Review Article

Safety of Noninvasive Brain Stimulation in Children and Adolescents

Chandramouli Krishnan[*,1], Luciana Santos[1], Mark D. Peterson, Margaret Ehinger

Department of Physical Medicine and Rehabilitation, University of Michigan Medical School, Ann Arbor, MI, USA

A B S T R A C T

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

* Corresponding author. Neuromuscular & Rehabilitation Robotics Laboratory (NeuRRo Lab), Department of Physical Medicine and Rehabilitation, University of Michigan, 325 E Eisenhower Parkway, Suite 3013, Ann Arbor, MI, 48108, USA. Tel.: +1 319 321 0117; fax: +1 734 615 1770.
  E-mail address: mouli@umich.edu (C. Krishnan).
[1] These authors contributed equally.

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 synaptic 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 $\left[\%AE = \left(n/N \right) \times 100 \right]$. 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

Table 1
Description of subject demographics, clinical characteristics, and adverse effects reported for transcranial current stimulation (tCS) and repetitive transcranial magnetic stimulation.

References	N (n < 18)	Age (y)	Diagnosis	Adverse events[b]
Bogdanov et al. (1994)	21[a]	6–18	Infantile cerebral palsy	Not reported
Alon et al. (1998)	7	2.5–7.5	Cerebral palsy	Well tolerated
				No reports of seizures, episodes of nausea or vomiting or sleep disruption
Shelyakin et al. (2001)	18	4–8	Infantile cerebral palsy and organic CNS lesions	No negative adverse effects
Ilyukhina et al. (2005)	30	4–6	Delayed neuropsychological development	No adverse effects
San-Juan et al. (2011)	2 (1 < 18)	17 and 31	Rasmussen's encephalitis	No complications or skin injuries
Schneider et al. (2011)	10	6–21	Autism (language disorder)	No adverse effects
Mattai et al. (2011)	13	10.5–17.6	Schizophrenia	Redness, tingling, itching, fatigue
Varga et al. (2011)	5	6.1–11	Epilepsy	No adverse effects
Yook et al. (2011)	1	11	Seizure	No adverse effects
Andrade et al. (2013)	14	5–12	Language disorders	Tingling, burning sensation, scalp pain, local redness, headache, sleepiness, trouble concentrating, mood changes, irritability
Auvichayapat et al. (2013)	36	6–15	Epilepsy	Well tolerated
				Erythematous rash with no pain or pruritus (one patient)
Young et al. (2013)[c]	11 (8 < 18)	7–18	Dystonia	Uncomfortable at the stimulation electrodes
Grecco et al. (2014)	12	5–10	Cerebral Palsy	No adverse effects
Duarte et al. (2014)	12	Mean (SD): 7.8 (2.0)	Cerebral palsy	Tingling, redness in the supraorbital region
				No other behavioral changes, headache, or discomfort
Prehn-Kristensen et al. (2014)	12	10–14	ADHD	No effect on mood, alertness, or memory
Young et al. (2014)	14 (12 < 18)	7–19	Dystonia	Skin discomfort
Brasil-Neto et al. (2004)	5 (1 < 18)	6–50	Frontal focal epilepsy	No untoward effects
Graff-Guerrero et al. (2004)[e]	2	11 and 7	Epilepsia Partialis Continua	No major side effects
Morales et al. (2005)	2	8 and 16	Epilepsy	Case A:
				Well tolerated; no adverse effects
				Case B:
				Leg pain and mild headache (resolved after stimulation)
Kinoshita et al. (2005)	7 (1 < 18)	16–33	Extratemporal lobe epilepsy	No adverse effects
Fregni et al. (2006)	27[a]	Mean (SD): 21.6 (7.4) y/20.8 (5.2)	Epilepsy/healthy	Not reported
Loo et al. (2006)	2	16	Depression	No adverse effects
Valle et al. (2007)	17	Mean (SD): 9.1 (3.2)	Cerebral palsy	No adverse effects
Bloch et al. (2008)	9 (5 < 18)	16–18	Depression	Mild headache
Kirton et al. (2008)[d]	5 (4 < 18)	10–16.7	Stroke	Neurocardiogenic syncope, mild headache, nausea, neck stiffness
Rotenberg et al. (2008)	1	14	Rasmussen's encephalitis	Well tolerated with no adverse effects
Jardri et al. (2009)	1	11	Schizophrenia	Well tolerated
Mylius et al. (2009)	1	6	Pantothenate kinase-associated neurodegenerative disease (PKAN)	Not reported
Sokhadze et al. (2009)[e]	8 (5 < 18)	12–27	Autism	No adverse effects
Baruth et al. (2010)[e]	16 (14 < 18)	9–26	Autism spectrum disorder	Itching, mild headache
Kirton et al. (2010)[d]	5 (4 < 18)	10.3–16.7	Stroke	Neurocardiogenic syncope
Sokhadze et al. (2010)[e]	13 (11 < 18)	8–27	Autism spectrum disorder	No adverse effects
Hu et al. (2011)	1	15	Depression	Seizure, hypomania
Kwon et al. (2011)	10	9–14	Tourette's syndrome	Well tolerated
				No adverse effects or worsening of symptoms
Sun et al. (2011)	17 (8 < 18)	3–32	Epilepsy	Well tolerated; no adverse effects
Wall et al. (2011)	8	14.6–17.8	Depression	Well tolerated
Casanova et al. (2012)	25	Mean (SD): 12.9 (3.1)	Autism	No adverse effects
Croarkin et al. (2012)[c]	8	14–17	Depression	Scalp discomfort
Helfrich et al. (2012)	25	8–14	ADHD	Mild headache; well tolerated
Jardri et al. (2012)[e]	10	Mean (SD): 15.5 (2.3)	Childhood-onset schizophrenia	Scalp discomfort
Sokhadze et al. (2012)[e]	20 (18 < 18)	9–21	Autism spectrum disorder	No adverse effects
Sun et al. (2012)	60[a]	Group 1: Mean (SD): 21.3 (7.5) Group 2: Mean (SD): 19.7 (6.4)	Epilepsy	Mild or moderate headache, tinnitus; well tolerated
Weaver et al. (2012)	9 (4 < 18)	14–21	ADHD	Mild headache, scalp discomfort
Wu et al. (2012)	40	8–17	Tourette's syndrome/healthy	Mild headache, neck stiffness, finger twitching; no reports of seizures
Chiramberro et al. (2013)	1	16	Depression	Seizure
Le et al. (2013)	25	7–16	Tourette Syndrome	Mild sleepness
Wall et al. (2013)	14	13.9–17.8	Depression	Scalp discomfort, no adverse neurocognitive effect
Gillick et al. (2014)[e]	10	8–15	Congenital hemiparesis	Self-limiting headache, dizziness, mood changes, fatigue, abnormal muscle contractions
Gomez et al. (2014)	10	7–12	ADHD	Slight headache, neck pain, slight brief dizziness
Oberman et al. (2014)	19 (17 < 18)	9–18	Autism	Mild headache, mild fatigue; no serious adverse effects

Table 1 (*continued*)

References	N (n < 18)	Age (y)	Diagnosis	Adverse events[b]
Sokhadze et al. (2014)[e]	27 (22 < 18)	Mean (SD): 14.8 (3.2)	Autism spectrum disorder	Mild headache, jaw twitches, itching

N: number of subjects that underwent stimulation. ADHD: Attention Deficit Hyperactivity Disorder.
[a] Unknown number of subjects under 18 years old.
[b] Adverse effects as described by the authors.
[c] Each of these studies reported dropout of one subject from the study due to discomfort and did not include the subject in their analysis.
[d] Sample consists of same subjects.
[e] Adverse effects were gathered by contacting the authors through email. Note that the total number of subjects reported in the manuscript ($n > 513$) does not include the studies that did not report adverse effects, those with unknown number of subjects under 18 years old, and was adjusted for samples representing the same subjects.

of diagnoses reported, autism, cerebral palsy, epilepsy, and depression were the most common. There were nine single-session studies (3 rTMS and 6 tCS) [32,34,35,43,47,56,73–75]. As a therapeutic tool, TMS and tCS were applied as many times as 2–3 sessions/day [45,46,72,76]. Twenty-two publications reported conducting the NIBS sessions on consecutive weekdays [31,38,39,45,46,51,65–67,69,70,72,76–85], and five reported weekly sessions [24,55,57,86,87].

rTMS was the most frequently examined NIBS modality, with 35 publications addressing the application of TMS on children and adolescents (3.0–17.8 years old) [38–40,44–46,52,55–57,64–67,70,71,73,75–81,83,85–94]. The duration of the interventions ranged from one day to 18 weeks, and the stimulation provided was administered in frequencies ranging from 0.3 Hz to 10 Hz; two studies reported priming the subject with a frequency of 6 Hz before the procedure [46,52]. The intensity of stimulation ranged from 55% active motor threshold to 128% resting motor threshold, with one study using 20% resting motor threshold as a control condition [80] (Table 2).

