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Applications of transcranial direct current stimulation in children and pediatrics

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Abstract: Transcranial direct current stimulation (tDCS) is a neuromodulatory noninvasive brain stimulation tool with potential to increase or reduce regional and remote cortical excitability. Numerous studies have shown the ability of this technique to induce neuroplasticity and to modulate cognition and behavior in adults. Clinical studies have also demonstrated the ability of tDCS to induce therapeutic effects in several central nervous system disorders. However, knowledge about its ability to modulate brain functions in children or induce clinical improvements in pediatrics is limited. The objective of this review is to describe relevant data of some recent studies that may help to understand the potential of this technique in children with specific regard to effective and safe treatment of different developmental disorders in pediatrics. Overall, the results show that standard protocols of tDCS are well tolerated by children and have promising clinical effects. Nevertheless, treatment effects seem to be partially heterogeneous, and a case of a seizure in a child with previous history of infantile spasms and diagnosed epilepsy treated with tDCS for spasticity was reported. Further research is needed to determine safety criteria for tDCS use in children and to elucidate the particular neurophysiological changes induced by this neuromodulatory technique when it is applied in the developing brain.

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Introduction

In recent years, different studies have demonstrated the potential of transcranial direct current stimulation (tDCS) to modulate regional and remote cortical excitability beyond the time of stimulation in adult humans (Nitsche and Paulus, 2000, 2001, 2011; Nitsche et al., 2003a, 2005). As a result of these neurophysiological changes, multiple cortical functions, such as motor responses, learning, memory, associative processes, and other cognitive processes, are also susceptible to be modulated through tDCS (Shin et al., 2015). tDCS is moreover extensively studied for its therapeutic potential in the treatment of neurological, psychiatric, and behavioral disorders and symptoms (Brunoni et al., 2012). It has been suggested to be potentially useful for treatment of depression, anxiety, pain, motor disorders, and aphasia, among other diseases (Shin et al., 2015). These potential applications have been frequently explored in adults. Studies in children and adolescents are relatively rare, possibly caused by doubts about the effectiveness and safety of this technique when applied in a brain in process of maturation. In addition, these studies are heterogeneous in sample size, stimulation parameters, number of tDCS sessions, and the clinical profiles evaluated. Therefore, the main objective of this review is to determine differences in tDCS protocols used in children, in order to contrast information regarding the specific usefulness of this noninvasive brain stimulation method in pediatrics.

For this purpose, the following sections describe some recent studies that show the potential of tDCS in children and adolescents with regard to different stimulation parameters, highlight the need to determine safety principles of this noninvasive brain stimulation technique in children, and to elucidate specific physiological mechanisms that stimulation induces in the developing brain. Specific tDCS protocols as well as the age of the participants in these studies are reported to evaluate possible differences between investigations, which can

help optimize potential therapeutic effects of this tool in future research.

tDCS in children and pediatrics

The number of tDCS studies conducted in children and adolescents is much lower than in adults. A complete review about studies of tDCS and other noninvasive brain stimulation techniques (with greater emphasis on transcranial magnetic stimulation) in childhood and adolescence can be found in Quintana (2005), Croarkin et al. (2011), Vicario and Nitsche (2013a,b), and Rubio et al. (2016). The effects of tDCS on learning and motor performance have been most frequently studied in healthy children (Ciechanski and Kirton, in press). On the other hand, early transcranial polarization studies were conducted to treat patients with infantile cerebral palsy in the 1990s (Bogdanov et al., 1994; Nitsche et al., 2003a). In recent years, most frequently studied pathologies in pediatrics via tDCS include cerebral palsy, refractory epilepsy, autism, deficits of language development, attention-deficit/hyperactivity disorder (ADHD), as well as several other psychiatric disorders (Stagg and Nitsche, 2011; Muszkat et al., 2016).

