Brain Stimulation 13 (2020) 565–575

Contents lists available at ScienceDirect

Brain Stimulation

journal homepage: http://www.journals.elsevier.com/brain-stimulation

Safety and tolerability of transcranial magnetic and direct current stimulation in children: Prospective single center evidence from 3.5 million stimulations

E. Zewdie [a, b, c, d, e, *], P. Ciechanski [a, d, e], H.C. Kuo [a, b, c, d, e], A. Giuffre [a, b, c, d, e], C. Kahl [b, c, d, e], R. King [b, c, d, e], L. Cole [a, b, c, d, e], H. Godfrey [b, c, d, e], T. Seeger [a, e], R. Swansburg [b, c, d, e], O. Damji [a, d, e], T. Rajapakse [b, c, d, e], J. Hodge [a, e], S. Nelson [e], B. Selby [e], L. Gan [e], Z. Jadavji [a, e], J.R. Larson [a, e], F. MacMaster [b, c, d, e], J.F. Yang [f], K. Barlow [b, c, d, e], M. Gorassini [g], K. Brunton [c], A. Kirton [a, b, c, d, e]

[a] Calgary Pediatric Stroke Program, University of Calgary, Calgary, Alberta, Canada
[b] Departments of Pediatrics and Clinical Neurosciences, University of Calgary, Calgary, Alberta, Canada
[c] Alberta Children's Hospital Research Institute, University of Calgary, Calgary, Alberta, Canada
[d] Department of Neurosciences, University of Calgary, Calgary, Alberta, Canada
[e] Cumming School of Medicine, University of Calgary, Calgary, Alberta, Canada
[f] Department of Physical Therapy, University of Alberta, Edmonton, Alberta, Canada
[g] Department of Biomedical Engineering, University of Alberta, Edmonton, Alberta, Canada

ARTICLE INFO

Article history:
Received 7 August 2019
Received in revised form
20 November 2019
Accepted 23 December 2019
Available online 30 December 2019

Keywords:
TMS
tDCS
Children
HD-tDCS
Safety
Tolerability

ABSTRACT

Background: Non-invasive brain stimulation is being increasingly used to interrogate neurophysiology and modulate brain function. Despite the high scientific and therapeutic potential of non-invasive brain stimulation, experience in the developing brain has been limited.
Objective: To determine the safety and tolerability of non-invasive neurostimulation in children across diverse modalities of stimulation and pediatric populations.
Methods: A non-invasive brain stimulation program was established in 2008 at our pediatric, academic institution. Multi-disciplinary neurophysiological studies included single- and paired-pulse Transcranial Magnetic Stimulation (TMS) methods. Motor mapping employed robotic TMS. Interventional trials included repetitive TMS (rTMS) and transcranial direct current stimulation (tDCS). Standardized safety and tolerability measures were completed prospectively by all participants.
Results: Over 10 years, 384 children underwent brain stimulation (median 13 years, range 0.8–18.0). Populations included typical development (n = 118), perinatal stroke/cerebral palsy (n = 101), mild traumatic brain injury (n = 121) neuropsychiatric disorders (n = 37), and other (n = 7). No serious adverse events occurred. Drop-outs were rare (<1%). No seizures were reported despite >100 participants having brain injuries and/or epilepsy. Tolerability between single and paired-pulse TMS (542340 stimulations) and rTMS (3.0 million stimulations) was comparable and favourable. TMS-related headache was more common in perinatal stroke (40%) than healthy participants (13%) but was mild and self-limiting. Tolerability improved over time with side-effect frequency decreasing by >50%. Robotic TMS motor mapping was well-tolerated though neck pain was more common than with manual TMS (33% vs 3%). Across 612 tDCS sessions including 92 children, tolerability was favourable with mild itching/tingling reported in 37%.
Conclusions: Standard non-invasive brain stimulation paradigms are safe and well-tolerated in children and should be considered minimal risk. Advancement of applications in the developing brain are warranted. A new and improved pediatric NIBS safety and tolerability form is included.
© 2020 The Authors. Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

* Corresponding author. Alberta Children's Hospital, Oki Drive Calgary, AB, T3B 6A8, Canada.
E-mail address: ephrem.zewdie@ucalgary.ca (E. Zewdie).

https://doi.org/10.1016/j.brs.2019.12.025
1935-861X/© 2020 The Authors. Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Introduction

Transcranial magnetic stimulation (TMS) and transcranial direct-current stimulation (tDCS) are promising therapeutic and research tools. Over the past two decades, a large body of adult research exploring these non-invasive brain stimulation (NIBS) technologies has emerged [1,2]. While the number of pediatric NIBS studies continues to grow [3–5], the developing brain remains largely under-represented in the current literature. Of the >16000 human TMS/tDCS studies, only 675 (4%) have a pediatric focus. A review of tDCS studies to date found that <2% of nearly 7000 subjects were under 18 years of age [1]. This lack of evidence in a vulnerable population with unique neurobiology and disease states mandates the additional study of NIBS safety in children. This is especially pressing as scientists, clinicians, ethics boards, and concerned parents are seeking evidence when evaluating the potential risks of NIBS in children. The lack of evidence regarding NIBS safety and tolerability in youth is likely hampering progress across many brain and mental health disorders of the developing brain where the global burden of disease is large.

Safety and tolerability of TMS applications in adults has been well studied. When applied within established safety guidelines [6], TMS paradigms are generally considered minimal risk [7]. Headache and neck pain are the most commonly reported adverse effects [8–10] but are typically mild and lasted for few minutes [11]. Although the use of high-frequency repetitive TMS (rTMS) has raised theoretical concerns of inducing seizures, this risk appears to be extremely low. A systematic review of 280 subjects with epilepsy who underwent rTMS reported seizures in only 1.4%, most of whom already had frequent seizures [9]. Other studies of at risk populations further suggest the risk of rTMS-associated seizure is <0.1% [8,10,12]. In one study of >250 healthy adult subjects, no seizures were reported.

Although similar studies are scarce in children, available evidence suggests similar safety. A review on the application of TMS across 322 children (3–17.8 years old) across 48 studies described potentially serious adverse events in 4 cases (1.2%). Two children had seizures possibly related to TMS while two others had syncope [13]. Headache (11.5%) was the most commonly reported side effect of rTMS in children [13].

tDCS safety and tolerability data in adults is also well-established. A recent study by Bikson and colleagues [1] evaluated the safety of tDCS across >33,000 sessions in >7000 participants and found no serious adverse events. The same study also documented a paucity of experience in participants less than 18 years of age. Tingling, itching, and burning are the most commonly reported side effects in adults [14]. While systematic studies are lacking, the same appears to be true in children and serious adverse events have not been reported [15].

The potential of NIBS is clearly evident in adults, with similar promise increasingly demonstrated in children and adolescents. While limited studies [13] have suggested the incidence of adverse events is <1%, there is a large disparity across populations, methods, and safety measures. Defining the safety and tolerability of NIBS across the different stages of developmental neurobiology and pediatric disease-states is essential. Families and research ethics boards remain concerned about the possible risks of NIBS in children, hindering progress. To address this gap in the literature, we report the safety and tolerability of TMS and tDCS in a large, prospective, and diverse sample of 382 children who received a total of more than 3.5 million stimulations within a structured pediatric NIBS program.

Methods

Studies and populations

All studies performed at the Alberta Children's Hospital Pediatric Non-invasive Brain Stimulation Laboratory (Calgary, Canada) since its inception in 2008 were reviewed for inclusion. Date of study ranged from January 1, 2009 to May 2018. Inclusion criteria for the current study were: (1) aged 0–18 years, (2) received one form of NIBS at least once, (3) completion of at least one Pediatric TMS Safety and Tolerability Measure [16], and (4) informed consent/assent. All studies were approved by the University of Calgary Conjoint Health Research Ethics Board.

The details regarding each study, including age, condition and stimulation parameters, are summarized in Table 1. A full description of the methods of each study is beyond the scope of this report. Additional details can be found in those studies already published [17–25] or are available online (e.g. clinicaltrials.gov).

Neurologically and developmentally normal (typically developed, controls)) participants were recruited from the community and the Healthy Infants and Children's Clinical Research Program (HICCUP, www.hiccupkids.ca). Inclusion and exclusion criteria were comparable across these studies including the absence of any neuropsychiatric/developmental diagnoses.

