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SCIENTIFIC REVIEW

Non-invasive brain stimulation in childhood epilepsy

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ABSTRACT

Transcranial Magnetic Stimulation (TMS) and Transcranial Direct Current Stimulation (tDCS) are new neurophysiological techniques that allow neurologists and neuroscientists to investigate brain function and neural networks in normal humans as well as in those with neurological and neuropsychiatric disorders.

In epilepsy, these techniques reveal abnormal excitability of the brain in focal and generalized epilepsy. Different patterns of excitatory and inhibitory changes detected by TMS can be used in the clinic for evaluating patients with epilepsy and to help with diagnosis, monitoring and treatment.

Repetitive TMS (rTMS) and tDCS have the ability to modulate cortical excitability over prolonged periods and are being investigated for the treatment of epilepsy. However, further studies are needed to find optimal stimulation paradigms that reliably reduce seizures, and to confirm long term benefits and safety of these interventions.

There are fewer TMS and tDCS studies in children and it's not clear if patterns of excitability changes are similar to those seen in adults or if there are unique patterns in childhood epilepsies. Interventional trials assessing safety and efficacy of TMS and tDCS offer hope to children with treatment resistant epilepsies.

Keywords: Transcranial magnetic stimulation, Transcranial direct current stimulation, intra-cortical facilitation, intra-cortical inhibition

INTRODUCTION

Transcranial Magnetic Stimulation (TMS) and Transcranial Direct Current Stimulation (tDCS) are novel neurophysiological tools that allow us to explore neural networks and modulate cortical excitability. They are non-invasive and well tolerated. They have been used to study brain function in normal subjects as well as those with neurological and neuropsychiatric disorders for more than two decades and appear to be safe [1, 2]. There is increasing effort to exploit the potential of TMS and tDCS in diagnostic and therapeutic applications [1, 3, 4, 5]. Although the studies have involved mainly adults, these techniques have proven equally useful in studies of brain development and neurological and neuropsychiatric disorders in children [6, 7, 8]. The aim of this paper is to review the use of non-invasive brain stimulation (NIBS) in childhood epilepsy, but results from adult studies are included since there is more information available in this age group and many adult studies have included a small number of children among their patients.

Transcranial Magnetic Stimulation involves the delivery of a brief magnetic pulse over the scalp which induces a small electric current in the underlying brain (Fig. 1). This focal stimulation is usually assessed by applying a sufficient stimulus over the motor cortex to evoke a brief muscle contraction (motor evoked potential or MEP) in one or more contralateral muscles. The stimulus parameters required to evoke MEPs depends on excitability of cortical as well as spinal neurons [9]. Single and paired TMS pulses delivered over the motor cortex are used to evaluate motor thresholds, cortical excitability and inhibition, inter-hemispheric interactions, and integrity of the corticospinal tract (Fig. 2) [5, 9, 10].

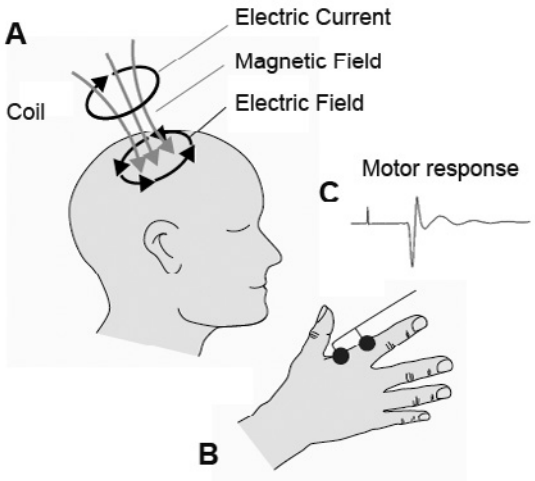

Figure 1. Experimental setup in Transcranial Magnetic Stimulation (TMS).
A. Brief current applied to the TMS coil generates a changing magnetic field which induces an electric field within the tissue. Sufficient stimulus results in activation of corticospinal neurons in the motor cortex below the coil which evokes a twitch in a contralateral muscle. Surface (electromyogram) electrodes applied to the first dorsal interosseus muscle (B) is used to record the motor evoked potential (C). This figure was adapted from Fig. 1 of Frye et al. [7].

