequency repetitive transcranial magnetic stimulation in adolescents with treatment-resistant major depressive disorder. *J Child Adolesc Psychopharmacol*. 2012;22:56-64.
75. Hu SH, Wang SS, Zhang MM, et al. Repetitive transcranial magnetic stimulation-induced seizure of a patient with adolescent-onset depression: a case report and literature review. *J Int Med Res*. 2011;39:2039-2044.
76. Bloch Y, Grisaru N, Harel EV, et al. Repetitive transcranial magnetic stimulation in the treatment of depression in adolescents: an open-label study. *J ECT*. 2008;24:156-159.
77. Jardri R, Bubrovszky M, Demeulemeester M, et al. Repetitive transcranial magnetic stimulation to treat early-onset auditory hallucinations. *J Am Acad Child Adolesc Psychiatry*. 2012;51:947-949.
78. Jardri R, Delevoye-Turrell Y, Lucas B, et al. Clinical practice of rTMS reveals a functional dissociation between agency and hallucinations in schizophrenia. *Neuropsychologia*. 2009;47:132-138.
79. Loo C, McFarquhar T, Walter G. Transcranial magnetic stimulation in adolescent depression. *Australas Psychiatry*. 2006;14:81-85.
80. Pedapati EV, Gilbert DL, Horn PS, et al. Effect of 30 Hz theta burst transcranial magnetic stimulation on the primary motor cortex in children and adolescents. *Front Hum Neurosci*. 2015;9:91.
81. Rotenberg A, Bae EH, Takeoka M, Tormos JM, Schachter SC, Pascual-Leone A. Repetitive transcranial magnetic stimulation in the treatment of epilepsia partialis continua. *Epilepsy Behav*. 2009;14:253-257.
82. Sun W, Fu W, Mao W, Wang D, Wang Y. Low-frequency repetitive transcranial magnetic stimulation for the treatment of refractory partial epilepsy. *Clin EEG Neurosci*. 2011;42:40-44.
83. Valle AC, Dionisio K, Pitskel NB, et al. Low and high frequency repetitive transcranial magnetic stimulation for the treatment of spasticity. *Dev Med Child Neurol*. 2007;49:534-538.
84. Frye RE, Rotenberg A, Ousley M, Pascual-Leone A. Transcranial magnetic stimulation in child neurology: current and future directions. *J Child Neurol*. 2008;23:79-96.
85. Krishnan C, Santos L, Peterson MD, Ehinger M. Safety of noninvasive brain stimulation in children and adolescents. *Brain Stimul*. 2015;8:76-87.
86. Pisani F, Oteri G, Costa C, Di Raimondo G, Di Perri R. Effects of psychotropic drugs on seizure threshold. *Drug Saf*. 2002;25:91-110.
87. Sarkar S, Gangadhar S, Subramaniam E, Praharaj SK. Seizure with sertraline: is there a risk? *J Neuropsychiatry Clin Neurosci*. 2014;26:E27-E28.
88. Mendhekar DN, Gupta D, Girotra V. Sertraline-induced hypomania: a genuine side-effect. *Acta Psychiatr Scand*. 2003;108:70-74.
89. Haddad PM, Sharma SG. Adverse effects of atypical antipsychotics: differential risk and clinical implications. *CNS Drugs*. 2007;21:911-936.
90. Behere RV, Anjith D, Rao NP, Venkatasubramanian G, Gangadhar BN. Olanzapine-induced clinical seizure: a case report. *Clin Neuropharmacol*. 2009;32:297-298.
91. Wyderski RJ, Starrett WG, Abou-Saif A. Fatal status epilepticus associated with olanzapine therapy. *Ann Pharmacother*. 1999;33:787-789.
92. Zangen A, Roth Y, Voller B, Hallett M. Transcranial magnetic stimulation of deep brain regions: evidence for efficacy of the H-coil. *Clin Neurophysiol*. 2005;116:775-779.
93. Bersani FS, Minichino A, Enticott PG, et al. Deep transcranial magnetic stimulation as a treatment for psychiatric disorders: a comprehensive review. *Eur Psychiatry*. 2013;28:30-39.
94. Kirton A, Deveber G, Gunraj C, Chen R. Neurocardiogenic syncope complicating pediatric transcranial magnetic stimulation. *Pediatr Neurol*. 2008;39:196-197.
95. Grazzi L. Headache in children and adolescents: conventional and unconventional approaches to treatment. *Neurol Sci*. 2004;25:S223-S225.
96. Rossi S, Hallett M, Rossini PM, Pascual-Leone A, Safety of TMSCG. Safety, ethical considerations, and application guidelines for the use of transcranial magnetic stimulation in clinical practice and research. *Clin Neurophysiol*. 2009;120:2008-2039.
97. Meinardi H, Cramer JA, Baker GA, da Silva AM. General discussion of the assessment and representation of the elements seizure frequency and seizure severity. *Quantitative Assess Epilepsy Care*. 1993;255:73-81.
98. Garvey MA, Ziemann U, Bartko JJ, Denckla MB, Barker CA, Wassermann EM. Cortical correlates of neuromotor development in healthy children. *Clin Neurophysiol*. 2003;114:1662-1670.
99. Bestmann S, Baudewig J, Siebner HR, Rothwell JC, Frahm J. Functional MRI of the immediate impact of transcranial magnetic stimulation on cortical and subcortical motor circuits. *Eur J Neurosci*. 2004;19:1950-1962.
100. Fitzgerald PB, Brown TL, Daskalakis ZJ, Chen R, Kulkarni J. Intensity-dependent effects of 1 Hz rTMS on human corticospinal excitability. *Clin Neurophysiol*. 2002;113:1136-1141.
101. Achenbach TM, Rescorla LA. *Manual for the ASEBA School-Age Forms & Profiles*. Burlington, VT: University of Vermont, Research Center for Children, Youth, & Families; 2001.
102. Riley AW, Forrest CB, Starfield B, Rebok GW, Robertson JA, Green BF. The Parent Report Form of the CHIP-Child Edition: reliability and validity. *Med Care*. 2004;42:210-220.
103. March JS Karayal O, Crisman A. The pediatric adverse event rating scale. Proceedings of the 54th Annual Meeting of the American Academy of Child and Adolescent Psychiatry. 2007.
104. Carpay HA, Arts WF, Vermeulen J, et al. Parent-completed scales for measuring seizure severity and severity of side-effects of antiepileptic drugs in childhood epilepsy: development and psychometric analysis. *Epilepsy Res*. 1996;24:173-181.
105. de Rojas T, Bautista FJ, Madero L, Moreno L. The first step to integrating adapted common terminology criteria for adverse events for children. *J Clin Oncol*. 2016;34:2196-2197.