Equipment

Single- and paired-pulse TMS to the hand motor cortex was delivered using a figure-of-eight flat-iron, 70 mm TMS coil (200^2 or BiStim2, Magstim, UK) and a double cone coil (Magstim, UK) to the leg motor area. Motor mapping and rTMS was performed using a figure-of-eight air-film coil (Rapid2, Magstim). Motor mapping was completed using a TMS Robot (Axilium, Strasbourg, France). Brainsight2 (Rogue, Montreal, Canada) was used for Neuronavigation. All tDCS trials used either a Neuroconn DC Stimulator (Neuroconn, Illmenau, Germany) or Soterix 1 × 1 Stimulator (Soterix Medical Inc., New York, USA) via two saline-soaked sponge electrodes (25 or 35 cm^2). High Density (HD)-tDCS was delivered using a 4 × 1 HD Adapter (Soterix Medical Inc.), with four small circular electrodes oriented in a ring-like orientation around a central electrode (1.2 cm diameter, Sintered ring HD-electrode, Soterix Medical Inc., New York), that was connected to a Soterix 1 × 1 Stimulator.

Neurophysiological assessments

Single pulse TMS paradigms

All single pulse TMS studies employed a Magstim 200^2 stimulator and figure-of-eight flat-iron coil. Single, suprathreshold (e.g. 120%RMT), pulses were typically given with 4–5 s intervals between stimuli. The *motor 'hotspot'* was the location in M1 that produced the largest and most consistent motor evoked potential (MEP). MEP measurements were normalized across individuals to resting and/or active motor thresholds. *Resting motor threshold* (RMT) was defined as the minimum TMS intensity that elicited reproducible MEP responses of at least 50 μV in 5/10 consecutive stimuli [26]. *Active motor threshold* (AMT) was the minimum intensity to elicit responses of at least 200 μV in 5/10 trials during active contraction at 10–20% of the maximum contraction strength (MVC) maintained via visual feedback. *Stimulus Response Curves* were input/output curves obtained in proportion to RMT/AMT by administering stimulations from 100% to 150% RMT (10% increments, 10 stimulations per intensity in a random order). *Cortical*

Table 1
Neurophysiology Participants Demography and TMS Parameters
Study names and participant conditions are listed with details available as referenced or online. Types of stimulation are single pulse (SP) and paired pulse (PP). The types of coils used were either Flat Iron (FI) or Air-Film (AF) Magstim coils or Double Cone (DC). Coil position was typically on primary motor cortex (M1), occasionally on primary visual cortex (V1). Number of sessions (**#** sessions) represents the number of days when TMS was received.

Condition	Study	Detail	n =	Age (med)	**Type TMS**	**Coil** Type	Target	# sessions	# stim
Typically Develop (controls)	*Effects of tDCS on Motor Learning in Children*	Double blind, randomized, sham controlled trial of M1 tDCS on learning	24	8-18 (14)	SP, PP	FI	M1 Hand	2	52900
	Paired Afferent Stimulation (PAS) in Children	Suprathreshold TMS (0.2 Hz, 7.5 min) paired with median nerve stimulation	30	6-18 (13)	SP	FI	M1 Hand	2	12320
	Mapping Primary Motor Cortex with Robotic TMS	Robotic TMS mapping of M1 across 40 grid points (4 stimulations per point).	12	10-18 (15)	SP	AF	M1+	2	72000
	Accelerated Motor learning in PEDiatrics (AMPED)	Double blind, randomized, sham controlled trial of M1 tDCS/HD-TDCS	24	12-18 (16)	SP	AF	M1+	3	43200
	PLAYGAME trial – controlled trial of mild TBI in children	Controls for neurophysiology outcome measures (see below)	28	9-18 (14)	SP, PP	FI	M1 Hand	1	17780
Perinatal Stroke (Stroke)	*Plastic Adaptation Stimulated by TMS and Constraint for Congenital Hemiparesis After Perinatal Stroke (PLASTIC CHAMPS)*	Factorial, double blind, sham controlled, randomized trial of rTMS and/or CIMT plus intensive therapy for hemiparesis	45	8-18 (12)	SP, PP	FI	M1 Hand	2	103500
	tDCS for children with perinatal stroke and hemiparesis	Blinded RCT 10 Days Active/Sham tDCS + CIMT	25	8-18 (13)	SP, PP	FI	M1 Hand	2	48000
	Stimulation for Perinatal Stroke Optimizing Recovery Trajectories (SPORT)	Phase 3, multicenter, randomized, sham controlled trial of tDCS added to intensive therapy camp (**in progress*)	18*	6-18 (12)	SP	AF	M1 Hand	3	21600
	Intensive Exercise in Children with Early Brain Injury to Improve Motor Function	Randomized, controlled, blinded trial of intensive walking in infants and toddlers	12	0.8–4 (2)	PP	DC	M1 Leg	3	720
	Aphasia Case Study	Low frequency rTMS contra Broca + speech therapy, 10 consecutive weekdays	1	17	SP, PP	FI	M1 Hand	2	350
Mild Traumatic Brain Injury (TBI)	*Post-concussion Syndrome in Youth: Assessing GABAergic Effects of Melatonin (PLAY GAME)*	Randomized, double blind, placebo-controlled trial of melatonin for post-concussion syndrome in children	107	9-17 (14)	SP, PP	FI	M1 Hand	2	135890
	rTMS to treat Persistent Post Concussive Symptoms (PPCS)	High Frequency rTMS	14	12-18 (16)	SP, PP	FI	M1 Hand	2	16520
Major Depression (MDD)	*rTMS for treatment resistant depression in adolescents and young adults (REMADY)*	Open-label, imaging biomarker trial of DLPFC high-frequency rTMS for 3 weeks in adolescents with med resistant MDD	28	12-21 (15)	SP	AF	M1 Hand	3	2800
Tourette's syndrome	*TMS Intervention in Children with Tourette's Syndrome (TICS)*	Open-label trial of low-frequency rTMS of SMA for 15 Days in children with TS	9	9-16 (11)	SP, PP	FI, AF	M1 Hand	2	10620
Headache	Neurophysiology of migraine in children and adolescents	Occipital TMS exploring phosphene thresholds in children with migraine	5	12-18 (14)	PP	AC	V1	2	3000
Pain	*Complex regional pain syndrome case study*	Open-label, n = 1 trial of M1 high-frequency rTMS for 10 Days	1	17	SP	DC	M1 Leg	2	1140
	Total		383						**542,340**

silent period (cSP) was measured by delivering 15 pulses at 120% RMT during contraction of the contralateral hand at 20% of MVC. *Ipsilateral silent period* (iSP) was obtained by delivering 10 pulses at 120% RMT during concentration of the ipsilateral hand at 50% of MVC.

Paired pulse TMS paradigms

All paired-pulse TMS studies employed a pair of Magstim 200^2 stimulators connected to each other (Bistim2, Magstim) and two figure-of-eight flat-iron coils. A combined *short-interval intracortical inhibition* (SICI) and *intracortical facilitation* (ICF) paradigm was comparable to methods described in adults [27] and our pediatric populations as reported in detail elsewhere [21]. *Short-interval intracortical facilitation* (SICF) [28,29] and *long-interval intracortical inhibition* (LICI) protocols followed published evidence [30]. To assess *interhemispheric inhibition* (IHI), a test stimulus over one M1 was preceded by a conditioning stimulus of the opposite M1 including both short- (8–10 ms) and long- (40–50 ms) interstimulus intervals [31,32]. Supra-threshold double pulse stimulation, both pulses 70 and 80% MSO and 10 ms interstimulus interval (ISI), we delivered with double cone coil over leg M1 to facilitate recruitment of MEP in children < 4 years [33].

Neuromodulation paradigms

Four neuromodulatory paradigms were applied across studies based on adult evidence available at the time of study [34]. *Repetitive TMS (rTMS)* included low frequency at 1 Hz and high frequency at 10 Hz, both typically administered for 20–40 min. *Paired afferent stimulation* (PAS) were consistent with adult protocols [35,36] including suprathreshold median nerve stimulation preceding M1 single pulse TMS at an ISI of 25 ms.Traditional *1x1 tDCS* also adhered to typical standards published in adults. Constant current was passed between two sponge electrodes using standard anodal and cathodal montages [37,38]. *HD-tDCS* used an EEG cap system to surround a central active (anodal) electrode with four reference electrodes (cathodes) in a ring-like fashion to generate more focal currents over the desired cortical target.