Healthy children

tDCS is a neuromodulatory intervention that induces alterations of cortical excitability via subthreshold neuronal membrane polarization. It alters cortical excitability and spontaneous activity for a time exceeding the period of stimulation. The electrode with anodal current increases cortical excitability, and the electrode with cathodal current reduces it. Furthermore, this current flow is able to modulate cortico-cortical connectivity (Rivera-Urbina et al., 2015) and also top-down cortico-subcortical connectivity (Polanía et al., 2012). Membrane polarity changes depend on current density and stimulation duration. Prolonged stimulation results in neuroplastic after-effects, which depend on the glutamatergic systems and resemble mechanisms of long-term potentiation (LTP) and depression (Nitsche et al., 2008; Stagg and Nitsche, 2011). The catecholaminergic system seems to modulate the N-methyl-d-aspartate (NMDA) receptor-dependent LTP-like plasticity induced by tDCS, since the after-effects of anodal tDCS are enhanced by amphetamine (Nitsche et al., 2004).

Physiological studies, which have been conducted primarily on the motor cortex of adult volunteers, suggest a dependency of the after-effects of stimulation on stimulation polarity, intensity, and duration. As a neuromodulatory intervention, the effects of tDCS furthermore show some nonlinear features. Longer and stronger stimulation, as compared to the standard protocols, or repetitive stimulation with specific intervals (Nitsche and Paulus, 2001; Nitsche et al., 2003a) can not only prolong but also convert the direction of after-effects (Monte-Silva et al., 2010, 2013; Fricke et al., 2011; Batsikadze et al., 2013). Moreover, activity differences of neurotransmitter and neuromodulator systems have a prominent impact on stimulation effects (Nitsche et al., 2012). Since physiology, pharmacology, and anatomy differ between adults and children/adolescents, it cannot be taken for granted that identical stimulation protocols induce the same effects in different age groups. Respective physiological studies in children and adults are rare but suggest an adaptation of stimulation protocols for application in children and adolescents (Nitsche et al., 2003b; Cohen Kadosh et al., 2012; Minhas et al., 2012; Kessler et al., 2013). Moliadze et al. (2015a) found that 1 mA anodal or cathodal tDCS applied over the left primary motor cortex for 10 min increased motor evoked potential (MEP) amplitudes when compared with sham stimulation in children (mean age, 13.9 ± 0.4 years). This result clearly differs from those obtained in adults, where cathodal tDCS with the same intensity reduces MEPs (Nitsche et al., 2003b; Batsikadze et al., 2013). However, when stimulation intensity was 0.5 mA, cathodal tDCS reduced MEP amplitudes in children. Thus, it might be assumed that tDCS, maybe caused by smaller head size, thinner cranial bone, and other factors, is more effective in children and adolescents, as compared to adults. This assumption is supported by computational models and high-resolution magnetic resonance imaging, which suggest that the peak electrical field elicited by a specific tDCS intensity in children and adolescents is higher than in adults (Minhas et al., 2012). Because of these results, it was suggested that tDCS protocols should be adapted to age in pediatrics. Although tDCS protocols in children may be associated with particular physiological processes related to the plastic and cognitive changes of this development and maturation stage, they seem to be as well tolerated as in adults (Andrade et al., 2014).

Regarding the functional effects of tDCS in healthy children, some studies on cognitive, motor, and learning processes have been performed (Palm et al., 2016). In a recent study, Ciechanski and Kirton (in press) evaluated the effects of tDCS on performance of different motor tasks (the Jebsen-Taylor Test and the Serial Reaction Time Task) in right-handed healthy school children (mean age, 14.0 ± 3.2 years). They trained the