Of the more than 322 enrolled children and adolescents that underwent TMS, only four (1.2%) encountered major negative side effects. Of these, two subjects experienced a seizure (0.62%) [64,70] and two others had syncope (0.62%) [89,91]. TMS studies reported several minor negative side effects, the most common being headache (11.5%) and scalp discomfort (2.5%) (Figs. 1 and 2A). The headaches (and scalp discomfort) reported were almost always transient and resolved spontaneously without any medical intervention. Only two studies reported that subjects needed a single-dose of acetaminophen/ibuprofen for the treatment of headache [75]. The other TMS-related minor adverse effects (e.g., neck stiffness, twitching, fatigue, etc.) were also temporary and often resolved within 24 h after the stimulation. Table 1 summarizes population data and adverse effects.

Our search also resulted in 16 publications in which greater than 191 children and adolescents (2.5–17.6 years old) underwent tCS (Tables 1 and 3) [23–25,31,32,34,35,43,47,51,68,69,72,74,82,84]. There were 14 studies that used tDCS and two studies that used transcranial alternating current stimulation (tACS) (Table 3). There were 15 studies that addressed the adverse effects of tCS (13 tDCS and 2 tACS). The intensity of current used ranged from 0.03 to 2.0 mA, and stimulation was applied from 18 to 50 min per session, with total treatment ranging from 1 to 102 sessions. Detailed information on current parameters can be found in Table 3.

tCS was well-tolerated and no studies reported any serious adverse effects; however, subjects commonly reported minor side effects such as tingling ($n = 22$), itching ($n = 11$), and redness ($n = 9$). Pooled analysis indicated that the frequency of the adverse effects (i.e., incidence) ranged between 1% and 11.5% (Fig. 2B). Tingling and itching sensations were reported to be brief and transient, and typically subsided after the completion of stimulation. Redness associated with the stimulation resolved within 1–2 h after the end of the treatment [43,51]. Six subjects complained of

minor scalp discomfort [34,35]; four continued the study following a reduction in current intensity [34,35], while another withdrew from the study [35]. None of the adverse effects required any medical intervention.

Discussion

NIBS modalities are considered to be promising methods to enhance brain plasticity and neuromotor function among individuals with neurological disorders. As a result, it is not surprising to see a tremendous increase in both short-term and long-term studies evaluating the efficacy and effectiveness of NIBS for various disease conditions (Fig. 3). While rTMS is the most extensively studied NIBS technique, there is a growing interest in the use of tDCS for facilitating neuroplasticity (Fig. 3). This is because tDCS is simple and relatively inexpensive, and can be administered in conjunction with cognitive and motor training protocols [95,96]. However, there are very few studies that address the safety of these techniques, especially in children. In this review, we sought to examine the safety of NIBS (i.e., specifically rTMS and tDCS) among children and adolescents. Our analyses of the existing published literature to date revealed a very low incidence of serious adverse events (<1%), and suggests that these NIBS modalities are safe in children and adolescents.

Safety of rTMS

The present review of the literature confirms that rTMS poses little risk to children and adolescents, especially when the specific safety guidelines for the application of rTMS are followed. However, several major and minor adverse effects were reported that are worth describing in further detail. The most severe side effects were seizures and neurocardiogenic syncope, and minor side effects included headache, scalp discomfort, twitching, fatigue, and tinnitus. Specifically, one report described a case in which rTMS led to seizure and hypomania in a 15 year old girl who was diagnosed with adolescent-onset depressive disorder [64]. Another case report described rTMS induced seizures in an adolescent with major depression [70]. Although previous reviews of TMS on children and adolescents have not reported seizure as an adverse event [60,63], studies on adults have reported seizure as a side effect of rTMS [3]. Epileptogenic medications (i.e., medications that lower seizure threshold), alcohol consumption, and prior seizure history may play a significant role in triggering seizure during rTMS [58,97]. The subjects in the case reports, which we present in this review, had no history of seizure, cerebral trauma, or any other conditions that could induce seizure, and the researchers were following the safety parameters recommended in the guidelines [3]. However, the subjects were taking medications (Sertraline 100–150 mg/day [64,70], olanzapine 75 mg/day [70]) that have a potential risk for seizure induction during the application of rTMS [3]. Moreover, one of the subjects had consumed high levels of alcohol (reported

Table 2
Transcranial magnetic stimulation (TMS) parameters used in the studies included in the review.

Authors	Intensity	Frequency (Hz)	Train Number	Train Duration(s)	Inter-train interval (s)	Total number of pulses/session	Sessions	Time (minutes)	Coil	Treatment site
Brasil-Neto et al. (2004)	5% below MT	0.3	5	60	60	100	2 sessions/week 3 months	9	Circular	Vertex (Cz)
Graff-Guerrero et al. (2004)	Case (A) 50% MSO; Case (B) 128% RMT	20	15	2	58	600	1 session	15	Fig.-8	Left frontal cortex; Epileptogenic focus
Morales et al. (2005)	Case (A) 100% MSO; Case (B) 90–100% MT	Case A: 1 (1st session); 6 Hz-priming & 1 Hz (2nd session); 1 (day 2); Case B: 1 (1st session); 6 Hz-priming & 1 Hz (2nd session)	Continuous; 10; Continuous; Continuous; Continuous; 10	5	25	4 × 600; 300; 600; 4 × 600; 300; 50	3 sessions/2 days; 2 sessions/day	16–40; 2 × 15	Circular; Fig.-8	Left motor cortex; Seizure focus
Kinoshita et al. (2005)	90% RMT or 100% AMT	0.9	Not reported	5	25	900	2 sessions/day 5 days/week 1 week	15	Circular	FCz or PCz
Fregni et al. (2006)	90% RMT	1	Continuous			900	2 sessions 1 session/week	15	Fig.-8	Left primary motor cortex
Loo et al. (2006)	Case (A) 110% RMT; Case (B) 110% RMT	Case A: 10; Case B: 10	40; 40	5	25	2000; 2000	29 sessions; 38 sessions	20; 20	Not specified	Not specified
Valle et al. (2007)	Group (A) 95% RMT; Group (B) 90% RMT	Group A: 1; Group B: 5	Continuous; 5	60	120	1500; 1500	5 consecutive days; 5 consecutive days	25; 15	Fig.-8; Fig.-8	Motor cortex; Motor cortex
Bloch et al. (2008)	80% MT	10	20	2	58	1200	14 working days	20	Circular	Left DLPFC
Kirton et al. (2008)[b]	100% RMT	1	Continuous			1200	8 days	20	Fig.-8	Motor cortex
Rotenberg et al. (2008)	100% MT	1	Continuous			1800	9 consecutive days	30	Fig.-8	Epileptogenic focus
Jardri et al. (2009)	100% MT	1	Continuous			1000	10 consecutive working days	17	Fig.-8	R and L temporo-parietal junction
Mylius et al. (2009)	95% RMT	1	Continuous			1200	5 consecutive days	20	Fig.-8	Left premotor cortex
Sokhadze et al. (2009)	90% MT	0.5	15	10	20–30	150	2 sessions/week 3 weeks	7.5–10	Fig.-8	DLPFC
Baruth et al. (2010)	90% MT	1	15	10	20–30	150	1 session/week 12 weeks	7.5–10	Fig.-8	Left/Right DLPFC
Kirton et al. (2010)[b]	100% RMT	1	Continuous			1200	8 days	20	Fig.-8	Motor cortex
Sokhadze et al. (2010)	90% MT	0.5	15	10	20–30	150	2 sessions/week 3 weeks	7.5–10	Fig.-8	Left DLPFC
Hu et al. (2011)	80% RMT	10	20	4	26	800	Daily	26	Fig.-8	Left prefrontal lobe
Kwon et al. (2011)	100% RMT	1	4	300	120	1200	10 sessions	26	Fig.-8	Supplementary motor area
Sun et al. (2011)	90% RMT	0.5	Continuous			3 × 500	1 session/day Daily 2 weeks	70	Fig.-8	Epileptogenic zone
Wall et al. (2011)	120% RMT	10	75	4	26	3000	30 sessions 5 days/week 6–8 weeks	37.5	Not specified	Left DLPFC
Casanova et al. (2012)	90% MT	1	15	10	20–30	150	1 session/week 12 weeks	7.5–10	Fig.-8	Left DLPFC; Right DLPFC
Croarkin et al. (2012)	120% RMT	10	75	4	26	3000	30 sessions 5 days/week 6-8 weeks	37.5	Not specified	Left prefrontal cortex
Helfrich et al. (2012)	80% RMT or 100% MSO	1	Continuous			900	1 session	15	Fig.-8	Left primary motor cortex
Jardri et al. (2012)	90% MT	1	Continuous			1200	2 sessions/day 5 consecutive days	20	Not specified	Left temporoparietal junction