Safety and tolerability measures

Pediatric NIBS screening form

Prior to administering any form of neurostimulation, all participants completed non-invasive brain stimulation screening questionnaire [39]. The questionnaire aimed to identify participants with known contraindications (e.g. metal in the head, cardiac pacemaker, pregnancy) or those at any increased risk of complications (e.g. unstable epilepsy, history of syncope).

Pediatric NIBS safety and tolerability assessment

In accordance with all studies being approved by the institutional research ethics board, a standardized process was in place for reporting of any potentially serious adverse events. Larger clinical trials may have also had formal data safety monitoring boards including medical safety officers with additional interim analyses and reporting procedures.

A modified pediatric TMS safety and tolerability measure [16] was administered at the end of all single session studies and at both first session and predefined time points in multi-session studies. Possible adverse events (headache, presyncope, nausea, etc.) were screened and quantified (mild/moderate/severe). Any other potential side effects were recorded and quantified. Subjects also ranked their experience relative to 7 other common childhood experiences to assess relative tolerability. For example, the most favourable experience was rated as "1" (e.g. playing a game) and the least was rated as "8" (e.g. throwing up). The questions were read once to the child and they completed the ranking by themselves. In the case of very young children (<4 years old), no formal questionnaire was used. Parents were asked to report if their child was more irritable after the TMS session.

Statistical analysis

To compare mean age differences between different modalities (TMS, rTMS and tDCs), a one-way ANOVA with post hoc Student's t-tests and Bonferroni-correction was performed. To compare differences in gender proportions, a Chi-Square Fisher Exact test was used. Logistic regression was used to test potential associations between age and tolerability rank and occurrence of side effects as well as RMT and occurrence of side effects. A Chi-Square Fisher Exact test was also used to compare percentage occurrence of side effects between different clinical populations. Analyses were performed using SPSS 25.0.

Results

Populations

A total of 384 participants underwent at least one NIBS procedure. Mean age was comparable between the TMS (12.2 ± 4.5 yrs) and tDCS (12.9 ± 3.4 yrs) groups but was significantly higher in rTMS (13.6 ± 3.4 yrs) groups ($F = 3.46$, $p = 0.03$). Gender proportions were comparable between all three modalities ($\chi^2 = 2.24$, $p = 0.69$). Tables 1–3 summarize the population demographics for neurophysiology TMS, rTMS and tDCS, respectively. Neurophysiological TMS included single- and paired-pulse TMS, and neuromodulatory TMS includes rTMS and tDCS.

Over 3.5 million TMS stimulations were delivered in total. Neurophysiological studies (single and paired-pulse) included 383 participants (median age 13 years, range 0.8–18 years, 47% female). The most common conditions were children with typical development, perinatal stroke, and traumatic brain injury (TBI). A total of 542,340 single and paired TMS pulses were delivered across the neurophysiology protocols (Table 1).

Neuromodulation TMS for intervention studies included 119 participants (median age 14 years, range 6–21, 43% female) across 5 studies (Table 2). The total number of rTMS pulses applied was 2,945,040. The most common conditions were children with typical development, major depressive disorder, and stroke.

Ninety-two participants had at least one tDCS session (median age 14 years, range 6–18, 38% female). Four studies applied tDCS with the most common populations being children with typical development and perinatal stroke. The motor cortex was the target of tDCS in all participants except for one participant where the target was the auditory cortex. The proportion of different tDCS approaches included anodal (22%), cathodal (34%), HD-tDCS (6%) and sham (37%). The median dose of electrical current applied was 1 mA (range 1–2 mA) (Table 3). The duration for all tDCS was 20 min.

Serious adverse events and dropouts

There were no serious adverse events. Despite 221(58%) participants having brain injuries and/or epilepsy, no seizures occurred in association with single, paired, or rTMS or with tDCS. Of 382 participants, only two drop outs occurred (<1%). Two adolescents (aged 15 and 17 years) with major depressive disorder (MDD), were undergoing high-frequency rTMS over the dominant DLPFC (of 28 in study). Both withdrew by the second session, reporting stimulation discomfort as the reason. Attempts at temporarily lowering

Table 2
Participants Demography and TMS Parameters for Intervention.
Stimulation Frequency of 1 Hz is considered low frequency and 10 Hz is considered high frequency. Coil position was typically on primary motor cortex (M1), occasionally on primary visual cortex (V1). Number of sessions (**#** sessions) represents the number of days when TMS was received. Coil position was on primary motor cortex (M1), Dorsolateral Prefrontral Cortex (DLPFC) or Supplementary Motor Area (SMA).

Condition	Study	n =	Age (med)	rTMS Frequency	**Coil** Type	Target	# sessions	# stim
Typically Develop (controls)	*Paired Afferent Stimulation (PAS) in Children*	28	6-18 (13)	1 Hz	FI	Hand M1	2	5040
Perinatal Stroke (Stroke)	*Plastic Adaptation Stimulated by TMS and Constraint for Congenital Hemiparesis After Perinatal Stroke (PLASTIC CHAMPS)*	45	8-18 (12)	1 Hz	AF	Hand M1	10	540000
Mild Traumatic Brain Injury (TBI)	*rTMS to treat Persistent Post Concussive Symptoms (PPCS)*	14	12-18 (16)	10 Hz	AF	Left DLPFC	20	840000
Major Depression (MDD)	*rTMS for treatment resistant depression in adolescents and young adults (REMADY)*	32	12-21 (15)	10 Hz	AF	Left DLPFC	15	1260000
Tourette's syndrome	*TMS Intervention in Children with Tourette's Syndrome (TICS)*	11	9-16 (11)	1 Hz	AF	Bilateral SMA	15	270000
Pain	*Complex regional pain syndrome case study*	1	17	10 Hz	AF	Left DLPFC	15	30000
	Total	**119**						**2,945,040**

stimulation intensity and optimizing coil orientation were not successful.

Adverse events and side effects

The experienced sensations associated with TMS, rTMS and tDCS are summarized below and in Fig. 1. There was no association between age or resting motor threshold with any of the reported side effects (all r<0.2, p>0.4).

Headache

Across all neurophysiology studies, headache was reported in 13% of TMS sessions. As shown in Fig. 1a, compared to typically developing, headache was more frequent in participants with perinatal stroke ($\chi^2 = 13.8$, $p < 0.001$) and Tourette syndrome ($\chi^2 = 18.3$, $p = 0.02$) but not TBI ($\chi^2 = 1.3$, $p = 0.52$). All but 5% of headaches following TMS were ranked mild or moderate. TMS associated headache also appeared to decrease when procedures switched from landmarking on a swim-cap to neuronavigation though lack of record details prevented quantifying this effect.

Across all rTMS studies, headache was reported in <17% of TMS sessions. Headaches were more common in TBI subjects as compared to MDD ($\chi^2 = 5.9$, $p = 0.03$). Headache occurrence was similar between typically developing and participants with Tourette syndrome ($\chi^2 = 0.4$, $p = 0.9$), and participants with perinatal stroke ($\chi^2 = 4.7$, $p = 0.4$).

Headache associated with active tDCS was reported in 25% of participants with perinatal stroke. In typically developing children, mild headache was reported in 9.5% ($\chi^2 = 5.4$, $p = 0.04$). Presence of headache was not associated with type of tDCS (active or sham) both in typically developing ($\chi^2 = 0.04$, $p = 0.9$) or stroke ($\chi^2 = 0.05$, $p = 0.9$) participants.

Neck pain

Overall, rTMS and TMS associated neck pain was reported in <30% of participants. Neck pain was reported in 33% of robotic TMS sessions. For TMS neurophysiology sessions, neck pain was less common in typically developing (8.7%) compared to stroke (17.8%, $\chi^2 = 4.9$, $p = 0.05$), which was similar to Tourette (20.2%, $\chi^2 = 2.7$, $p = 0.1$) and TBI (21.1%, $\chi^2 = 3.6$, $p = 0.1$). Frequency of neck pain following rTMS was comparable across groups (all $\chi^2 = 0.5$, $p = 0.4$). Severity of neck pain was mild and self-limiting and may have decreased with the adoption of neuronavigation. For tDCS, neck pain was uncommon with the highest reported incidence of 20% reported in the sham group of stroke participants.