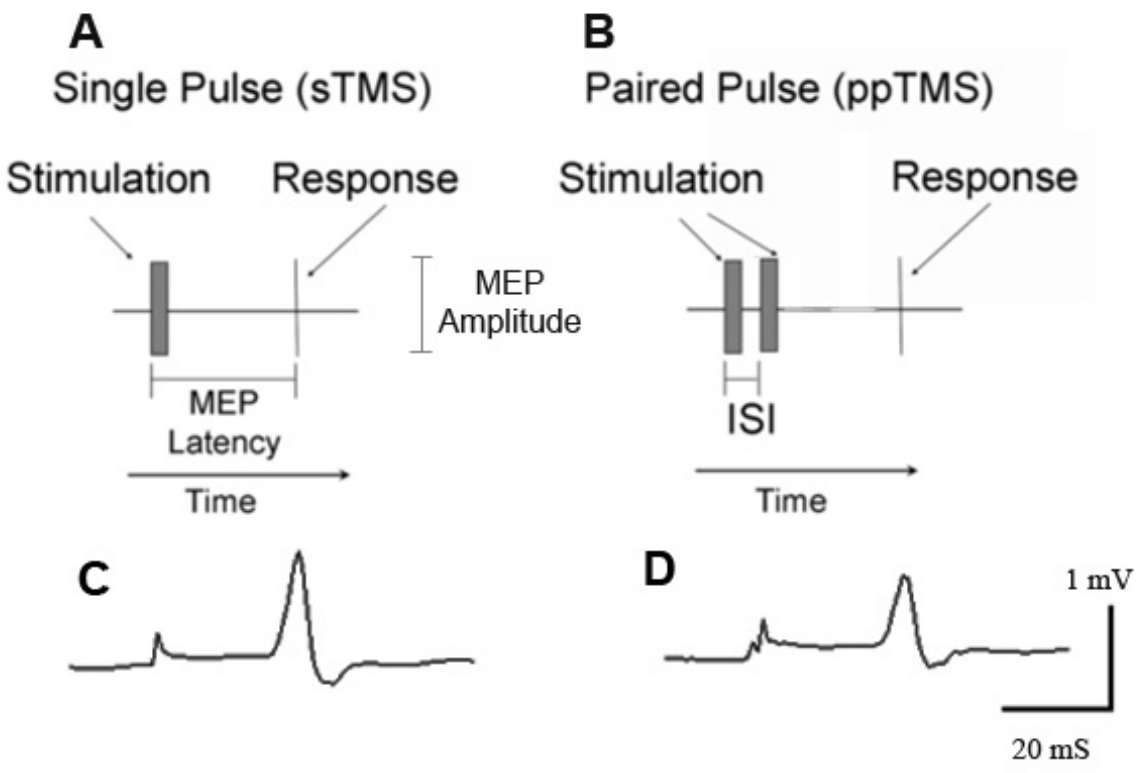

Figure 2. Single and paired pulse stimulation techniques.
A. Single pulse stimulation induces a motor evoked potential (MEP), whose latency and amplitude can be measured as shown. B. Paired pulse stimulation is used to investigate intracortical excitation and inhibition by varying the interpulse interval and the intensity of the first (conditioning) and second (test) stimulus. C and D show MEPs recorded in a normal subject. In C the stimulus amplitude was set to evoke an MEP of approximately 1mV in amplitude. In D 2 stimuli were delivered at 2 ms interval, the conditioning stimulus intensity was set at 80% of the resting motor threshold (RMT) which was then followed by the test stimulus at the same intensity as in C. The evoked MEP in D is smaller than C due to intracortical inhibition initiated by the conditioning stimulus. Abbreviations: ISI: interstimulus interval, MEP: motor evoked potential, mV: millivolts, mS: milliseconds. This figure was adapted from Fig. 1 of Frye et al. [7].