Study									
Sokhadze et al. (2012)	90% RMT	1	15	20–30	150	7.5–10	1 session/week 12 weeks	Fig.-8	DLPFC and opposite side of DLPFC
Sun et al. (2012)	Group (A) 90% RMT Group (B) 20% RMT	0.5	Continuous		3 × 500	70	1 session/day Daily 2 weeks	Fig.-8	Epileptogenic focus
Weaver et al. (2012)	100% MT	10	50	26	2000	25	10 sessions 5 sessions/week	Fig.-8	Prefrontal cortex
Wu et al. (2012)[a]	55–80% AMT	30–50	Continuous Intermitent Θ-burst	8	600 600	0.667 3.167	43 sessions	Fig.-8	Motor cortex
Chiramberro et al. (2013)	100% RMT	10	60	25	3000	30	5 days/week 4 weeks	Fig.-8	Left DLPFC
Le et al. (2013)	110% RMT	1	Continuous		1200	20	5 days/week 4 weeks	Fig.-8	Supplementary motor area
Wall et al. (2013)	120% RMT	10	75	26	3000	37.5	30 sessions 6–8 weeks	Not specified	Left DLPFC
Gillick et al. (2014)	90% RMT 90% RMT	6 Hz-priming & 1 Hz	20 Continuous	25	600 600	10 10	5 alternative weekdays	Fig.-8	Contralesional primary motor cortex
Gomez et al. (2014)	90% RMT	1	Continuous		1500	25	5 consecutive days	Butterfly	Left DLPFC
Oberman et al. (2014)[a]	80% AMT	50	Continuous Θ-burst		600	0.667	1 session	Fig.-8	Left motor cortex
Sokhadze et al. (2014)	90% MT	1 Hz	9	20–30	180	5.7–7	18 sessions 1 session/week 18 weeks	Fig.-8	Left/Right/Bilateral DLPFC

R: right; L: left; MSO: maximum stimulator output; MT: motor threshold; RMT: resting motor threshold; AMT: active motor threshold; DLPFC: dorsolateral prefrontal cortex.

[a] Theta-burst stimulation (TBS).

[b] Sample consists of same subjects.

levels: 0.20% of blood alcohol ½ hour after seizure), despite being a "minor", prior to rTMS application [70]. For these reasons, researchers should carefully screen and remove potentially eligible subjects from inclusion if they report recent intake of alcohol or if they are taking epileptogenic medications, especially when there is not a significant benefit-to-risk ratio [3].

In another study included in this review, authors discussed the occurrence of neurocardiogenic syncope in 2 patients under 18 years of age following rTMS [89]. Both patients, who were participants of an rTMS randomized control trial, had a prior history of syncope (or presyncope) [98]. Even though the authors reported syncope as an adverse event, it is important to note that both cases of syncope occurred during subjects' initial exposure to TMS (i.e., single-pulse TMS), and not during rTMS. Vasovagal response has not been reported as an adverse effect of rTMS among children (as noted in a previous review) [60,63]; however, syncope has been reported as an adverse effect of rTMS in an elderly adult subject with depression [99]. This particular event was not thought to be related to the rTMS, as syncope occurred 6 h after cessation of the stimulation period [99]. In both children and adults, reported TMS-induced syncope lasted only a few minutes and subjects recovered spontaneously after cessation of stimulation, without any additional treatment [98,99]. Further, these studies reported that patients respond favorably to further rTMS without any subsequent syncopal events, suggesting that, unlike seizures, syncopal attacks may not require exclusion of the subject from the study. For safety purposes, we recommend screening subjects to identify possible history of syncope and/or predisposition to autonomic disorders, and employing suitable measures to minimize the incidence of syncope in these subjects (e.g., adequate hydration, recent food intake, gradual increase in TMS intensity, etc.) [98].

Several studies included in this review reported mild side effects after the application of rTMS [38,39,46,52,80,81,83,94]. The most commonly reported mild side effect was headache, with ∼35% of the studies citing at least one subject with this event. While the exact cause of TMS-related headache is not entirely clear, it is thought to be caused by the activation of muscles and nerves near the stimulation coil, which results in contraction/ twitches of the scalp and upper face muscles in some patients [3,58]. In all cases, headaches attributed to rTMS were mild and brief and were also observed in the *sham* TMS group [100]; a phenomenon that is consistent with the adult literature [101]. Mild headaches were also reported in conjunction with rTMS among children in a previous review [63], and as a side effect among adults in several previous studies [101,102]. Machii and others [101] reported that frontal area and low frequency rTMS were associated with higher rates of headaches in adults; however, our review did not corroborate a link between treatment area, or TMS intensity/frequency, and localized headache.

An additional minor side effect attributed to rTMS is tinnitus. Our review found two reported cases of tinnitus (0.6% incidence) [80]. While previous reviews on children/adolescents did not report the occurrence of tinnitus [59,60,63], tinnitus has been reported as a side effect of rTMS in adults [101]. While the exact reason for the occurrence of tinnitus is not clear, it appears that intensity, frequency, and site of treatment may play a role. In both cases reported in this review, the subjects underwent high intensity stimulation (90% RMT). These are consistent with Machii and colleagues [101], who reported 3 cases of tinnitus in adult subjects that had no history of the illness, and 2 complaints of tinnitus exacerbation in patients with a history of tinnitus after high intensity stimulation. In all 5 cases reported by Machii et al., patients were also subjected to high frequency stimulation; however, both subjects highlighted in this review underwent low
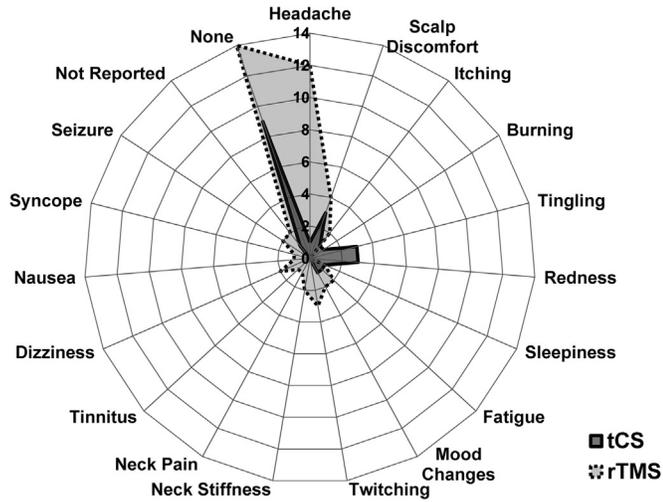
Figure 1. Radial plot depicting the reported adverse effects of repetitive transcranial magnetic stimulation (rTMS) and transcranial current stimulation (tCS) in children and adolescents from 51 studies (35 rTMS and 16 tCS). The angular data represent the reported adverse effects and the circular data represent the total number of studies reporting a particular adverse effect. 23 studies (14 rTMS and 9 tCS) reported no adverse effects. Scalp discomfort and minor headaches were the most commonly reported adverse effect of rTMS. Tingling, redness, and scalp discomfort were the most commonly reported adverse effect of tCS. Note that a study was counted for an adverse effect even if one subject was reported to have an adverse effect.

frequency stimulation. It is important to note, though, that the study that had reported tinnitus included both adults and children, and it was not clear from the manuscript whether tinnitus occurred in children or in adults. We made several attempts to contact the corresponding author to retrieve this information, but did not receive a response from them. As a result, we assumed that both cases occurred in children, although it is to be recognized that this may not be the case.