Purdue Pegboard Test (PPT) with their left hand over three consecutive days, combined with anodal or sham tDCS. Motor learning measures were taken before and after training. Compared with sham stimulation, 1 mA anodal tDCS applied over the right primary motor cortex during performance with the left hand improved PPT execution Interestingly, also 1 and 2 mA cathodal tDCS over the left primary motor cortex improved performance of the left hand in the three motor tasks (for protocol details of this and other studies please see Table 1). These results indicate that contralateral anodal stimulation improved motor performance of the left hand through a direct increase in cortical excitability of the target area. Cathodal ipsilateral stimulation might have improved performance by a reduction of interhemispheric inhibition. This effect of interhemispheric interaction on cortical excitability induced by motor cortex tDCS has also been described in adults (Tazoe et al., 2014). Taking into account the excitability-enhancing effect of 1 mA cathodal tDCS in children in the study of Moliadze et al. (2015a), it cannot be ruled out, however, that excitability-enhancing ipsilateral tDCS had a performance-improving effect. The authors of this study report no adverse effects after repetitive tDCS and consider their protocol as safe for application in children. They also proposed that due to their encouraging results, the respective protocols might be suited to improve motor functions also in clinical conditions, e.g. to enhance rehabilitation results in children suffering from cerebral palsy. Similar results with regard to safety and tolerability of tDCS in healthy pediatric populations have been reported by another study in which anodal, cathodal, and sham tDCS (1 mA for 10 min) was applied over the left primary motor cortex of children and adolescents (aged 11–16 years) (Moliadze et al., 2015b). Also in this study, the protocol was well tolerated, as monitored by self-reports of the participants, and no serious adverse events were reported after real or sham stimulation. Furthermore, no epileptiform activity or pathological oscillations were observed in electroencephalographic (EEG) recordings after stimulation. Thus, effective protocols to induce functional and physiological effects in adults might need specific adaptations in children because their development characteristics. Different stimulation protocols have shown, however, that tDCS is a safe tool in healthy children.

Cerebral palsy and dystonia

Cerebral palsy is the most prevalent physical disability of childhood. Children with this disorder have muscle weakness or reduced mobility due to brain damage. Dystonia refers to abnormal muscle contractions and movements due to multiple causes. The impact of tDCS on symptoms of cerebral palsy and dystonia has been investigated by a few studies in children and adolescents. Most published studies report some clinical improvements without important adverse effects (Grecco et al., 2013, 2014a,b; Young et al., 2013, 2014; Duarte et al., 2014; Gillick et al., 2014, 2015a,b; Collange Grecco et al., 2015), with one exception that will be mentioned in the discussion section (Ekici, 2015). A null effect was also reported in one case (Bhanpuri et al., 2015). For cerebral palsy, it was described that anodal tDCS applied over the cerebellum combined with treadmill training can improve signs of ataxia in these patients (Grecco et al., in press). Although the small sample size of this pilot study makes it difficult to generalize results, the significant performance improvements associated with anodal tDCS are consistent with similar effects obtained in other motor pathologies in adults, for example improvements in motor function of chronic stroke patients (Rocha et al., 2016). In another study exploring the effects of tDCS on clinical symptoms in cerebral palsy, the anodal electrode was placed over the primary motor cortex and the cathode over the contralateral supraorbital region and such the most often used montage for motor cortex stimulation in adults (Salvador et al., 2015). Here, a single anodal tDCS session combined with virtual reality mobility training improved static balance (body sway velocity in the anteroposterior and mediolateral directions) of 4- to 12-year-old children with cerebral palsy compared to sham stimulation (Lazzari et al., 2015). The authors suggest that physical therapy effects were potentiated by anodal stimulation of the affected cortex through improved functional activation of the neural systems involved in static balance. It can be concluded therefore that specific symptoms of cerebral palsy might be reduced when physical therapies are reinforced by neuromodulation of the involved cortical networks (Lazzari et al., 2015).

For tDCS and dystonia in children, in contrast, no significant improvement was observed after 5 days of primary motor cortex anodal or cathodal tDCS, at 2 mA for 9 min, as compared to sham stimulation, in children with mean age of 15.3 ± 4.2 (Bhanpuri et al., 2015). However, decreased motor overflow in children with dystonia has been described in two different studies (in children with 13.1 and 12.64 mean age, respectively) under similar real vs. sham stimulation parameters, but after two sessions of 1 mA tDCS separated by 20 min performed on a single day (Young et al., 2013, 2014). It can be argued that two 1 mA tDCS sessions with 20-min break might have induced late phase plasticity (Monte-Silva et al., 2010) and thus be more effective than one-time daily application (Monte-Silva

Table 1: tDCS protocols and results of relevant studies conducted in children and adolescents.