Unpleasant tingling

Most TMS neurophysiology sessions were not associated with unpleasant tinging (12%). Rates were comparable between typically developing, Tourette and TBI but more common in in stroke participants (31%, $\chi^2 = 16.7$, $p < 0.001$, Fig. 1a). rTMS-associated

Table 3
tDCS Neuromodulation Participants Demography and tDCS ParametersCurrent intensity of tDCS used in all studies is 1 mA (mA).

Condition	Study	n =	Age (med)	**Type of tDCS**	Target	# sessions
Typically Develop (controls)	*Effects of tDCS on Motor Learning in Children*	24	8-18(14)	1 mA Anodal Cathodal Sham	Non-dominant Hand M1	5
	Accelerated Motor learning in PEDiatrics (AMPED)	24	12-18(16)	1 mA Anodal Sham HD	Non-dominant Hand M1	5
Perinatal Stroke (Stroke)	*tDCS for children with perinatal stroke and hemiparesis*	25	8-18 (13)	1 mA Cathodal Sham	Contralesional M1	10
	Stimulation for Perinatal Stroke Optimizing Recovery Trajectories (SPORT)	18	8-18(12)	1 mA Cathodal	Contralesional M1	10
Schizophrenia	*Open-label, n = 1 trial of tDCS for Auditory Hallucination*	1	16	1 mA Cathodal	Auditory Cortex	10
	Total	**119**				

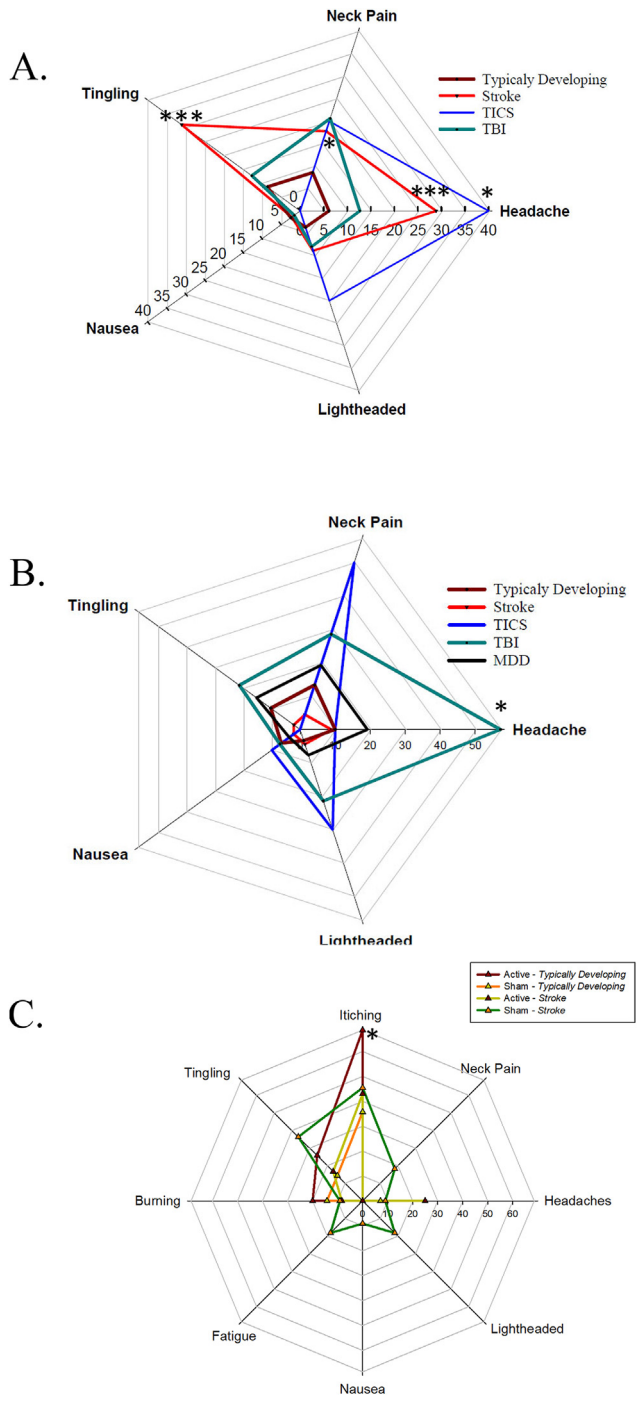


Fig. 1. Side effects across conditions for TMS, rTMS and tDCS. Comparison of A) TMS, B) rTMS and C) tDCS safety between different participant conditions, which are typically developing, stroke, Tourette's syndrome (TICS), Mild traumatic brain injury (TBI) and major depressive disorder (MDD). The values indicate percentage occurrence. The values indicate percentage occurrence. The asterisk(*) represent significant level * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

tingling sensations were reported in <25% of participants overall and were comparable across groups. As shown in Fig. 2c, following tDCS, 37% of participants experienced short-lasting tingling sensations under the tDCS electrodes. The sensation was always graded as mild or moderate and was comparable between the active and sham groups in both typically developing ($\chi^2 = 3.4$ $p = 0.6$) and stroke ($\chi^2 = 1.2$, $p = 0.4$) participants.

Presyncope

Light-headedness was uncommon, reported in 13% of all participants (Fig. 1). Compared to typically developing controls, similar light-headedness was experienced by stroke (8%, $\chi^2 = 0.9$, $p = 0.4$), TBI (9%, $\chi^2 = 1.4$, $p = 0.5$), and Tourette syndrome (20%, $\chi^2 = 6.3$, $p = 0.1$) participants following TMS neurophysiology sessions. Similarly, 30% of Tourette and 22% of TBI participants reported light-headedness following rTMS. Less than 10% of participants felt light-headed during tDCS sessions. There were no episodes of altered consciousness or termination of session due to these symptoms.

Itching and burning

Scalp itching or burning was only assessed within tDCS studies. It was reported by 55% of participants, classified as mild and transient in all cases. As shown in Fig. 1c, scalp itching was more common following active tDCS (70%) as compared to sham (36%, $\chi^2 = 4.5$, $p = 0.05$) in typically developing children. However, the occurrence of itching did not differ between active treatment and sham in trials of perinatal stroke ($n = 25$, $\chi^2 = 3.6$, $p = 0.1$).

Burning sensations under the tDCS electrodes following active and sham stimulations were experienced by similar proportions of 20% and 14% respectively in typically developing children. Similarly, 10% of stroke participants reported burning sensations, the proportion of which did not differ between active and sham tDCS. Subjects were not able to guess their assigned treatment group across multiple studies [17,19,22].

Nausea

Mild nausea was the least reported sensation following TMS, rTMS, and tDCS, occurring in 2%, 10%, and 5% respectively. There was no significant difference across groups (all $\chi^2<2.0$, $p>0.5$).

Study specific adverse event screening: motor skills

Individual studies included pre-specified functional safety outcomes. Multiple clinical trials of contralesional rTMS [40] and tDCS in hemiparetic children with perinatal stroke demonstrated no decrease in function of either hand including specific tests of unaffected hand function. Likewise, motor cortex tDCS did not decrease function of either hand in typically developing children.

Tolerability rankings

Initial questionnaires (recorded in the first session) were completed by all 367 participants with 339 of these subjects having repeated assessments over time (see below). TMS, rTMS, and tDCS tolerability results are summarized in Fig. 2. The width of the bars show the range of scores from all children where 1 is the most preferred activity of the 8 presented and 8 is the least preferred. The stars represent the median value.