The effect of rTMS on neuropsychological functions, such as attention, learning, and memory has been well studied in adults [103–105]. These studies report no adverse effects of TMS on memory or cognition. Unfortunately, we were only able to retrieve a single study that specifically examined this issue in adolescents with depression [40]. The authors of this study reported no negative impact of rTMS on neurocognitive functioning, such as learning, memory, and executive function. Further, the authors of

one of the rTMS studies included in this review [38] followed eight of the nine subjects three years after their initial treatment for depression and reported no evidence of cognitive deterioration in any of their patients [106]. These data further support the long-term safety of rTMS in adolescents.

Safety of tCS

Our findings support the safety of tCS in children and adolescents with neurologic and neuropsychiatric disorders. The adverse effects reported were rare, mild, and transient; with "redness", "slight tingling", "itching", and "burning sensation" as the most commonly reported events. It is important to note that while the literature regarding the use of TMS is comprehensive, there is a paucity of studies (especially long-term intervention) on the application of tCS among children and adolescents.

Safety of tDCS application in adults has been well tested and established, and the few adverse side effects that have been reported were mild and transient [19,107,108]. Poreisz and colleagues [61] provided a detailed account of the adverse events associated with tDCS among healthy subjects as well as patients, and stated that mild tingling was the most common adverse effect. Itching and tingling under the electrodes, followed by headache and burning sensation, were also the most common adverse effects reported by several authors during and/or after direct current application [19,61,109,110]. Our findings are in accordance with previous studies, in that the most common side effects were redness, tingling, and itching (Tables 1 and 3; Figs. 1 and 2). These discomforts are mostly related to the electrode site (especially on the electrode over the supraorbital region), and are associated with the onset of the bout of stimulation. Our review also highlights that the mild adverse events reported in conjunction with tCS usually disappeared within a few minutes after the beginning of the stimulation. None of adverse events lasted longer than 2 h after cessation of the stimulation, and no studies reported delayed onset side effects [35,43,82]. Approximately 60% of the studies reported that tCS was well tolerated, and no adverse events were noted. Given the physics and physiology of tCS, minor nuisance sensations such as tingling, itching, or slight burning are virtually unavoidable, and thus in all likelihood, these studies did not specifically consider reporting transient minor side effects. Therefore, to fully document all adverse effects related to tCS, we support the use of the
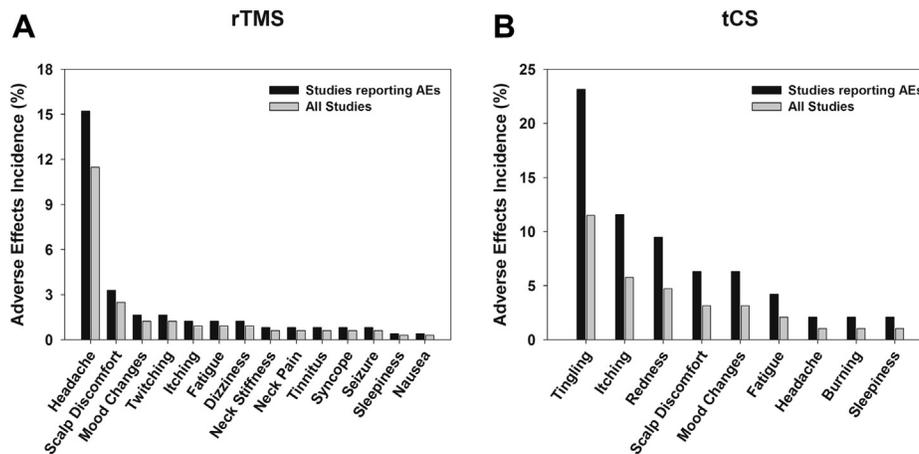

Figure 2. Bar graphs representing the incidence (i.e., frequency) of various adverse effects reported for (A) rTMS and (B) tCS in children/adolescents. The gray bars indicate the percentage of each adverse event calculated based on the total number of subjects ($N = 322$ for rTMS, $N = 191$ for tCS) and the black bars indicate a conservative estimate of the percentage of each adverse event calculated based on the total number of subjects on the studies that reported an adverse event ($N = 243$ for rTMS and $N = 95$ for tCS). The conservative estimate assumed that only those studies that reported an adverse event attempted to capture the incidence of adverse effects using appropriate follow-up or questionnaires.

Table 3
Transcranial current stimulation (tCS) parameters used in the studies included in the review.

Articles	Electrode size (cm^2)	Intensity (mA)/Current density (mA/cm^2)	Electrode site	Time (Minutes)	Sessions
Bogdanov et al. (1994)	6.0	I: 0.2–0.8 D: 0.04–0.16	A: frontal region C: sensorimotor cortex/mastoid process	Up to 20 (1st 3 sessions) 45–50 (subsequent)	7–15 sessions 3–4 sessions/week
Alon et al. (1998)[b]	11.34	I: 0.5 peak D: 0.044 peak	Right and left temporal area	10	Twice a day 7 days/week 8-weeks
Shelyakin et al. (2001)	5.0	I: 0.3–0.7 D: 0.06–0.14	A: projection of the posterior temporal area C: projection of the parietal area	20–40	Every day or every two day Up to 15 sessions
Ilyukhina et al. (2005)	Not reported	I: 0.03–0.08 D: Unknown	A: left frontal and parietal cortex C: not reported	15–20	Up to 6 sessions 1-2 weeks interval between sessions
Mattai et al. (2011)[a]	25.0	I: 2.0 D: 0.08	A: DLPFC or non-dominat forearm C: STG or non-dominat forearm	20	1 session/day 5 days/week 2 weeks
San-Juan et al. (2011)	0.15	Case (A): I: 1.0/D: 6.6 Case (B): I: 2.0/D: 13.2	Case A A: contralateral supraorbital area C: scalp (C3) Case B A: scalp (F2) C: scalp (F8)	60	4 (0, 7, 30 and 60 days)
Schneider et al. (2011)	25.0	I: 2.0 D: 0.08	A: DLPFC (F3) C: Right supraorbital area	30	1 session
Varga et al. (2011)	25.0	I: 1.0 D: 0.04	A: epileptogenic focus (Peak −ve) C: epileptogenic focus (Peak +ve)	20	1 session
Yook et al. (2011)	25.0	I: 2.0 D: 0.08	A: left supraorbital C: right temporo-parietal area	20	1 session/day 5 days/week 2 weeks
Andrade et al. (2013)[a]	35.0	I: 1.0 (1st min) 2.0 (30 min) D: 0.057	A: broca area C: right supraorbital	1 30	1 session/day 5 consecutive days
Auvichayapat et al. (2013)[a]	35.0	I: 1.0 D: 0.029	A: contralateral shoulder area C: epileptogenic focus	20	1 session
Young et al. (2013)a	35.0	I: 1.0 D: 0.029	A: contralateral supraorbital C: motor cortex	9 + 20 (pause) + 9	1 session
Grecco et al. (2014)	25.0	I: 1.0 D: 0.04	A: motor cortex C: contralateral supraorbital	20	1 session/day 5 days/week 2 weeks
Duarte et al. (2014)[a]	25.0	I: 1.0 D: 0.04	A: motor cortex C: contralateral supraorbital	20	1 session/day 5 days/week 2 weeks
Prehn-Kristensen et al. (2014)[b]	0.503	I: 0.25 peak D: 0.497 peak	A: bilateral frontolateral (F3, F4) C: bilateral mastoid (M1, M2)	5 × 5 1 min rest between blocks	1 session
Young et al. (2014)[a]	35.0	I: 1.0 D: 0.029	A: contralateral supraorbital C: motor cortex	9 + 20 (pause) + 9	1 session

A: anode; C: cathode; I: intensity; D: density; STG: superior temporal gyrus; DLPFC: dorsolateral prefrontal cortex.
[a] Studies that reported mild adverse effects.
[b] Studies that used transcranial alternating current stimulation.

questionnaire proposed by Brunoni and colleagues, which systematically characterizes the severity of each of the possible adverse effects of tCS, along with a risk attribution scale [110].

There are various factors that can influence a subject's perception of comfort during the application of tDCS. It is well known that intensity of current, as well as density and electrode size can modulate the tingling and itch perception during transcranial stimulation. A recent study by Dundas and colleagues [111] has also demonstrated a relationship between the solution concentration for electrode placement and the perception of comfort, such that higher concentrations (220 mM) are perceived as less comfortable than lower concentrations of NaCl solution (15 mM). Although current density and electrode sizes have been well-described by the published papers in this review, no papers reported electrolytic concentration of saline solution used during stimulation. A limitation of this review was an inherent assumption that most studies used normal saline (i.e., 0.9% NaCl solution), due to its common availability. The 0.9% saline solution contains 154 mM of NaCl per liter, which is slightly above the recommended concentration for

optimal subject comfort [111]. Hence, it may be beneficial to reduce the concentration (e.g., <100 mM) of the saline solution in the event that a subject reports unusual discomfort during tDCS application. We suggest that all future studies report the concentration of the electrolyte solution along with the related observed adverse effects, as this would enable researchers to better understand the relationship between electrolyte concentration and perceived comfort during stimulation.