Weak direct currents applied to the scalp (tDCS) induce long lasting changes in cortical excitability which is controlled by polarity, duration and strength of stimulus (Fig. 3) [2, 11, 12]. Anodal tDCS increases, whilst cathodal tDCS reduces cortical excitability [2, 11]. tDCS modulates brain excitability and regional brain activity by altering the membrane potential of neurons and activation of N-methyl-D-aspartate (NMDA) receptors [13, 14]. The effects of tDCS over the motor cortex are usually measured by TMS (TMS evoked MEP size) [11], but tDCS induces widespread effects in the brain as demonstrated by a PET study [15].

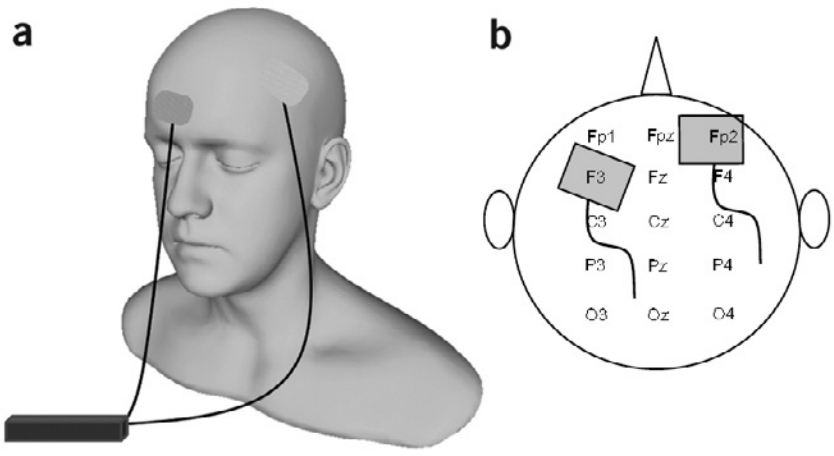

Figure 3. Transcranial Direct Current Stimulation tDCS of the left frontal area.
The active electrode is positioned over the left hemisphere and the reference above the supra-orbital ridge on the opposite side, as seen on a mannequin on the left (a) and on a schematic drawing of standard EEG surface locations on the right (b). Depending on the polarity of the active electrode, cathodal or anodal stimulation can be performed. This figure was adapted from Fig. 1 of Dayan et al. [71] and Fig. 1 of Nitsche et al. [2].

EXPLORING CORTICAL EXCITABILITY IN EPILEPSY USING TMS

Epilepsy is associated with hyperexcitable neurons and hypersynchrony of neural circuits [16]. Thus, TMS is well suited to investigate cortical excitability in epilepsy and is used to understand epileptogenic mechanisms, and effects of treatment (Table 1) [3, 4, 17, 18, 19, 20]. Cortical excitability changes may be reflected in changes in motor thresholds (resting and active motor thresholds), intra-cortical facilitation (ICF), cortical silent period (CSP) or short- and long-interval intra-cortical inhibition (SICI, LICI) [5, 9, 21, 22]. Pharmacological studies suggest that Gamma-aminobutyric Acid A (GABA-A) receptor mechanisms are involved in SICI, while GABA-B receptor mechanisms are involved in LICI and CSP [23, 24]. ICF appears to be mediated by glutaminergic cortical interneurons and is influenced by NMDA receptors [25]. These cortical excitability changes have been investigated in the motor cortex of patients with generalized and focal epilepsy (including focal epilepsy involving non-motor cortical areas), and the studies are listed in Table 1.