For the first TMS session, mean tolerability rank score was 4.3 ± 1.7. Similarly, for the first rTMS treatment, mean tolerability rank score was 4.3 ± 1.5. For first tDCS session ($n = 92$), mean tolerability rank score was 4.4 ± 1.5. No association was observed between participant age and tolerability ranking for TMS ($r = 0.22$), rTMS ($r = 0.32$), or tDCS ($r = 0.16$, all $p > 0.31$). For all 3 modalities, participants ranked the experience between attending a birthday party (3.6 ± 1.6) and a long card ride (4.8 ± 1.7). Mean rankings of TMS did not differ between clinical populations ($F = 2.71$, $p = 0.06$). Rankings for high frequency rTMS was worse in MDD group

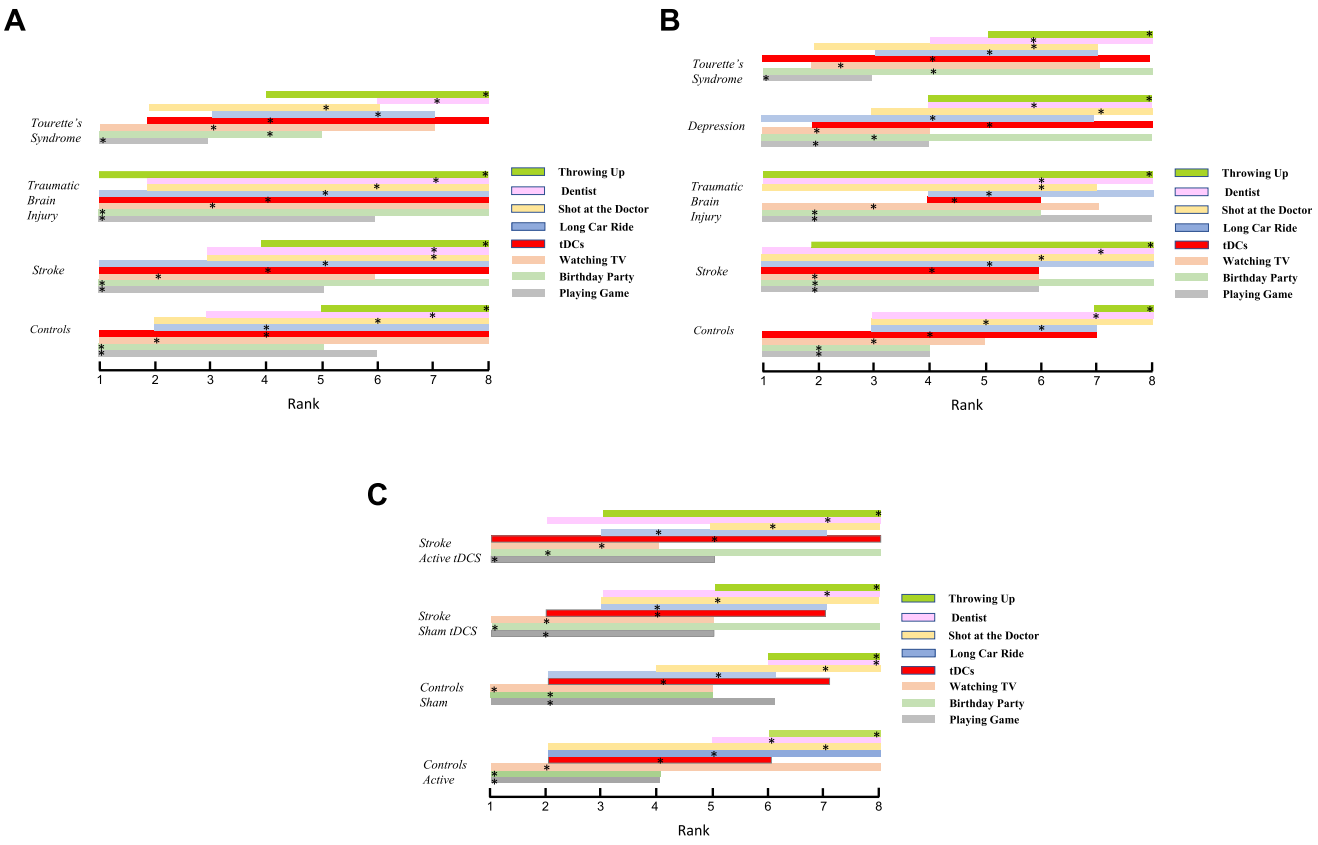


Fig. 2. Tolerability across conditions and simulation. Tolerability ranking of A) TMS, B) rTMS and C) tDCS compared to seven other tasks listed in the legend. Width of the bars indicates the range of ranks. The asterisk(*) indicates the median of ranks.

compared to TBI group (5.3 vs 4.7, $F = 5.83$, $p < 0.001$) but not compared to other groups. tDCS ranking did not differ between typically developing and stroke groups or between active and sham treatments ($F = 0.825$, $p = 0.49$).

Change in side effects

Tolerability changed over time (Fig. 3). Following repeated sessions of single and paired-pulse TMS, the percent occurrence of all side-effects (headaches, neck pain, tingling, nausea and lightheadedness) remained below 5% in typically developing children (Fig. 3a). In stroke subjects, headache, neck pain and tingling occurrence decreased by 16% ($p = 0.04$), 16% ($p = 0.04$), and 20% ($p = 0.04$), respectively (Fig. 3b). For rTMS, weekly tolerability assessments in MDD participants saw headache decrease by 40% ($p = 0.04$) by the second week and was <5% ($p = 0.02$) by the third week (Fig. 3c). All other side effects also decreased by at least 5% by the third week. Headache decreased by 25% ($p = 0.03$) by the fourth week in participants with TBI (Fig. 3d). In participants with perinatal stroke, all rTMS side effects were initially reported in <10% and decreased to <5% at the end of the second week (Fig. 3e). Headache and neck pain remained stable over 2 weeks in participants with TICS (Fig. 3f).

In typically developing children, occurrence of itching following tDCS decreased by 48% ($p = 0.05$) during day 3 (Fig. 3g). A decrease in all side effects ($p < 0.05$), except for neck pain, were seen in participants with perinatal stroke undergoing tDCS (Fig. 3h).

Discussion

In this largest, prospective, single-center pediatric cohort to date, we provide substantial new evidence supporting the safety, feasibility, and favourable tolerability of NIBS in children. Both neurophysiological (single- and paired-pulse TMS) and neuromodulatory (rTMS, tDCS) modalities were well-tolerated with no serious adverse events across millions of stimulations and hundreds of children with a variety of neurological conditions. Combined with existing evidence, our study supports the conclusion that established NIBS modalities can be considered minimal risk in school-aged children. Safety conclusions are made based on lack of severe adverse effects, such as seizure, hearing damage or pain.

Thousands of adults have received rTMS across a broad range of neurological and mental health conditions [41]. Guidelines first published in 1998 [6] and now updated [41] provide clear parameters for established practices. Particular attention to safety in well designed, large trials of common populations has supported this evidence base. For example, in a large, sham-controlled rTMS trial for adults with treatment resistant MDD [42], there was no difference in adverse events by treatment arm (active rTMS and sham). No seizures occurred and a single occurrence of syncope was deemed unlikely to be related to the study [42]. Large controlled, blinded trials of rTMS for adult pain including thorough side effect screening during and after sessions also reported no adverse effects [43]. Despite this huge experience in adults, only isolated case incidents of possible TMS- or rTMS-associated seizures have been reported [44]. To date, pediatric NIBS studies have generally lacked