Recently, a few reports have indicated the occurrence of skin lesions after repeated tDCS application in adults with no history of skin disease or injury [51,112,113]. There is also a report of delayed onset contact dermatitis after a single bout of tDCS in a single adult subject [114]. Interestingly, none of the studies in our review among children and adolescents reported any of these same adverse effects that have been noted in adults. The reported skin lesions after repeated tDCS application in adults have been attributed to the use of water soaked sponge electrodes, instead of the conventional saline soaked sponge electrodes [113,115]. Hence, it is possible that skin related adverse effects were not observed in our review, as all studies used saline
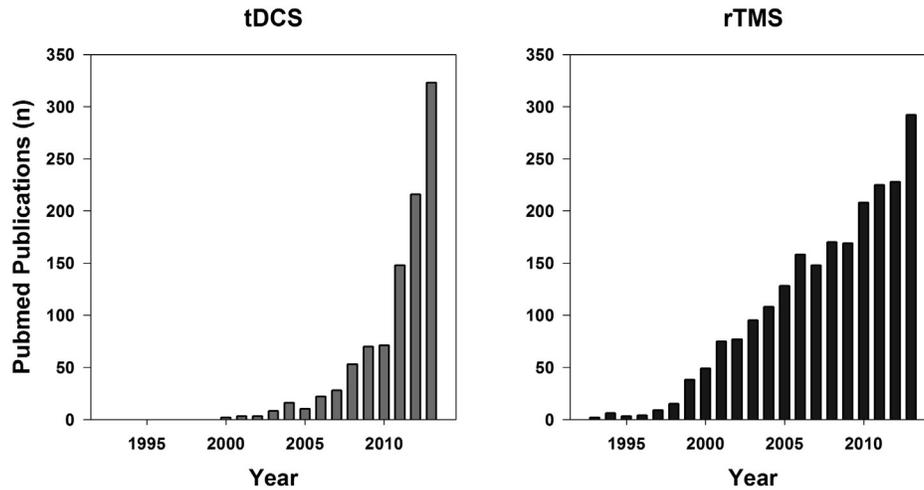
Figure 3. Bar charts representing number of published papers per year on tDCS (left panel) and rTMS (right panel) until 2013. The search was conducted on the PubMed database using the search terms "transcranial direct current stimulation" and "repetitive transcranial magnetic stimulation."

soaked sponge electrodes. It is also plausible that skin lesions did not occur because very few studies occurred over a long duration. Regardless, and based on the currently-available evidence, we recommend that researchers carefully and regularly monitor the skin under the electrode site, before each tDCS session, and only use saline soaked sponges to minimize risk of skin lesions.

It is important to note that only seven [23,25,69,72,82] of the 16 tCS studies had interventions beyond 10 sessions, and were prospective in nature. While these studies demonstrated adequate safety of tCS in children and adolescents, future research is needed to better understand the benefits and tolerance of long-term use of tCS in children. Although several studies have demonstrated no brain tissue damage on animal models and humans after direct stimulation [19,22,116,117], there is a well-accepted threshold of tCS current density (<142.9 A/m^2 or 14.29 mA/cm^2) [118], above which

has been theorized to be harmful to the brain structures. The current density commonly used for tCS studies, including those presented in this review (0.029–13.2 mA/cm^2), is typically lower than the aforementioned threshold. Moreover, unlike rTMS, tCS does not elicit action potentials in the cortical neurons, which is thought to minimize the risk of serious adverse events, such as seizures. It is thus reasonable to posit that tCS could be as safe as rTMS for long-term interventions in children.

Recommendations for NIBS reporting standards

Despite the growing number of publications pertaining to NIBS modalities in children, adolescents, and adults, there are no definitive standards for reporting NIBS data, especially for tCS. Further, very few studies systematically quantify adverse events by reporting
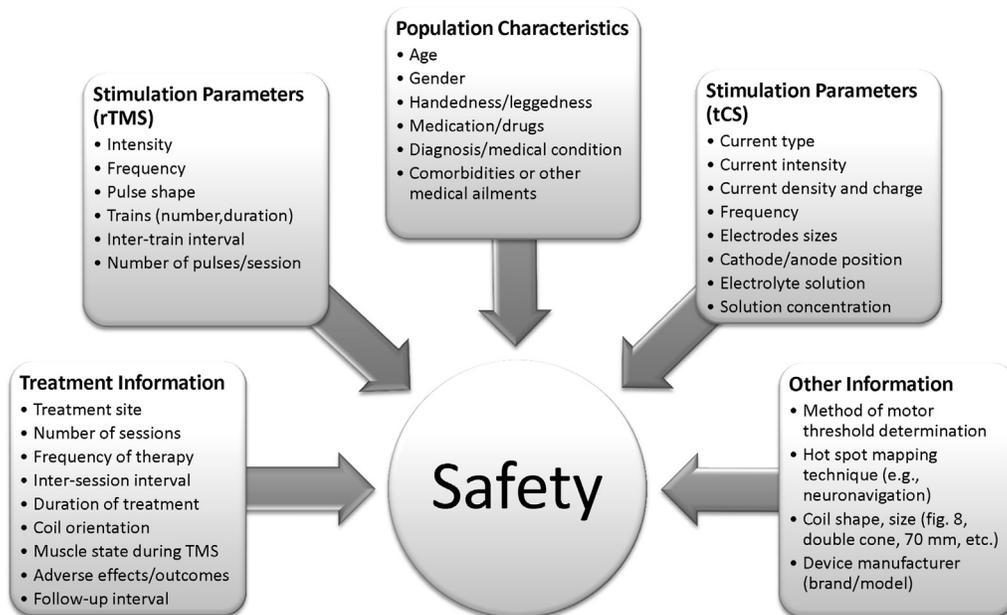

Figure 4. Reporting guidelines for noninvasive brain stimulation (NIBS) research. We suggest that authors consider including detailed information regarding various factors that could influence safety and efficacy when constructing manuscripts for publication. A checklist for reporting standards is also included in the Supplementary Material, which could serve as a guideline for writing NIBS manuscripts.

the frequency of a side-effect. As a result and at present, it was impossible to perform an appropriate meta-analysis on this topic, or to understand the granular associations between every potential combination of NIBS parameter and potential safety outcomes. In order to improve the critical appraisal of published investigations for device safety and efficacy, we suggest that authors include detailed information regarding various factors that could influence safety and efficacy (e.g., stimulation parameters, technical factors, patient demographics, etc.) and clearly report the frequency of all adverse effects observed in their population when constructing manuscripts for publication (Fig. 4 and Supplementary Materials 1 & 2).

Potential limitations

There are some limitations to this review that are worth discussing. While our pooled sample size exceeds 500 subjects, it is still relatively small to detect rare adverse events. Further, as mentioned, very few studies have evaluated the long-term effects of NIBS in children/adolescents, which makes it difficult to understand the effects of long-term use of NIBS in this population. Moreover, unlike for TMS use, there are no clear dosage and safety guidelines for tCS use (other than the density criteria), which restrict our ability to evaluate whether tCS studies utilized parameters that are physiologically safe. Finally, many of the studies included in the review were not designed as a safety study, *per se*, and perhaps did not quantify adverse effects through appropriate questionnaires or follow-ups. As a result, it is likely that the frequency of adverse events reported may not reflect the true incidence of an adverse event in this population. It is to be noted that while there are a few studies in adults that have included physiological data (e.g., MRI-based structural or physiological alterations), or blood samples (e.g., serum markers of neuron specific enolase or protein S-100) to quantify alterations at the molecular levels [116,119,120], such studies are lacking in the youth population. Therefore, we recommend that readers consider these limitations while interpreting the study results.