Table 1. Studies of cortical excitability in children and adults with epilepsy

Reference	No of patients, controls	Type of epilepsy	AED use	TMS study
Adults				
Reutens & Berkovic, 1992 [31]	45, 71	GE	DN, CE	MT
Reutens et al. 1993 [32]	11, 50	GE		MT
Gianelli et al. 1994 [35]	20, 10	GE	DN, CE	MT
Caramia et al. 1996 [36]		GE		SICI
Brodtmann et al. 1999 [37]	7, 16	GE	DN	MT, ICF, LICI
Cantello et al. 2000* [41]	17, 11	GE, FE	CE, RE	MT, ICF, SICI, CSP
Cicinelli et al. 2000* [40]	16, 16	FE		MT, CSP
Manganotti et al. 2000 [28]	15, 12	GE	DN, CE, RE	MT, ICF, SICI, LICI, CSP
Hamer et al. 2005 [42]	23, 20	FE	RE	MT, ICF, SICI, CSP
Badawy et al. 2006 [18]	30, 13	GE, FE	DN	MT, ICF, SICI, LICI
Badawy et al. 2007* [38]	62, 29	GE, FE	DN	MT, ICF, SICI, LICI
Kotova & Vorobeva 2007 [39]	31	FE	DN, CE	MT
Badawy et al. 2012 [43]	58, 20	GE, FE	DN, RE	MT, ICF, SICI, LICI
Badawy et al. 2013a [33]	77, 30	GE, FE	DN, CE, RE	MT, SICI, LICI
Badawy et al. 2013b* [34]	137	GE	DN, CE, RE	MT, ICF, SICI, LICI
Meta analysis				
Brigo et al. 2012 [17]	265, 424	GE		MT
Children				
Nezu et al. 1997 [44]	13, 10	BFEC	DN, CE	MT
Inghilleri et al. 1998 [45]	1	FE	RE	MT, SICI, LICI, CSP
Shimazu et al. 2001 [46]	1	FE	Surg, RE	MT, SICI

*Children or adolescents included in study
Abbreviations: BFEC: Benign Focal Epilepsy of Childhood, CE: Controlled Epilepsy (Seizures controlled on AEDs), CSP: Contralateral silent period, DN: Drug naive, FE: Focal epilepsy, GE: Generalized epilepsy, ICF: Intracortical facilitation, LICI: Long interval cortical inhibition, MT: Motor threshold, RE: Refractory Epilepsy (to AEDs), SICI: Short interval cortical inhibition, Surg: Epilepsy surgery

A number of parameters are known to affect cortical excitability including age, use of medications, ovarian cycle, migraine and sleep deprivation [4, 26, 27, 28; 29]. There is a large variation in cortical excitability measured by TMS between subjects, and less so in the same subjects between sessions [30]. Technical factors, such as coil size and orientation, may result in variation in the results reported by different studies. In addition, intra-cortical facilitation and inhibition measured by paired pulse TMS can vary with the size of the test MEPs [5]. These factors cause some variability in the results from different studies, and may affect the feasibility of using TMS in clinical testing.

The TMS studies of cortical excitability in adults with epilepsy show changes which are dependent on type of epilepsy and its treatment [3, 17, 19]. In untreated adults with epilepsy cortical inhibition is reduced and excitability is increased, whereas these changes are reversed by effective treatment with anti epileptic drugs (AEDs). Among untreated patients with generalized epilepsy syndromes reduced motor thresholds are consistently seen in Juvenile Myoclonic Epilepsy (JME) [17, 31]. Motor thresholds increase after effective treatment but are unchanged if seizures are refractory [32, 33, 34, 35]. Paired pulse stimulation shows that intra-cortical inhibition (SICI and LICI) is reduced and intra-cortical facilitation (ICF) increased in untreated patients; when treatment with AEDs results in seizure control there is an increase in SICI and LICI and reduction in ICF [28, 31, 32, 33, 36, 37, 38]. These treatment induced changes are not seen in refractory epilepsy [33]. TMS studies in adults with focal epilepsy often show asymmetrical changes in excitability; there is increased excitability and reduced inhibition in the affected hemisphere prior to treatment, but there is increased inhibition with treatment and seizure control [33, 39, 40, 41]. Asymmetric excitability changes however persist in adults with refractory epilepsy [33, 42].

Transcranial Magnetic Stimulation is used to explore susceptibility to seizures in vulnerable populations e.g. after a stroke [20], or in siblings and relatives of patients with epilepsy [34]. Althoguh epilepsy is a heterogenous disorder with diverse etiopathologies, few TMS studies have compared epilepsies with different etiologies or electroclinical spectra. In untreated patients with generalized epilepsy motor thresholds are found to be similar to controls, except in Juvenile Myoclonic Epilepsy and Progressive Myoclonic Epilepsy where they are reduced [17]. In contrast, motor thresholds were found to be increased in children with Lennox Gastaut syndrome [43]. Thus, excitability changes detected by TMS are not only influenced by seizure susceptibility and treatment but also underlying pathophysiology.