Electrode Positions and polarity	Electrode size	tDCS intensity	Duration of stimulation	Measures	Findings	Adverse effects	References
Right M1 anodal tDCS Left M1 cathodal tDCS Left M1 cathodal tDCS Sham tDCS Three consecutive days	25 cm^2 electrode size	1 mA 1 mA 2 mA	For the duration of tasks	PPT, JTT, and SRTT in healthy school-aged children	Motor improvement of the left hand after 1 mA contralateral anodal tDCS, and 1–2 mA ipsilateral cathodal tDCS	Stimulation was well tolerated and safe, with no adverse effects	Ciechanski and Kirton, in press
Cerebellar anodal tDCS combined with treadmill training	5×5 cm^2 electrode size	1 mA	20 min	Static balance, Pediatric Balance Scale, and Pediatric Evaluation of Disability Inventory in children with ataxic cerebral palsy and balance deficit	Significant improvements of static balance	No moderate or severe side effects were reported. Four children reported tingling during anodal tDCS, and three during sham tDCS	Grecco et al., in press
Anodal/cathodal/sham C3 or C4 (the other electrode over the contralateral forehead) Five consecutive days	4×7 cm^2 electrode size	2 mA	9 min	Barry-Albright Dystonia Scale in children with childhood dystonia	Anodal stimulation worsened symptoms	Tingling sensations at the start of anodal and sham stimulation. Mild headaches after anodal stimulation in one patient	Bhanpuri et al., 2015
Cathodal/sham over the seizure focus. Anode on the contralateral shoulder Single session	35 cm^2 electrode size	1 mA	20 min	EEG and Quality of Life Questionnaire in children with focal epilepsy	Reduction of epileptic discharge frequency immediately and 24 and 48 h after cathodal tDCS	Patients tolerated tDCS well, with no serious adverse effects	Auvichayapat et al., 2013
Anode over the left DLPFC and cathode over the right shoulder vs. sham left DLPFC Five consecutive days	35 cm^2 electrode size	1 mA	20 min	CARS, ATEC, and CGAS in children with autism	Increases in CGAS and decreased ATEC scores	No adverse effects in the active or sham groups were reported	Amatachaya et al., 2014
Anode over the left DLPFC and cathode over the contralateral shoulder vs. sham left DLPFC Two single sessions separated 1 week	35 cm^2 electrode size	1 mA	20 min	PAF measures from EEG, and ATEC, in children with autism	Increased PAF, and improvements in the social and health/behavior domains of ATEC	No serious adverse effects were found. Transient erythematous rash (less than 10 min) was reported in three participants with active tDCS	Amatachaya et al., 2015
Anode over the left DLPFC and cathode over the right DLPFC (case report) 28 consecutive daily sessions	5×5 cm^2 electrode size	1 mA	20 min	Kanner Catatonia Rating Scale before and after tDCS in an adolescent with autism and drug-resistant catatonia	Reductions of catatonic symptom scores	Adverse effects were not recorded in this case report	Costanzo et al., 2015

Table 1 (continued)