Conclusion

This is the first attempt to evaluate and provide a comprehensive review on safety of both TMS and tCS in children and adolescents. Our review identified 51 studies involving children less than 18 years of age of which 48 discussed adverse events. In over 322 subjects, rTMS caused seizure in two subjects and neurocardiogenic syncope in two subjects. In all four cases, the subjects had potential risk factors for seizure or neurocardiogenic syncope prior to involvement. In more than 191 children that underwent tCS, no subject experienced any major side effects. These data support the feasibility, tolerability, and safety of NIBS, and especially tCS, for children and adolescents. When conducting NIBS studies on human subjects, researchers should be aware of the most common adverse effects attributed to the application of NIBS. All risks should be openly discussed with patients, parents, and/or caregivers so that they can make informed treatment decisions and consent/assent. *A priori* screening of all subjects, based on the established guidelines, would substantially help to better identify high risk patients and minimize adverse events. We recommend that future studies systematically record and report all adverse events so that all potential side effects of NIBS may be adequately understood (e.g., Supplementary Material 1). We also suggest providing adequate detail on the TMS/tCS parameters and dosage so that potential mediating links between these factors and safety outcomes can be discerned (e.g., Supplementary Material 2). There is a need to conduct more controlled clinical trials, with longer follow-up periods, in order to evaluate the long-term effects of these technologies in a young population, as well as to develop optimum parameters for generating the desired therapeutic effects.

Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.brs.2014.10.012.

The supplementary PDF files are fillable forms that can be used (1) to systematically document adverse events and/or (2) as a checklist to prepare rTMS or tCS manuscripts for publication. To ensure that these documents open properly, please download/save the files first and open it with Adobe Acrobat Professional software.

References

[1] Guleyupoglu B, Schestatsky P, Edwards D, Fregni F, Bikson M. Classification of methods in transcranial electrical stimulation (tES) and evolving strategy from historical approaches to contemporary innovations. J Neurosci Methods 2013;219(2):297–311.

[2] Nitsche MA, Paulus W. Excitability changes induced in the human motor cortex by weak transcranial direct current stimulation. J Physiol 2000;527(Pt 3):633–9.

[3] Rossi S, Hallett M, Rossini PM, Pascual-Leone A, Safety of TMS Consensus Group. Safety, ethical considerations, and application guidelines for the use of transcranial magnetic stimulation in clinical practice and research. Clin Neurophysiol 2009;120(12):2008–39.

[4] Kobayashi M, Pascual-Leone A. Transcranial magnetic stimulation in neurology. Lancet Neurol 2003;2(3):145–56.

[5] Eldaief MC, Press DZ, Pascual-Leone A. Transcranial magnetic stimulation in neurology: a review of established and prospective applications. Neurol Clin Pract 2013;3(6):519–26.

[6] Paulus W, Peterchev AV, Ridding M. Transcranial electric and magnetic stimulation: technique and paradigms. Handb Clin Neurol 2013;116:329–42.

[7] Webster BR, Celnik PA, Cohen LG. Noninvasive brain stimulation in stroke rehabilitation. NeuroRx 2006;3(4):474–81.

[8] Radhu N, de Jesus DR, Ravindran LN, Zanjani A, Fitzgerald PB, Daskalakis ZJ. A meta-analysis of cortical inhibition and excitability using transcranial magnetic stimulation in psychiatric disorders. Clin Neurophysiol 2013;124(7):1309–20.

[9] Edwards MJ, Talelli P, Rothwell JC. Clinical applications of transcranial magnetic stimulation in patients with movement disorders. Lancet Neurol 2008;7(9):827–40.

[10] Nitsche MA, Paulus W. Noninvasive brain stimulation protocols in the treatment of epilepsy: current state and perspectives. Neurotherapeutics 2009;6(2):244–50.

[11] Boggio PS, Nunes A, Rigonatti SP, Nitsche MA, Pascual-Leone A, Fregni F. Repeated sessions of noninvasive brain DC stimulation is associated with motor function improvement in stroke patients. Restor Neurol Neurosci 2007;25(2):123–9.

[12] Davis NJ, van Koningsbruggen MG. "Non-invasive" brain stimulation is not non-invasive. Front Syst Neurosci 2013;7:76.

[13] Krishnan C, Dhaher Y. Corticospinal responses of quadriceps are abnormally coupled with hip adductors in chronic stroke survivors. Exp Neurol 2012;233(1):400–7.

[14] Krishnan C, Ranganathan R, Kantak SS, Dhaher YY, Rymer WZ. Active robotic training improves locomotor function in a stroke survivor. J Neuroeng Rehabil 2012;9:57.

[15] Pascual-Leone A, Tormos JM, Keenan J, Tarazona F, Canete C, Catala MD. Study and modulation of human cortical excitability with transcranial magnetic stimulation. J Clin Neurophysiol 1998;15(4):333–43.

[16] Madhavan S, Krishnan C, Jayaraman A, Rymer WZ, Stinear JW. Corticospinal tract integrity correlates with knee extensor weakness in chronic stroke survivors. Clin Neurophysiol 2011;122(8):1588–94.

[17] Peterchev AV, Wagner TA, Miranda PC, et al. Fundamentals of transcranial electric and magnetic stimulation dose: definition, selection, and reporting practices. Brain Stimul 2012;5(4):435–53.

[18] Mix A, Benali A, Eysel UT, Funke K. Continuous and intermittent transcranial magnetic theta burst stimulation modify tactile learning performance and cortical protein expression in the rat differently. Eur J Neurosci 2010;32(9):1575–86.

[19] Nitsche MA, Cohen LG, Wassermann EM, et al. Transcranial direct current stimulation: state of the art 2008. Brain Stimul 2008;1(3):206–23.

[20] Nitsche MA, Liebetanz D, Lang N, Antal A, Tergau F, Paulus W. Safety criteria for transcranial direct current stimulation (tDCS) in humans. Clin Neurophysiol 2003;114(11):2220–2. author reply 2–3.

[21] Nitsche MA, Nitsche MS, Klein CC, Tergau F, Rothwell JC, Paulus W. Level of action of cathodal DC polarisation induced inhibition of the human motor cortex. Clin Neurophysiol 2003;114(4):600–4.

[22] Nitsche MA, Paulus W. Sustained excitability elevations induced by transcranial DC motor cortex stimulation in humans. Neurology 2001;57(10):1899–901.

[23] Bogdanov OV, Pinchuk D, Pisar'kova EV, Shelyakin AM, Sirbiladze KT. The use of the method of transcranial micropolarization to decrease the severity hyperkineses in patients with infantile cerebral palsy. Neurosci Behav Physiol 1994;24(5):442–5.

[24] Ilyukhina VA, Kozhushko NY, Matveev YK, Ponomareva EA, Chernysheva EM, Shaptilei MA. Transcranial micropolarization in the combined therapy of speech and general psychomotor retardation in children of late preschool age. Neurosci Behav Physiol 2005;35(9):969–76.

[25] Shelyakin AM, Preobrazhenskaya IG, Kassil MV, Bogdanov OV. The effects of transcranial micropolarization on the severity of convulsive fits in children. Neurosci Behav Physiol 2001;31(5):555–60.

[26] Stagg CJ, Nitsche MA. Physiological basis of transcranial direct current stimulation. Neuroscientist 2011;17(1):37–53.

[27] Arul-Anandam AP, Loo C, Sachdev P. Transcranial direct current stimulation – what is the evidence for its efficacy and safety? F1000 Med Rep 2009:1.

[28] Krishnan C, Ranganathan R, Kantak SS, Dhaher YY, Rymer WZ. Anodal transcranial direct current stimulation alters elbow flexor muscle recruitment strategies. Brain Stimul 2014;7(3):443–50.

[29] Cotelli M, Manenti R, Petesi M, et al. Treatment of primary progressive aphasias by transcranial direct current stimulation combined with language training. J Alzheimers Dis 2014;39(4):799–808.

[30] Berthier ML, Pulvermuller F. Neuroscience insights improve neurorehabilitation of poststroke aphasia. Nat Rev Neurol 2011;7(2):86–97.

[31] Andrade AC, Magnavita GM, Allegro JV, Neto CE, Lucena RD, Fregni F. Feasibility of transcranial direct current stimulation use in children aged 5 to 12 Years. J Child Neurol 2014;29(10):1360–5.

[32] Schneider HD, Hopp JP. The use of the Bilingual Aphasia Test for assessment and transcranial direct current stimulation to modulate language acquisition in minimally verbal children with autism. Clin Linguist Phon 2011;25(6–7):640–54.

[33] Wu AD, Fregni F, Simon DK, Deblieck C, Pascual-Leone A. Noninvasive brain stimulation for Parkinson's disease and dystonia. Neurotherapeutics 2008;5(2):345–61.