In comparison with adults, there are fewer TMS studies in children with epilepsy [44, 45 46]; some studies in adults have included a small number of children and adolescents in their sample [e.g. 34, 38, 40, 41]. In children with focal refractory epilepsy there is reduced inhibition in the affected hemisphere; however motor thresholds were increased or unchanged [45, 46]. Motor thresholds in untreated children with Benign Focal Epilepsy of Childhood [BFEC] were found to be similar to controls, whereas thresholds increased after starting valproate [44].

There are a number of potential applications of TMS in diagnosis and monitoring of patients with epilepsy, but further studies exploring the usefulness of TMS in the clinic are needed. Promising areas include monitoring seizure vulnerability in those with infrequent seizures or childhood seizure susceptibility syndromes. TMS may help identify patients with brain injury who may be at risk of seizures (stroke, traumatic brain injury). Assessing and predicting the effectiveness of antiepileptic drugs and other treatments may be assisted by TMS studies.

MODULATING CORTICAL EXCITABILITY WITH REPETITIVE TMS

The capacity of non-invasive brain stimulation to induce lasting changes in brain excitability has been applied for enhancing neural function and in treating neurological and neuropsychiatric disorders [2, 6]. Stimulation is applied to the part of the brain which is relevant to the clinical condition, including sensory and association cortical areas. Repetitive TMS (rTMS) may be used to increase or decrease excitability of the stimulated brain area depending on the frequency, pattern and duration of stimulation. Cortical inhibition induced by low frequency rTMS has been investigated to treat patients with focal epilepsy (Table 2).

In focal epilepsy rTMS is commonly applied over the epileptogenic focus, e.g. cortical dysplasia, and seizure frequency during and 4-8 weeks after stimulation compared with 4-12 weeks prior to stimulation. In single case studies low frequency rTMS over the area of cortical dysplasia was shown to reduce seizure frequency as well as inter-ictal epileptiform discharges for 4-8 weeks [47, 48]. However, in open label studies involving small numbers of patients, results have been variable, with some studies showing statistically significant reduction in seizure frequency during and after rTMS [49, 50, 51, 52], while other studies did not [53, 54]. Similarly, reduction in interictal spike frequency after rTMS has been observed in some, but not all studies [51, 52, 54]. These differences could have been due to stimulus parameters and protocols, which varied considerably between different studies; but there were no obvious differences in the frequency and duration of rTMS between successful and unsuccessful trials. Stimulation frequencies varied from 0.3-1 Hz, amplitude from 90-110% of resting motor threshold, and treatment was given in a single session, or biweekly for 4 weeks, or daily for 2 weeks, or 3 sessions a day for 2 weeks, or every day for 5 days, or twice a week for 3 months. In one study [54] longer stimulus duration per day appeared to result in fewer seizures but did not reach significance.

Placebo controlled trials of rTMS have also produced variable results, with some studies finding significantly reduced seizure frequency [52, 55] while others did not [56]. Most controlled trials found a reduction in interictal epileptiform discharges after stimulation. In those with non-focal or multifocal epilepsy, rTMS has been applied to the vertex (Cz location) with no statistically significant reduction in seizure frequency [54].

There are fewer interventional studies using rTMS in children with epilepsy. In Santiago-Rodriguez et al.'s study [51], 5 of the 12 patients were children, and in Fregni et al.'s study [50] 3 of 8 patients were children: group data in both studies showed reduction in seizure frequency after rTMS applied to the seizure focus. In Kinshota et al.'s study [53], 1 of 7 patients was a 16 year old adolescent, and group data did not show any benefit of low frequency rTMS. In Epilepsia Partialis Continua (EPC), Morales et al. [57] did not find any effect of low frequency rTMS (1Hz alone or preceded by priming with 6Hz) on seizure frequency in two children. In contrast Graf-Guerrero et al. [58] used high frequency rTMS (single session of 20Hz, 2s train, inter train interval 58s, 15 trains applied over the ictal focus) in 2 children with EPC, and doc-