Electrode Positions and polarity	Electrode size	tDCS intensity	Duration of stimulation	Measures	Findings	Adverse effects	References
Left anodal/right cathodal parieto-temporal tDCS vs. sham tDCS, combined with reading training Three sessions a week for 6 weeks	5× 5 cm^2 electrode size	1 mA	20 min	Reading tasks: text, high- and low-frequency words and nonwords, in children and adolescents with dyslexia	Reduced low-frequency word reading errors and nonword reading time stable for 1 month	No adverse effects were reported	Costanzo et al., 2016a
Left anodal/right cathodal parieto-temporal tDCS or right anodal/left cathodal parieto-temporal tDCS vs. sham tDCS Single session	5× 5 cm^2 electrode size	1 mA	20 min	Reading tasks: word, nonword, and text reading; lexical decision; phonemic blending; verbal working memory; rapid automatized naming, in children and adolescents with dyslexia	Reduction of text reading errors with left anodal/right cathodal montage, and increased errors after left cathodal/right anodal montage	No adverse effects	Costanzo et al., 2016b
Slow oscillatory tDCS: anode over the left and right DLPFC (bilaterally), cathode over ipsilateral mastoids, or sham stimulation (crossover design) in the first or in the second sleep session	13 mm outer diameter; 8 mm inner diameter: 0.503 cm^2 area	Oscillating current at a frequency of 0.75 Hz	In the non-REM sleep stage 2, five intervals of 5 min each separated by 1-min intervals	Visuomotor go/no-go task for behavioral inhibition in children with ADHD	Slowed reaction times after stimulation	None of the participants reported any side effects during or after stimulation	Munz et al., 2015
Anode over the left DLPFC and cathode over the right supraorbital area Five consecutive sessions	7× 5 cm^2 (35 cm^2) electrode size	2 mA	30 min	Visual Attention Test and a Inhibitory Control Test before and after stimulation in children with ADHD	Improved scores in neuropsychological tests (Visual Attention Test and Inhibitory Control subtests)	Mild adverse effects (headache, neck pain, tingling, itching, burning sensation, local redness, sleepiness)	Bandeira et al., 2016
Anodes over the left and right DLPFC (bilaterally) or cathodes over the left and right STG (T3) vs. sham tDCS. Reference electrode over the non-dominant forearm 10 sessions (2 weeks)	25 cm^2 electrode size	2 mA	20 min	Side effects of tDCS vs. sham stimulation in children with childhood-onset schizophrenia	No significant adverse effects except tingling (37%) and itching (50%) after real stimulation (no reports for sham). Three participants reported fatigue after real tDCS.		Mattai et al., 2011

JTT, Jebsen-Taylor Test; SRTT, Serial Reaction Time Task; DLPFC, dorsolateral prefrontal cortex; CARS, Childhood Autism Rating Scale; ATEC, Autism Treatment Evaluation Checklist, CGAS, Children's Global Assessment Scale; ATEC, Autism treatment evaluation checklist; PAF, peak alpha frequency; STG, superior temporal gyrus.

et al., 2013). Moreover, presumably the stimulation protocols were not optimally suited to treat symptoms. It has recently been shown in adults with hand dystonia that only bilateral stimulation (with the cathode placed over the affected and the anode over the contralateral motor cortex), combined with motor training, resulted in relevant reduction of dystonic symptoms (Furuya et al., 2014). In general, the findings of these studies suggest that anodal tDCS, both over motor cortex and cerebellum, combined with motor therapies might increase the efficacy of these interventions in certain conditions. However, for dystonia, further investigations seem to be necessary to determine the most effective tDCS protocol.

Epilepsy

Epilepsy is a neurological disorder characterized by abnormal EEG activity, often of unknown origin, and symptoms such as myoclonus, seizures, and, in severe cases, momentary loss of consciousness. Because cathodal tDCS has the potential to reduce cortical excitability, it could be a useful tool to diminish cortical hyperexcitability in children with refractory focal epilepsy. Studies in animal models indeed have reported that direct current stimulation has anticonvulsant effects (Liebetanz et al., 2006) and suppresses epileptiform activity (San-Juan et al., 2015). In accordance, pilot studies in adults have shown significant reductions of seizures by tDCS (Fregni et al., 2006; San-Juan et al., 2015). In children, this rationale has been explored in a sham-controlled study using a single session of cathodal tDCS at 1 mA for 20 min (the cathode positioned over the seizure focus and the anode over the contralateral shoulder). The study involved 36 children aged between 6 and 15 years (Auvichayapat et al., 2013). tDCS resulted in significant reduction of epileptic EEG activity (reduction of epileptic discharge frequency) for 2 days, with no adverse effects noted. In a case study (Yook et al., 2011), an 11-year-old girl with focal cortical dysplasia and an average of eight attacks per month was treated with tDCS (2 mA, 20 min) 5 days a week for 2 weeks. The cathode was positioned over the cortical region where the abnormal EEG was recorded and the anode over the contralateral supraorbital region. After treatment, the frequency and the duration of seizure attacks were decreased for 2 months. When this treatment was repeated for another 2 weeks, only one seizure was recorded during a period of 2 months (Yook et al., 2011). No significant side effects were reported also in this study. Seizure frequency and epileptic activity were also reduced in children with Lennox-Gastout syndrome (a severe drug-resistant pediatric form of epilepsy with multiple seizure types and drop attacks) in a pilot study, in which cathodal tDCS (2 mA, 20 min) was applied over the primary motor cortex for five consecutive days in children between 6 and 15 years old (Auvichayapat et al., 2016). Because tDCS studies in children with epilepsy are scarce, future investigations are necessary to confirm these results and determine the potential of tDCS to control epileptiform activity in childhood epilepsy. Still, reduction of cortical excitability by cathodal stimulation applied over the cortical focus seems to be a well suited and safe approach for treatment of pediatric epilepsy.