[34] Young SJ, Bertucco M, Sanger TD. Cathodal transcranial direct current stimulation in children with dystonia: a sham-controlled study. J Child Neurol 2014;29(2):232–9.

[35] Young SJ, Bertucco M, Sheehan-Stross R, Sanger TD. Cathodal transcranial direct current stimulation in children with dystonia: a pilot open-label trial. J Child Neurol 2013;28(10):1238–44.

[36] Iyer MB, Schleper N, Wassermann EM. Priming stimulation enhances the depressant effect of low-frequency repetitive transcranial magnetic stimulation. J Neurosci 2003;23(34):10867–72.

[37] Pascual-Leone A, Rubio B, Pallardo F, Catala MD. Rapid-rate transcranial magnetic stimulation of left dorsolateral prefrontal cortex in drug-resistant depression. Lancet 1996;348(9022):233–7.

[38] 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(2):156–9.

[39] 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(1):56–64.

[40] Wall CA, Croarkin PE, McClintock SM, et al. Neurocognitive effects of repetitive transcranial magnetic stimulation in adolescents with major depressive disorder. Front Psychiatry 2013;4:165.

[41] Berlim MT, Van den Eynde F, Daskalakis ZJ. Clinical utility of transcranial direct current stimulation (tDCS) for treating major depression: a systematic review and meta-analysis of randomized, double-blind and sham-controlled trials. J Psychiatr Res 2013;47(1):1–7.

[42] Tergau F, Naumann U, Paulus W, Steinhoff BJ. Low-frequency repetitive transcranial magnetic stimulation improves intractable epilepsy. Lancet 1999;353(9171):2209.

[43] Auvichayapat N, Rotenberg A, Gersner R, et al. Transcranial direct current stimulation for treatment of refractory childhood focal epilepsy. Brain Stimul 2013;6(4):696–700.

[44] Brasil-Neto JP, de Araujo DP, Teixeira WA, Araujo VP, Boechat-Barros R. Experimental therapy of epilepsy with transcranial magnetic stimulation: lack of additional benefit with prolonged treatment. Arq Neuropsiquiatr 2004;62(1):21–5.

[45] Kinoshita M, Ikeda A, Begum T, Yamamoto J, Hitomi T, Shibasaki H. Low-frequency repetitive transcranial magnetic stimulation for seizure suppression in patients with extratemporal lobe epilepsy – a pilot study. Seizure 2005;14(6):387–92.

[46] Morales OG, Henry ME, Nobler MS, Wassermann EM, Lisanby SH. Electroconvulsive therapy and repetitive transcranial magnetic stimulation in children and adolescents: a review and report of two cases of epilepsia partialis continua. Child Adolesc Psychiatr Clin N Am 2005;14(1):193–210 [viii–ix].

[47] Varga ET, Terney D, Atkins MD, et al. Transcranial direct current stimulation in refractory continuous spikes and waves during slow sleep: a controlled study. Epilepsy Res 2011;97(1–2):142–5.

[48] Lipton RB, Dodick DW, Silberstein SD, et al. Single-pulse transcranial magnetic stimulation for acute treatment of migraine with aura: a randomised, double-blind, parallel-group, sham-controlled trial. Lancet Neurol 2010;9(4):373–80.

[49] Lo YL. Headache: migraine, magnetic stimulation and cortical excitability. Nat Rev Neurol 2010;6(8):425–7.

[50] Hummel FC, Cohen LG. Non-invasive brain stimulation: a new strategy to improve neurorehabilitation after stroke? Lancet Neurol 2006;5(8):708–12.

[51] Duarte Nde A, Grecco LA, Galli M, Fregni F, Oliveira CS. Effect of transcranial direct-current stimulation combined with treadmill training on balance and functional performance in children with cerebral palsy: a double-blind randomized controlled trial. PLoS One 2014;9(8):e105777.

[52] 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(1):44–52.

[53] Grecco LA, Duarte Nde A, de Mendonca ME, et al. Effect of transcranial direct current stimulation combined with gait and mobility training on functionality in children with cerebral palsy: study protocol for a double-blind randomized controlled clinical trial. BMC Pediatr 2013;13:168.

[54] Mondino M, Bennabi D, Poulet E, Galvao F, Brunelin J, Haffen E. Can transcranial direct current stimulation (tDCS) alleviate symptoms and improve cognition in psychiatric disorders? World J Biol Psychiatry 2014;15(4):261–75.

[55] Sokhadze EM, El-Baz AS, Sears LL, Opris I, Casanova MF. rTMS neuromodulation improves electrocortical functional measures of information processing and behavioral responses in autism. Front Syst Neurosci 2014;8:134.

[56] Graff-Guerrero A, Gonzales-Olvera J, Ruiz-Garcia M, Avila-Ordonez U, Vaugier V, Garcia-Reyna JC. rTMS reduces focal brain hyperperfusion in two patients with EPC. Acta Neurol Scand 2004;109(4):290–6.

[57] Baruth JM, Casanova MF, El-Baz A, et al. Low-frequency repetitive transcranial magnetic stimulation (rTMS) modulates evoked-gamma frequency oscillations in autism spectrum disorder (ASD). J Neurother 2010;14(3):179–94.

[58] 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):1–16.

[59] Quintana H. Transcranial magnetic stimulation in persons younger than the age of 18. J ECT 2005;21(2):88–95.

[60] Vicario CM, Nitsche MA. Non-invasive brain stimulation for the treatment of brain diseases in childhood and adolescence: state of the art, current limits and future challenges. Front Syst Neurosci 2013;7:94.

[61] Poreisz C, Boros K, Antal A, Paulus W. Safety aspects of transcranial direct current stimulation concerning healthy subjects and patients. Brain Res Bull 2007;72(4–6):208–14.

[62] Gilbert DL, Garvey MA, Bansal AS, Lipps T, Zhang J, Wassermann EM. Should transcranial magnetic stimulation research in children be considered minimal risk? Clin Neurophysiol 2004;115(8):1730–9.

[63] D'Agati D, Bloch Y, Levkovitz Y, Reti I. rTMS for adolescents: safety and efficacy considerations. Psychiatry Res 2010;177(3):280–5.

[64] 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(5):2039–44.

[65] 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(1):132–8.

[66] Mylius V, Gerstner A, Peters M, et al. Low-frequency rTMS of the premotor cortex reduces complex movement patterns in a patient with pantothenate kinase-associated neurodegenerative disease (PKAN). Neurophysiol Clin 2009;39(1):27–30.

[67] Rotenberg A, Depositario-Cabacar D, Bae EH, Harini C, Pascual-Leone A, Takeoka M. Transient suppression of seizures by repetitive transcranial magnetic stimulation in a case of Rasmussen's encephalitis. Epilepsy Behav 2008;13(1):260–2.

[68] San-Juan D, Calcaneo Jde D, Gonzalez-Aragon MF, et al. Transcranial direct current stimulation in adolescent and adult Rasmussen's encephalitis. Epilepsy Behav 2011;20(1):126–31.

[69] Yook SW, Park SH, Seo JH, Kim SJ, Ko MH. Suppression of seizure by cathodal transcranial direct current stimulation in an epileptic patient – a case report. Ann Rehabil Med 2011;35(4):579–82.

[70] 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(5):830–1.

[71] Fregni F, Boggio PS, Valle AC, et al. Homeostatic effects of plasma valproate levels on corticospinal excitability changes induced by 1Hz rTMS in patients with juvenile myoclonic epilepsy. Clin Neurophysiol 2006;117(6):1217–27.

[72] Alon G, Syron SC, Smith GV. Is transcranial electrical stimulation (TCES) a safe intervention for children with cerebral palsy? Neurorehabil Neural Repair 1998;12:65–72.

[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(11):e50073.

[74] Prehn-Kristensen A, Munz M, Goder R, et al. Transcranial oscillatory direct current stimulation during sleep improves declarative memory consolidation in children with attention-deficit/hyperactivity disorder to a level comparable to healthy controls. Brain Stimul 2014. http://dx.doi.org/10.1016/j.brs.2014.07.036.

[75] Oberman LM, Pascual-Leone A, Rotenberg A. Modulation of corticospinal excitability by transcranial magnetic stimulation in children and adolescents with autism spectrum disorder. Front Hum Neurosci 2014;8:627.

[76] 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(9):947–9.

[77] 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(7):534–8.

[78] 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(1):40–4.

[79] Wall CA, Croarkin PE, Sim LA, et al. Adjunctive use of repetitive transcranial magnetic stimulation in depressed adolescents: a prospective, open pilot study. J Clin Psychiatry 2011;72(9):1263–9.