Table 2. Trials of rTMS and tDCS for the treatment of epilepsy

Reference	No of patients	Type of epilepsy	AED use	Type of stimulation
Adults (open label)				
Menkes and Gruenthal 2000 [47]	1	FE	RE	0.5 Hz rTMS
Brasil-Neto et al. 2004* [49]	5	FE	RE	0.3 Hz rTMS
Fregni et al. 2005 [50]	8	FE	RE	0.5 Hz rTMS
Kinoshita et al. 2005* [53]	7	FE	RE	0.9 Hz rTMS
Misawa et al. 2005 [48]	1	FE (EPC)	RE	0.5 Hz rTMS
Santiago-Rodriguez et al. 2008* [51]	12	FE	RE	0.5 Hz rTMS
Adults (placebo controlled)				
Fregni et al. 2006 [55]	21	FE	RE	1 Hz rTMS
Cantello et al. 2007 [56]	43		RE	0.3 Hz rTMS
Joo et al. 2007 [54]	35	FE	RE	0.5 Hz rTMS
Sun et al. 2012 [52]	60	FE	RE	0.5 Hz rTMS
Children (open label)				
Graff-Guerrero et al. 2004 [58]	2	FE (EPC)	RE	20 Hz rTMS
Morales et al. 2005 [57]	2	FE (EPC)	RE	1 Hz/ 6 Hz rTMS
Yook et al. 2011 [60]	1	FE	RE	Cathodal tDCS
Nagarajan et al. 2014 [61]	1	FE	RE	Cathodal tDCS
Varga et al. 2011 [63]	5	ESES	RE	Cathodal tDCS
Children (placebo controlled)				
Auvichayapat et al. 2013 [62]	36	FE	RE	Cathodal tDCS

*Children or adolescents included in study
Abbreviations: EPC: Epilepsia partialis continua, FE: Focal epilepsy, RE: Refractory to treatment, rTMS: repetitive Transcranial Magnetic Stimulation, tDCS: transcranial Direct Current Stimulation

umented a dramatic improvement in one (seizure frequency reduced and stopped in the next 24 hours) but minimal improvement in the other child.

Variability in the clinical efficacy of rTMS may be related to a number of factors including the type and severity of epilepsy, as well as the interaction of antiepileptic drugs and TMS. Effects of TMS on cortical excitability have been shown to be blocked by many of the drugs used for treatment [25] and the modulatory effects of rTMS have not been explored in patients on AEDs.

MODULATING CORTICAL EXCITABILITY WITH TRANSCRANIAL DIRECT CURRENT STIMULATION

Transcranial Direct Current Stimulation induces long lasting changes in cortical excitability [2, 12]. The effects of tDCS may be assessed by measuring the size of MEPs evoked by TMS before and after tDCS. Anodal tDCS of 1-2mA applied for 5-20 mins increases cortical excitability. Cathodal tDCS of 1mA applied for 5 to 20 minutes reduces cortical excitability, lasting for up to 2 hours after the stimulus [2, 12].

Recent reports indicate that increasing stimulus amplitude of cathodal tDCS to 2mA reverses this effect and increases cortical excitability [12]. Thus, the direction of excitability change induced by tDCS is not only dependant on stimulus polarity but also its intensity. There is also considerable variability in the responses seen after tDCS in different subjects [59]. This may also account for variability in therapeutic responses seen in clinical studies. In addition, the relationship between neuroplastic effects of tDCS (as measured by TMS induced MEPs) and clinical efficacy is not clear.