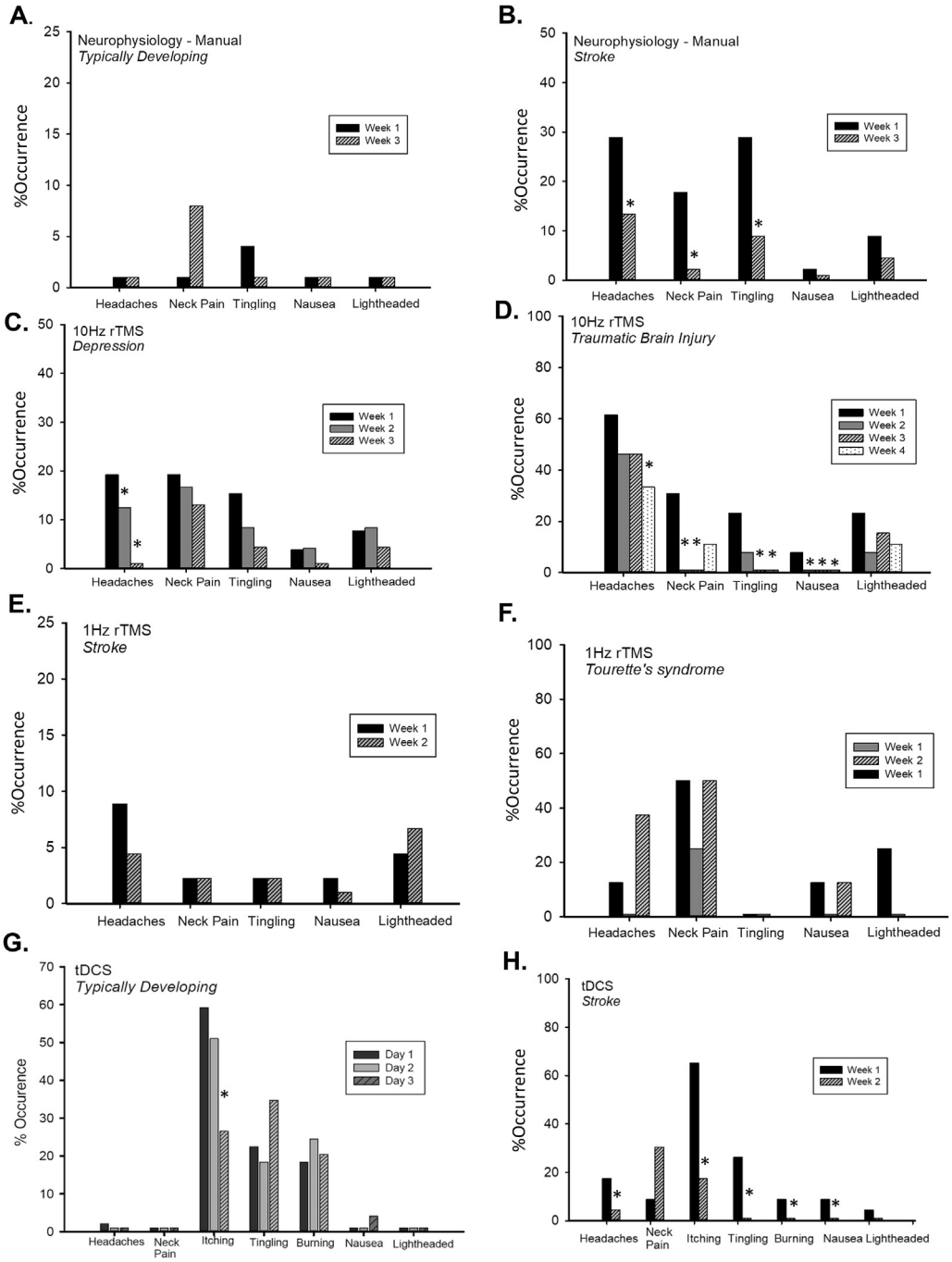


Fig. 3. Tolerability over time.Change in percentage occurrence of sensations following A) TMS in typical developing, B) TMS in stroke, C) rTMS in MDD, D) rTMS in TBI, E) rTMS in Stroke F) rTMS in TICs, G) StDCS in typically developing, H) StDCS in stroke measured during three weeks of intervention in participants with depression. The asterisk(*) represent significant level $p < 0.05$ compare to day 1 or week 1.

such power to systematically explore safety issues in specific populations.

Issues of TMS safety in children have been previously considered across a variety of small series and pooled analyses. Single-pulse and paired-pulse TMS has been used to assess brain maturation, neurophysiology, and motor development safely in the developing brain [45,46]. Across 75 TMS studies involving >2000 children and adolescents, no serious adverse events were reported [16,47]. Accordingly, experts have suggested that single- and paired-pulse TMS studies confer only minimal risk to children [33]. With rTMS however, there is less experience. Heightened concerns for rTMS exposure include seizure risk, hearing damage, pain, and neurocognitive effects. Safety and ethical issues regarding the use of rTMS in adolescents was reviewed by Croarkin et al. [48].

There are limited studies reporting about safety of theta burst stimulation in children. A study that characterized the effect of theta burst stimulation in typically developing children and those with Tourette's Syndrome, there was no serious adverse events [49]. Similar study compared the safety of theta bust stimulation

with single and paired pulse stimulation in 165 children and found no seizure or severe adverse events [50].

The application of tDCS to pediatric populations has been increasing rapidly. However, this population continues to be underrepresented in comparison to adults [1], and there remains a pressing need to investigate the mechanisms, behavioural effects, and safety of tDCS in the developing brain. Unique anatomy and the developmental changes that take place throughout childhood suggest that tDCS effects will vary and differ from adults. For example, the developing brain is thought to have a shifted balance of excitation-inhibition, resting closer to the seizure-threshold [51]. Our studies have not identified any seizure-like activity, and epileptogenic monitoring by others supports this finding [52].

Previous investigations in adults suggesting no decline in psychomotor function, verbal fluency, emotional behaviour or other neuropsychological [53] effects are important but require replication in children with age-adjusted outcome measures. Work by our group suggests that application of five concurrent days of conventional tDCS and HD-tDCS, in typically-developing children, does not cause any changes in neurocognitive function, measured using the CNS Vitals assessment [22]. Longitudinal tDCS studies in children have been few and additional studies on sequential dosing are required.

A recent safety analysis found no serious adverse effects reported in nearly 500 children receiving tDCS over 2800 sessions [13]. While these findings support safety of the application of tDCS in children, additional considerations are required. Evidence from computational current modeling suggests that local electric field strength may be two-fold greater in children compared to adults [54,55]. A large study from our team suggests that peak electric fields in cortical grey matter may be up to seven-fold higher in children compared to adults [56]. Current strengths of 2 mA (current density of 0.80 mA/cm^2) appear to be equally tolerable as both 1 mA (current density of 0.40 mA/cm^2) and sham tDCS [15]. Likewise, tolerability of 1 mA HD-tDCS is comparable to that of 1 mA conventional tDCS [22]. Another pediatric-specific review of the safety of NIBS technologies also suggested that tDCS is safe in children with underlying neurological or psychiatric conditions [13]. While tingling, itching, redness and scalp discomfort were reported in pediatric populations, the incidence of these findings appeared to be lower than in adults [14]. In contrast, studies that employed rigorous tDCS-sensation reporting as a prespecified outcome found incidence rates in children and adolescents similar to those reported in adults [15]. While the tolerability and feasibility of standard tDCS practices in children appears to be confirmed, vigilance toward additional complex and study-specific safety outcomes remains essential.

A limitation of our tolerability and safety assessments is the lack of long term follow up data, as well as, the lack of standardized and comprehensive tools to assess the complete status of the participant before and after brain stimulation. Using the methods described above, other important factors that may have influenced tolerability of TMS and tDCS, such as stress level, fatigue, sleep, hearing and vision conditions were not considered. As a result, we propose an improved pediatric NIBS tolerability form (Appendix A). The improved NIBS tolerability questionnaire considers mental status before the start of stimulation, including the amount of sleep the participant had the night before, headache patterns, drug or alcohol use. It also includes behavioural observations during the session. In the same way that the original TMS tolerability form of Garvey et al. [16] has served as a valuable tool in over the first 25 years of pediatric brain stimulation, we hope this model might facilitate further progress in the future.

In conclusion, we demonstrate safety and tolerability of the most common NIBS modalities and paradigms in pediatric populations, spanning a broad age range and variety of clinical conditions. Both TMS and tDCS appear to pose minimal risk to school-aged children, however, best practices with a focus on patient safety remain paramount. Routine use of prospective, study-specific safety and tolerability evaluations should be used in all pediatric NIBS studies. Due to the lack of pediatric-specific guidelines, we suggest that established adult guidelines be combined with emerging evidence and careful consideration of relevant pediatric issues to best advance neurostimulation research in children.

Authors contributions

Zewdie E: Conceptualization, Methodology, Formal Analysis, Investigation, Supervision Writing-Original Draft **Ciechanski P:** Conceptualization, Methodology, Formal Analysis, Investigation, Writing-Original Draft **Kuo H:** Conceptualization, Methodology, Formal Analysis, Writing-Review & Editing **Giuffre A:** Conceptualization, Methodology, Formal Analysis, Writing-Review & Editing **Kahl C:** Conceptualization, Methodology, Formal Analysis, Writing-Review & Editing **King R:** Conceptualization, Methodology, Formal Analysis, Writing-Review & Editing **Cole L:** Conceptualization, Methodology, Formal Analysis, Writing-Review & Editing **Godfrey H:** Conceptualization, Methodology, Formal Analysis, Writing-Review & Editing **Seeger T:** Conceptualization, Methodology, Formal Analysis, Writing-Review & Editing **Swansburg R:** Methodology, Project Administration, Writing-Review & Editing **Damji O:** Conceptualization, Methodology, Formal Analysis, Writing-Review & Editing **Jadavji Z:** Investigation, Project Administration, Writing-Review & Editing. **Larson RJ:** Project Administration, Methodology, Writing-Review & Editing **Rajapakse T:** Conceptualization, Methodology, Writing-Review & Editing **Hodge J:** Investigation, Project Administration, Writing-Review & Editing **Selby B:** Project Administration, Methodology, Writing-Review & Editing **Gan L:** Project Administration, Methodology, Writing-Review & Editing **Nelson S:** Project Administration, Methodology, Formal Analysis, Writing-Review & Editing **MacMaster F:** Conceptualization, Methodology, Supervision, Writing-Review & Editing **Yang JF:** Conceptualization, Methodology, Supervision, Writing-Review & Editing. **Barlow K:** Conceptualization, Methodology, Supervision, Writing-Review & Editing. **Gorassini M:** Conceptualization, Methodology, Supervision, Writing-Review & Editing. **Brunton K:** Investigation, Project Administration, Writing-Review & Editing **Kirton A:** Conceptualization, Methodology, Supervision, Writing-Original Draft

Declaration of competing interest

The authors declare no competing financial interests.