[80] Sun W, Mao W, Meng X, et al. Low-frequency repetitive transcranial magnetic stimulation for the treatment of refractory partial epilepsy: a controlled clinical study. Epilepsia 2012;53(10):1782–9.

[81] Weaver L, Rostain AL, Mace W, Akhtar U, Moss E, O'Reardon JP. Transcranial magnetic stimulation (TMS) in the treatment of attention-deficit/hyperactivity disorder in adolescents and young adults: a pilot study. J ECT 2012;28(2):98–103.

[82] Mattai A, Miller R, Weisinger B, et al. Tolerability of transcranial direct current stimulation in childhood-onset schizophrenia. Brain Stimul 2011;4(4):275–80.

[83] 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(2):257–62.

[84] Grecco LA, Duarte ND, Mendonca ME, et al. Transcranial direct current stimulation during treadmill training in children with cerebral palsy: a randomized controlled double-blind clinical trial. Res Dev Disabil 2014;35(11):2840–8.

[85] 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(5):760–2.

[86] Casanova MF, Baruth JM, El-Baz A, Tasman A, Sears L, Sokhadze E. Repetitive transcranial magnetic stimulation (rTMS) modulates event-related potential (ERP) indices of attention in autism. Transl Neurosci 2012;3(2):170–80.

[87] Sokhadze EM, Baruth JM, Sears L, Sokhadze GE, El-Baz AS, Casanova MF. Prefrontal neuromodulation using rTMS improves error monitoring and correction function in autism. Appl Psychophysiol Biofeedback 2012;37(2):91–102.

[88] Loo C, McFarquhar T, Walter G. Transcranial magnetic stimulation in adolescent depression. Australas Psychiatry 2006;14(1):81–5.

[89] Kirton A, Chen R, Friefeld S, Gunraj C, Pontigon AM, Deveber G. Contralesional repetitive transcranial magnetic stimulation for chronic hemiparesis in subcortical paediatric stroke: a randomised trial. Lancet Neurol 2008;7(6):507–13.

[90] Sokhadze EM, El-Baz A, Baruth J, Mathai G, Sears L, Casanova MF. Effects of low frequency repetitive transcranial magnetic stimulation (rTMS) on gamma frequency oscillations and event-related potentials during processing of illusory figures in autism. J Autism Dev Disord 2009;39(4):619–34.

[91] Kirton A, Deveber G, Gunraj C, Chen R. Cortical excitability and interhemispheric inhibition after subcortical pediatric stroke: plastic organization and effects of rTMS. Clin Neurophysiol 2010;121(11):1922–9.

[92] Sokhadze E, Baruth J, Tasman A, et al. Low-frequency repetitive transcranial magnetic stimulation (rTMS) affects event-related potential measures of novelty processing in autism. Appl Psychophysiol Biofeedback 2010;35(2):147–61.

[93] 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):1–4.

[94] 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(7):636–9.

[95] Segrave RA, Arnold S, Hoy K, Fitzgerald PB. Concurrent cognitive control training augments the antidepressant efficacy of tDCS: a pilot study. Brain Stimul 2014;7(2):325–31.

[96] Reis J, Fritsch B. Modulation of motor performance and motor learning by transcranial direct current stimulation. Curr Opin Neurol 2011;24(6):590–6.

[97] Rossi S, Hallett M, Rossini PM, Pascual-Leone A. Screening questionnaire before TMS: an update. Clin Neurophysiol 2011;122(8):1686.

[98] Kirton A, Deveber G, Gunraj C, Chen R. Neurocardiogenic syncope complicating pediatric transcranial magnetic stimulation. Pediatr Neurol 2008;39(3):196–7.

[99] Figiel GS, Epstein C, McDonald WM, et al. The use of rapid-rate transcranial magnetic stimulation (rTMS) in refractory depressed patients. J Neuropsychiatry Clin Neurosci 1998;10(1):20–5.

[100] 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 2014. http://dx.doi.org/10.1016/j.apmr.2014.09.012.

[101] Machii K, Cohen D, Ramos-Estebanez C, Pascual-Leone A. Safety of rTMS to non-motor cortical areas in healthy participants and patients. Clin Neurophysiol 2006;117(2):455–71.

[102] Janicak PG, O'Reardon JP, Sampson SM, et al. Transcranial magnetic stimulation in the treatment of major depressive disorder: a comprehensive summary of safety experience from acute exposure, extended exposure, and during reintroduction treatment. J Clin Psychiatry 2008;69(2):222–32.

[103] Loo CK, Mitchell PB, McFarquhar TF, Malhi GS, Sachdev PS. A sham-controlled trial of the efficacy and safety of twice-daily rTMS in major depression. Psychol Med 2007;37(3):341–9.

[104] O'Connor M, Brenninkmeyer C, Morgan A, et al. Relative effects of repetitive transcranial magnetic stimulation and electroconvulsive therapy on mood and memory: a neurocognitive risk-benefit analysis. Cogn Behav Neurol 2003;16(2):118–27.

[105] Vanderhasselt MA, De Raedt R, Leyman L, Baeken C. Acute effects of repetitive transcranial magnetic stimulation on attentional control are related to antidepressant outcomes. J Psychiatry Neurosci 2009;34(2):119–26.

[106] Mayer G, Aviram S, Walter G, Levkovitz Y, Bloch Y. Long-term follow-up of adolescents with resistant depression treated with repetitive transcranial magnetic stimulation. J ECT 2012;28(2):84–6.

[107] Iyer MB, Mattu U, Grafman J, Lomarev M, Sato S, Wassermann EM. Safety and cognitive effect of frontal DC brain polarization in healthy individuals. Neurology 2005;64(5):872–5.

[108] Gandiga PC, Hummel FC, Cohen LG. Transcranial DC stimulation (tDCS): a tool for double-blind sham-controlled clinical studies in brain stimulation. Clin Neurophysiol 2006;117(4):845–50.

[109] Kessler SK, Turkeltaub PE, Benson JG, Hamilton RH. Differences in the experience of active and sham transcranial direct current stimulation. Brain Stimul 2012;5(2):155–62.

[110] Brunoni AR, Amadera J, Berbel B, Volz MS, Rizzerio BG, Fregni F. A systematic review on reporting and assessment of adverse effects associated with transcranial direct current stimulation. Int J Neuropsychopharmacol 2011;14(8):1133–45.

[111] Dundas JE, Thickbroom GW, Mastaglia FL. Perception of comfort during transcranial DC stimulation: effect of NaCl solution concentration applied to sponge electrodes. Clin Neurophysiol 2007;118(5):1166–70.

[112] Palm U, Keeser D, Schiller C, et al. Skin lesions after treatment with transcranial direct current stimulation (tDCS). Brain Stimul 2008;1(4):386–7.

[113] Frank E, Wilfurth S, Landgrebe M, Eichhammer P, Hajak G, Langguth B. Anodal skin lesions after treatment with transcranial direct current stimulation. Brain Stimul 2010;3(1):58–9.

[114] Riedel P, Kabisch S, Ragert P, von Kriegstein K. Contact dermatitis after transcranial direct current stimulation. Brain Stimul 2012;5(3):432–4.

[115] Palm U, Feichtner KB, Hasan A, et al. The role of contact Media at the skin-electrode interface during transcranial direct current stimulation (tDCS). Brain Stimul 2014;7(5):762–4.

[116] Nitsche MA, Niehaus L, Hoffmann KT, et al. MRI study of human brain exposed to weak direct current stimulation of the frontal cortex. Clin Neurophysiol 2004;115(10):2419–23.

[117] Vandermeeren Y, Jamart J, Ossemann M. Effect of tDCS with an extracephalic reference electrode on cardio-respiratory and autonomic functions. BMC Neurosci 2010;11:38.

[118] Liebetanz D, Koch R, Mayenfels S, Konig F, Paulus W, Nitsche MA. Safety limits of cathodal transcranial direct current stimulation in rats. Clin Neurophysiol 2009;120(6):1161–7.

[119] Chaieb L, Antal A, Pisoni A, et al. Safety of 5 kHz tACS. Brain Stimul 2014;7(1):92–6.

[120] Ullrich H, Kranaster L, Sigges E, Andrich J, Sartorius A. Neuron specific enolase and serum remain unaffected by ultra high frequency left prefrontal transcranial magnetic stimulation in patients with depression: a preliminary study. J Neural Transm 2013;120(12):1733–6.