Autism

Autism is a developmental disorder that actually includes multiple clinical forms that are grouped into the broader concept of autism spectrum disorders (ASDs). The most frequent characteristics of autism are ritualistic and repetitive behaviors, anhedonia, deteriorating social relations, and interactive communication deficits. Neuroanatomical and functional studies point to an alteration of synaptic maturation and cortical connectivity during early neurodevelopment, leading to a thinner cortical gray matter and alterations of frontal lobe connections, which may explain the different clinical manifestations (Courchesne and Pierce, 2005). From a theoretical point of view, noninvasive brain stimulation could be a useful way to modulate possible cortical mechanisms of this disorder and its functional effects (Schneider and Hopp, 2011). In children aged between 5 and 8 years, specific improvements in the scores of the Autism Treatment Evaluation Checklist and Children's Global Assessment Scale, but not in the Childhood Autism Rating Scale, were described after five consecutive sessions of anodal tDCS applied over the left dorsolateral prefrontal cortex (1 mA for 20 min), with the cathode placed on the right contralateral shoulder, when compared to sham stimulation (Amatachaya et al., 2014). Prefrontal stimulation was conducted to modulate language and cognitive functions, in which the prefrontal cortex is involved (Schneider and Hopp, 2011). With the same stimulation protocol, but applied in two single sessions of anodal tDCS separated by 1 week, improvements in the social scale and health and behavioral problems scale of the Autism Treatment Evaluation Checklist (but not in the language scale nor the sensory and cognitive awareness scale) and peak alpha EEG power have been described in children with the same age range (Amatachaya et al., 2015). In a case study (Costanzo et al., 2015), an adolescent girl (14 years old) with autism and comorbid catatonia was treated by 28 daily tDCS sessions

(each week from Monday to Friday), in association with the patient's usual medication (20 mg/day of promazine, 400 mg/day of quetiapine, and 600 mg/day of carbolithium). The anode was placed over the left dorsolateral prefrontal cortex and the cathode over the right (1 mA for 20 min). This treatment protocol resulted in a 30% reduction of catatonic symptoms for 1 month after the end of treatment (Costanzo et al., 2015). Although further studies are needed, these findings point to the prefrontal cortex as a target for neuromodulation via tDCS, resulting in a noninvasive brain stimulation method with potential to modulate alterations in frontal lobe and its connectivity and, consequently, to reduce the frontal clinical manifestations of autism.

Dyslexia

Alterations in reading and writing during development (which in clinical settings are named dyslexia) are other of the typical disorders in children. The effects of tDCS on reading abilities of children with dyslexia have been explored in a couple of studies. Because reading and written skills depend on mechanisms involving fronto-parieto-temporal visual, motor, cognitive, and language cortical areas, it is expected that modulation of some of these regions may influence critical language processes in children with deficits in the acquisition of written language and reading (see Vicario and Nitsche, 2013b, for an overview about the possible remediation protocols via tDCS). Anodal tDCS over the left parieto-temporal region (the cathode placed over the right homologue region), at 1 mA current intensity for 20 min, and three sessions a week for 6 weeks combined with reading training, resulted in improved reading of nonwords and low frequency words of children and adolescents with dyslexia, compared to sham stimulation (Costanzo et al., 2016a). The anodal tDCS group included nine participants with age range between 10.9 and 17.1 years (13.2 ± 2.6), and the sham group included nine participants with age range between 10.1 and 16 years (13.6 ± 2.1). In a related study involving children and adolescents with dyslexia and similar age range, this electrode montage was compared with cathodal tDCS over the left parieto-temporal region (the anode placed over the right homologue region) in a single session. Left parieto-temporal anodal tDCS induced a reduction in the number of errors during text reading, and left parieto-temporal cathodal tDCS resulted in increases of errors (Costanzo et al., 2016b). Therefore, tDCS could be an effective tool to modulate reading mechanisms in children with dyslexia, although future studies will have to determine the suitability of tDCS as a therapeutic approach in larger detail.