Acknowledgment

We would like to thank all the participants of the studies and their families. We also would like to thank the several funding agencies that funded the 27 studies included in this paper. We would like to thank Alberto NettelAguirre for his contribution to build the brain stimulation laboratories. We also would like to thank the Canadian Institutes of Health Research, Alberta Children's Hospital Foundation and Hotchkiss Brain Institute of University of Calgary that funded the Pediatric NIBS laboratory.

Appendix.A

NIBS TOLERABILITY QUESTIONNAIRE	
Subject ID:	**Date and time**:
Stimulation type (circle) **:** spTMS ppTMS rTMS tDCS TBS HD-tDCS tACS RNS sTMS Other:	

To be completed by staff ***prior*** to starting NIBS session:	
Previous night's sleep: How tired are you feeling? If tired, why? Have you exercised today?	Duration: _____ *hours* Quality: _____ (1-5) (Not at all) 1 2 3 4 5 (Very) _____ No ☐ Yes ☐ How long ago? _____
Have you consumed caffeine today?	No ☐ Yes ☐ How long ago? _____ Type _____ Amount _____
Have you used any drugs or alcohol in the past 24 hours? *(Include medication)*	No ☐ Yes ☐ How long ago? _____ Type _____ Amount _____
Do you suffer headaches? *If yes, how often: ____ times/week and how severe: ____ rank from 1(mild) to 5 (severe)*	

To be completed by staff ***after*** NIBS session:		
Please indicate the presence/absence of the following (✓= Yes), and ***rate severity*** *from mild (1) to severe (5)*		
Headache	Neck pain	Ringing in ears
Lightheadedness	Nausea	Hearing problems
Unpleasant tingling	Fatigue	Vision problems
Burning Sensation	Itching	Toothache
Serious adverse events or Other Comments:		
Interactivity:		
Conversation: (None) 1 2 3 4 5 (Lots) *Did participant initiate conversations?* Yes No	Activity: *(type and genre, i.e. Movie, Comedy)* _____	
How fidgety/active was participant during session? (Still) 1 2 3 4 5 (Active)	How frequently did staff countdown to stimulation? (Never) 1 2 3 4 5 (Always)	

Preference Ratings: Please rank the following common experiences from most enjoyable (1) to least enjoyable (8).

_____ Watching TV _____ Birthday Party _____**NIBS Session** Today _____ Going to Dentist

_____ Shot at Doctors _____ Throwing Up _____ Time with Friends _____ Long Car Ride

References

[1] Bikson M, Grossman P, Thomas C, Zannou AL, Jiang J, Adnan T, et al. Safety of transcranial direct current stimulation: evidence based update 2016. Brain Stimul 2016;9:641–61. https://doi.org/10.1016/j.brs.2016.06.004.

[2] Valero-Cabré A, Amengual JL, Stengel C, Pascual-Leone A, Coubard OA. Transcranial magnetic stimulation in basic and clinical neuroscience: a comprehensive review of fundamental principles and novel insights. Neurosci Biobehav Rev 2017;83:381–404. https://doi.org/10.1016/j.neubiorev.2017.10.006.

[3] Zewdie E, Kirton A. TMS basics: single and paired pulse neurophysiology. In: Kirton A, Gilbert DL, editors. Pediatric brain stimulation: mapping and modulating the developing brain. first ed. Elsevier; 2016. p. 475.

[4] Allen CH, Kluger BM, Buard I. Safety of transcranial magnetic stimulation in children: a systematic review of the literature. Pediatr Neurol 2017;68:3–17. https://doi.org/10.1016/j.pediatrneurol.2016.12.009.

[5] Hameed MQ, Dhamne SC, Gersner R, Kaye HL, Oberman LM, Pascual-Leone A, et al. Transcranial magnetic and direct current stimulation in children. Curr Neurol Neurosci Rep 2017;17:11. https://doi.org/10.1007/s11910-017-0719-0.

[6] 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.

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

[8] 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;117:455–71. https://doi.org/10.1016/j.clinph.2005.10.014.

[9] Bae EH, Schrader LM, Machii K, Alonso-Alonso M, Riviello JJ, Pascual-Leone A, et al. Safety and tolerability of repetitive transcranial magnetic stimulation in patients with epilepsy: a review of the literature. Epilepsy Behav 2007;10:521–8. https://doi.org/10.1016/j.yebeh.2007.03.004.

[10] Durmaz O, Ebrinc S, Ates MA, Algul A. Evaluation of repetitive transcranial magnetic stimulation for treatment-resistant major depression and the impact of anxiety symptoms on outcome. Psychiatr Clin Psychopharmacol 2017;27:14–8. https://doi.org/10.1080/24750573.2017.1293239.

[11] Tarapore PE, Picht T, Bulubas L, Shin Y, Kulchytska N, Meyer B, et al. Safety and tolerability of navigated TMS in healthy volunteers. Clin Neurophysiol 2016;127:1916–8. https://doi.org/10.1016/j.clinph.2015.11.043.

[12] Hosomi K, Morris S, Sakamoto T, Taguchi J, Maruo T, Kageyama Y, et al. Daily repetitive transcranial magnetic stimulation for poststroke upper limb paresis in the subacute period. J Stroke Cerebrovasc Dis 2016;25:1655–64. https://doi.org/10.1016/j.jstrokecerebrovasdis.2016.02.024.

[13] Krishnan C, Santos L, Peterson MD, Ehinger M. Safety of noninvasive brain stimulation in children and adolescents. Brain Stimul 2015;8:76–87. https://doi.org/10.1016/j.brs.2014.10.012.

[14] Kessler SK, Turkeltaub PE, Benson JG, Hamilton RH. Differences in the experience of active and sham transcranial direct current stimulation. Brain Stimul 2012;5:155–62. https://doi.org/10.1016/j.brs.2011.02.007.

[15] Ciechanski P, Kirton A. Transcranial direct-current stimulation (tDCS): principles and emerging applications in children. In: Kirton A, Gilbert D, editors. Pediatric brain stimulation: mapping and modulating the developing brain. first ed. Elsevier; 2016. p. 475.

[16] Garvey MA, Gilbert DL. Transcranial magnetic stimulation in children. Eur J Paediatr Neurol 2004;8:7–19.

[17] Ciechanski P, Kirton A. Transcranial direct-current stimulation can enhance motor learning in children. Cerebr Cortex 2017;27:2758–67. https://doi.org/10.1093/cercor/bhw114.

[18] Damji O, Keess J, Kirton A. Evaluating developmental motor plasticity with paired afferent stimulation. Dev Med Child Neurol 2015. https://doi.org/10.1111/dmcn.12704.

[19] Kirton A, Ciechanski P, Zewdie E, Andersen J, Nettel-Aguirre A, Carlson H, et al. Transcranial direct current stimulation for children with perinatal stroke and hemiparesis. Neurology 2017;88:259–67. https://doi.org/10.1212/WNL.0000000000003518.

[20] Seeger TA, Kirton A, Esser MJ, Gallagher C, Dunn J, Zewdie E, et al. Cortical excitability after pediatric mild traumatic brain injury. Brain Stimul 2016. https://doi.org/10.1016/j.brs.2016.11.011.

[21] Zewdie E, Damji O, Ciechanski P, Seeger T, Kirton A. Contralesional corticomotor neurophysiology in hemiparetic children with perinatal stroke: developmental plasticity and clinical function. Neurorehabilitation Neural Repair 2016;31:261–71. https://doi.org/10.1177/1545968316680485.