The effects of cathodal tDCS on seizure frequency and epileptiform activity have been investigated in a few children (Table 2). In single case studies, cathodal tDCS applied for several days a week for 2 weeks over the cortical focus reduced the frequency and duration of seizures for 2 months in one study [60], but did not reduce seizure frequency in the other [61]. In the latter study there was a significant reduction in the frequency and amplitude of interictal epileptiform discharges [61]. In a placebo controlled trial, Auvichayapat et al. [62] found that application of a single treatment of 1mA cathodal tDCS for 20 minutes over the seizure focus resulted in a small (clinically negligible), but statistically significant reduction in seizure frequency at 4 weeks. There was also a reduction in inter-ictal epileptiform discharges for up to 2 days after treatment. However, in 5 children with focal refractory epilepsy and continuous spike and wave discharges during slow sleep, cathodal tDCS (1mA for 20 mins) did not reduce discharge frequency [63].

SAFETY OF TMS AND TDCS IN CHILDREN

TMS has been used in over 800 normal children and over 300 children with neurological disorders, including more than 25 children with epilepsy and no serious short term adverse effects have been reported [7, 8, 29]. Most of these studies have used single or paired pulse TMS. There is little information on the long term effects of rTMS and tDCS in children [8]. Non-invasive brain stimulation is being trialled in a number of neurological and neuropsychiatric conditions in children, but there is no data on long-term cognitive and neuropsychological effects on the developing brain [6, 64]. These interventions should be used cautiously and studies planned with long-term follow up of children [65]. Induction of seizures is the most severe acute adverse effect of rTMS. In adults with epilepsy the risk of seizures is small (1.4%) after low frequency and high frequency rTMS [66] but is higher than in normal adults (<1%) [67].

Safety of tDCS has been addressed by several reports [e.g. 68, 69]. Common side effects include mild headache, itching and erythema at the electrode site, and transient visual symptoms. There are no published reports of tDCS inducing seizure. A single treatment of short duration tDCS does not cause heating effects under the electrodes, does not elevate serum neurone-specific enolase level (a sensitive marker of neuronal damage) and does not result in changes of diffusion-weighted or contrast-enhanced MRI, or pathological EEG changes [11, 69]. However, the safety of long term changes in neuronal excitability induced by tDCS treatments of long duration or repeated daily treatment still remain unknown [68, 69].

CONCLUSIONS

Preliminary studies of TMS and tDCS show promise, but more studies are needed to confirm the role and benefit of these techniques in the understanding, investigation and management of epilepsy and its comorbidities. TMS has the potential to be used in the evaluation of children with epilepsy, and help with diagnosis, monitoring and treatment. In the early interventional studies, epilepsies of different types and pathologies have been treated with stimulation protocols which vary in frequency and duration. It's still not clear who to treat, which stimulus parameters and protocols to use. Understandably, most studies were conducted in patients with refractory epilepsy and it's not known if these techniques are more effective in non-refractory epilepsy. There is also a lack of data extending beyond a few weeks or months to see if any early benefits are sustained over the long-term. Studies are needed to monitor the short and long-term safety of these procedures.

There is a need for new avenues and treatment options for children with epilepsy, especially those who are treatment resistant, and TMS and tDCS offer hope as additional and novel therapeutic interventions.

LIST OF ABBREVIATIONS:

- AEDs: Anti-epileptic Drugs
- BFEC: Benign Focal Epilepsy of Childhood
- CE: Controlled epilepsy (seizures controlled on AEDs)
- CSP: Cortical Silent Period
- DN: Drug naive
- EPC: Epilepsia partialis continua
- FE: Focal epilepsy
- GABA: Gamma-aminobutyric Acid
- GE: Generalized epilepsy
- ICF: Intra-cortical Facilitation
- JME: Juvenile Myoclonic Epilepsy
- LICI: Long-interval Intra-cortical Inhibition
- MEP: Motor evoked potential
- MT: Motor threshold
- NIBS: Non-invasive Brain Stimulation
- NMDA: N-methyl-D-aspartate
- PME: Progressive Myoclonic Epilepsy
- RE: Refractory epilepsy (to AEDs)
- rTMS: repetitive Transcranial Magnetic Stimulation
- SICI: short-interval intra-cortical inhibition
- tDCS: Transcranial Direct Current Stimulation
- TMS: Transcranial Magnetic Stimulation

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Competing interests

The authors have declared that no competing interest exists.

Author contributions

Both authors made equal contributions towards conception, literature search and writing of this review.

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