ADHD and psychiatric disorders

The clinical manifestations of ADHD are heterogeneous. Attention deficit and motor hyperactivity are core symptoms. Neurobiological mechanisms of this disorder are not completely understood. Neurophysiologically, increased absolute power of theta and delta resting state EEG waves as well as a higher theta/beta ratio have been described in male children with ADHD (Markovska-Simoska and Pop-Jordanova, in press). Furthermore, interhemispheric disconnectivity of the frontal lobes has been described (Robbie et al., 2016). tDCS could be a tool to modulate these EEG derivatives of cortical arousal and connectivity via alteration of respective cortical oscillatory activity and thereby improve performance (Cosmo et al., 2015). For cognitive deficits, impaired behavioral inhibition in children with ADHD (10–14 years) was monitored via a go/no-go reaction time task the day after application of slow oscillating (0.75 Hz of frequency) anodal tDCS bilaterally over F3–F4 (reference electrodes placed over the ipsilateral mastoids) during non-REM sleep (Munz et al., 2015). This protocol improved behavioral inhibition (as indicated by increased reaction time). Since no effects were found for intrinsic alertness and motor memory, it was concluded that lateral prefrontal slow oscillatory stimulation during sleep improves the executive functions of children with ADHD via an enhancement of endogenous oscillatory brain activity. As the authors suggest, this modulation of oscillatory activity during sleep might have been a relevant mechanism to regulate sleep-dependent restorative processes related to behavioral inhibition or executive functions (Munz et al., 2015). Another study reported significant improvement of visual attention and inhibitory control after five consecutive once-daily anodal tDCS sessions over the left dorsolateral prefrontal cortex (2 mA for 30 min) in children aged between 6 and 16 years (Bandeira et al., 2016). The results showed that processing speed, detection of stimuli, and the ability to switch from one activity to another were improved by tDCS. Therefore, modulation of the prefrontal cortex excitability by specific tDCS protocols could be a useful approach to regulate frontal symptoms in children with ADHD.

Symptoms of other psychiatric disorders such as depression and schizophrenia in adult populations are also susceptible to neuromodulation. Data on application of tDCS in child and adolescent psychiatry are however scarce (Stagg and Nitsche, 2011; David et al., 2013). In

childhood-onset schizophrenia (a rare version of schizophrenia with onset of psychotic symptoms before the age of 13), 10 sessions of bilateral anodal or cathodal tDCS (2 mA for 20 min) over the dorsolateral prefrontal cortex and superior temporal gyrus, respectively, induced no clinically significant alterations of mood, arousal, cognitive, and verbal performance in children between 10 and 17 years old (Mattai et al., 2011). The results of this study do also not show significant changes in autonomous functions, nor general adverse effects. tDCS effects on psychotic symptoms were not reported in this study dedicated to tDCS tolerability.

Exploration of the therapeutic impact of tDCS for the treatment of affective disorders might be a promising approach in pediatrics because relatively consistent results have been obtained in adults (Kuo et al., 2014). A key issue for application in children and adolescents might be adaption of stimulation protocols to physiological, pharmacological, and structural specifics of this age group, which has not been done systematically so far. Furthermore, most of the studies conducted so far are small pilot experiments, which often obtain surrogate markers of clinical symptoms for monitoring effects of the intervention. Future controlled trials with large samples may help to elucidate the potential of tDCS for the treatment of psychiatric disorders in pediatrics, as well as determine the safety and tolerability of this method in children and adolescents. The effects of tDCS in developmental disorders in children have been reviewed recently (Muszkat et al., 2016), and respective preliminary data suggest that this technique is well tolerated and not associated with significant adverse effects in this population.