[22] Cole L, Giuffre A, Ciechanski P, Carlson H, Zewdie E, Kuo HC, et al. Effects of high-definition and conventional transcranial direct-current stimulation on motor learning in children 08/18.

[23] Grab JG, Zewdie E, Carlson HL, Kuo H-C, Ciechanski P, Hodge J, et al. Robotic TMS mapping of motor cortex in the developing brain. J Neurosci Methods 2018;309:41–54. https://doi.org/10.1016/j.jneumeth.2018.08.007.

[24] Kuo M-F, Paulus W, Nitsche MA. Therapeutic effects of non-invasive brain stimulation with direct currents (tDCS) in neuropsychiatric diseases. Neuroimage 2014;85(3):948–60. https://doi.org/10.1016/j.neuroimage.2013.05.117.

[25] Hurd C, Livingstone D, Brunton K, Teves M, Zewdie E, Smith A, et al. Early intensive leg training to enhance walking in children with perinatal stroke: protocol for a randomized controlled trial. Phys Ther 2017;97:818–25. https://doi.org/10.1093/ptj/pzx045.

[26] Rossini PM, Barker AT, Berardelli A, Caramia MD, Caruso G, Cracco RQ, et al. Non-invasive electrical and magnetic stimulation of the brain, spinal cord and roots: basic principles and procedures for routine clinical application. Report of an IFCN committee. Electroencephalogr Clin Neurophysiol 1994;91:79–92.

[27] Kujirai T, Caramia MD, Rothwell JC, Day BL, Thompson PD, Ferbert A, et al. Corticocortical inhibition in human motor cortex. J Physiol (Lond) 1993;471:501–19.

[28] Ziemann U, Tergau F, Wassermann EM, Wischer S, Hildebrandt J, Paulus W. Demonstration of facilitatory I wave interaction in the human motor cortex by paired transcranial magnetic stimulation. J Physiol (Lond) 1998;511(Pt 1):181–90.

[29] Tokimura H, Ridding MC, Tokimura Y, Amassian VE, Rothwell JC. Short latency facilitation between pairs of threshold magnetic stimuli applied to human motor cortex. Electroencephalogr Clin Neurophysiol 1996;101:263–72.

[30] George MS, Wassermann EM, Williams WA, Steppel J, Pascual-Leone A, Basser P, et al. Changes in mood and hormone levels after rapid-rate transcranial magnetic stimulation (rTMS) of the prefrontal cortex. J Neuropsychiatry Clin Neurosci 1996;8:172–80.

[31] Chen R, Yung D, Li JY. Organization of ipsilateral excitatory and inhibitory pathways in the human motor cortex. J Neurophysiol 2003;89:1256–64.

[32] Eng D, Zewdie E, Ciechanski P, Kirton A. Interhemispheric inhibition in children with perinatal stroke. Clin Neurophys in press.

[33] Yang JF, Livingstone D, Brunton K, Kim D, Lopetinsky B, Roy F, et al. Training to enhance walking in children with cerebral palsy: are we missing the window of opportunity? Semin Pediatr Neurol 2013;20:106–15.

[34] Pell GS, Roth Y, Zangen A. Modulation of cortical excitability induced by repetitive transcranial magnetic stimulation: influence of timing and geometrical parameters and underlying mechanisms. Prog Neurobiol 2011;93:59–98. https://doi.org/10.1016/j.pneurobio.2010.10.003.

[35] Stefan K, Kunesch E, Cohen LG, Benecke R, Classen J. Induction of plasticity in the human motor cortex by paired associative stimulation. Brain 2000;123(Pt 3):572–84.

[36] Stefan K, Kunesch E, Benecke R, Cohen LG, Classen J. Mechanisms of enhancement of human motor cortex excitability induced by interventional paired associative stimulation. J Physiol 2002;543:699–708.

[37] Stagg CJ, Nitsche MA. Physiological basis of transcranial direct current stimulation. The Neuroscientist 2011;17:37–53. https://doi.org/10.1177/1073858410386614.

[38] Jamil A, Batsikadze G, Kuo H-I, Labruna L, Hasan A, Paulus W, et al. Systematic evaluation of the impact of stimulation intensity on neuroplastic after-effects induced by transcranial direct current stimulation. J Physiol (Lond) 2017;595:1273–88. https://doi.org/10.1113/JP272738.

[39] Keel JC, Smith MJ, Wassermann EM. A safety screening questionnaire for transcranial magnetic stimulation. Clin Neurophysiol 2001;112:720.

[40] Kirton JA A. Brain stimulation and constraint for hemiparesis after perinatal stroke: the PLASTIC CHAMPS trial. Eur J Paediatr Neurol 2015;19:S10. https://doi.org/10.1016/S1090-3798(15)30030-1.

[41] Lefaucheur J-P, André-Obadia N, Antal A, Ayache SS, Baeken C, Benninger DH, et al. Evidence-based guidelines on the therapeutic use of repetitive transcranial magnetic stimulation (rTMS). Clin Neurophysiol 2014;125:2150–206. https://doi.org/10.1016/j.clinph.2014.05.021.

[42] Lisanby SH, Husain MM, Rosenquist PB, Maixner D, Gutierrez R, Krystal A, et al. Daily left prefrontal repetitive transcranial magnetic stimulation in the acute treatment of major depression: clinical predictors of outcome in a multisite, randomized controlled clinical trial. Neuropsychopharmacology 2009;34:522–34. https://doi.org/10.1038/npp.2008.118.

[43] André-Obadia N, Peyron R, Mertens P, Mauguière F, Laurent B, Garcia-Larrea L. Transcranial magnetic stimulation for pain control. Double-blind study of different frequencies against placebo, and correlation with motor cortex stimulation efficacy. Clin Neurophysiol 2006;117:1536–44. https://doi.org/10.1016/j.clinph.2006.03.025.

[44] Schrader LM, Stern JM, Koski L, Nuwer MR, Engel Jr J. Seizure incidence during single- and paired-pulse transcranial magnetic stimulation (TMS) in individuals with epilepsy. Clin Neurophysiol 2004;115:2728–37.

[45] Garvey MA, Ziemann U, Bartko JJ, Denckla MB, Barker CA, Wassermann EM. Cortical correlates of neuromotor development in healthy children. Clin Neurophysiol 2003;114:1662–70.

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

[47] Chae J-H, Nahas Z, Wassermann E, Li X, Sethuraman G, Gilbert D, et al. A pilot safety study of repetitive transcranial magnetic stimulation (rTMS) in Tourette's syndrome. Cogn Behav Neurol 2004;17:109–17.

[48] Croarkin PE, Wall CA, McClintock SM, Kozel FA, Husain MM, Sampson SM. The emerging role for repetitive transcranial magnetic stimulation in optimizing the treatment of adolescent depression. J ECT 2010;26:323–9.

[49] 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;54:636–9.

[50] Hong YH, Wu SW, Pedapati EV, Horn PS, Huddleston DA, Laue CS, 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. https://doi.org/10.3389/fnhum.2015.00029.

[51] Rakhade SN, Jensen FE. Epileptogenesis in the immature brain: emerging mechanisms. Nat Rev Neurol 2009;5:380–91. https://doi.org/10.1038/nrneurol.2009.80.

[52] Moliadze V, Fritzsche G, Antal A. Comparing the efficacy of excitatory transcranial stimulation methods measuring motor evoked potentials. Neural Plast 2014:1–6. https://doi.org/10.1155/2014/837141. 2014.

[53] 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;64:872–5. https://doi.org/10.1212/01.WNL.0000152986.07469.E9.

[54] Kessler SK, Minhas P, Woods AJ, Rosen A, Gorman C, Bikson M. Dosage considerations for transcranial direct current stimulation in children: a computational modeling study. PLoS One 2013;8:e76112. https://doi.org/10.1371/journal.pone.0076112.

[55] Chhatbar PY, Ramakrishnan V, Kautz S, George MS, Adams RJ, Feng W. Transcranial direct current stimulation post-stroke upper extremity motor recovery studies exhibit a dose-response relationship. Brain Stimul 2016;9:16–26. https://doi.org/10.1016/j.brs.2015.09.002.

[56] Ciechanski P, Carlson HL, Yu SS, Kirton A. Modeling transcranial direct-current stimulation-induced electric fields in children and adults. Front Hum Neurosci 2018;12. https://doi.org/10.3389/fnhum.2018.00268.