Discussion

Clinical studies in children about the therapeutic effects of tDCS are, in general, not as conclusive as in adults. Studies suggest a significant effect of tDCS on several disorders, although due to the heterogeneity of protocols, results should be evaluated with caution. Different electrode montages have been chosen in respective studies depending on the specific disorder. For example, significant improvements of motor responses have been reported after anodal and also cathodal tDCS applied over the motor cortex. Reductions of epileptic discharges have been reported after cathodal tDCS over the epileptogenic region, as well as language improvements after anodal tDCS over the left hemisphere. Different electrode sizes and intensities of stimulation have also been evaluated; 25 cm^2 and 35 cm^2 are the most common electrode sizes reported, and 1 and 2 mA, the usual tDCS intensity. Protocols do also differ regarding the duration of stimulation (from 9 min to 30 min, although 20 min stimulation duration seems to be the most often applied stimulation duration) and number of sessions (from a single session to 2, 3, 5, 10, 18, or 28 sessions). These protocol variations should be considered when comparing results from different clinical studies in children. Nevertheless, current data suggest that tDCS is a promising noninvasive brain stimulation tool with potential to improve brain functions not only in adults but also in the pediatric population. Pilot studies have shown effects in the treatment of some pediatrics pathologies such as cerebral palsy, epilepsy, ASD, child development disorders, and ADHD. Because of limitations of the preliminary studies in this field (small-scale studies, heterogeneous and surrogate parameters and measures), further optimization studies in larger clinical populations are necessary to confirm the potential role of tDCS in pediatric treatment approaches.

For the safety and tolerability of tDCS in children, aspects of brain development involving anatomical and physiological differences during childhood as compared to the adult brain and head require strict control and caution when applying noninvasive brain stimulation. Although tDCS could be used to modulate pathological cortical states both in adults and children, special precautions are necessary in childhood because the medium- and long-term consequences of the plastic changes induced by tDCS in the developing brain are not well known. From investigations in which safety and tolerability of tDCS have been specifically explored, data indicate that the currently applied protocols are safe and well tolerated (Andrade et al., 2014; Ekici, 2015; Krishnan et al., 2015; Bikson et al., 2016) when exclusion criteria are taken into account. Studies about the use of tDCS in children report no serious adverse effects (see Table 1). However, a tDCS-associated seizure was reported in a 4-year-old boy suffering from epilepsy when he was treated with tDCS to reduce spasticity and improve motor functions in cerebral palsy (Ekici, 2015). Besides the effect of tDCS, reduced antiepileptic medication at that time and possible interactions with proserotonergic medication was considered as possible causes of this seizure, which makes a causal contribution of tDCS debatable. However, this adverse event underscores the relevance of exclusion criteria for noninvasive brain stimulation, which include the presence of epilepsy, if the intervention is not specifically performed to treat this disease.

In addition to the safety criteria for the use of tDCS in children, ethical considerations for the pediatric

population are another important issue concerning the use of tDCS that have to be faced (Reiner, 2013). Guidelines for the ethical use of medication for neuroenhancement in pediatrics are available (Rothman, 2013), but not for clinical approaches such as neuromodulation in respective patients by stimulation approaches. Suitable stimulation protocols for specific disorders and knowledge about possible interactions between tDCS and pediatric medication are also key targets to be analyzed in the future. Knowledge about optimal utilities of non-invasive brain stimulation tools for pediatric use is an important objective for clinical research that may provide new therapeutic approaches to support health in childhood, once safety profiles are well identified in this population.

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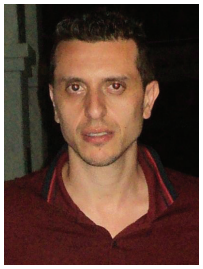

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