

EFFECT OF TRANSCRANIAL DIRECT STIMULATION ON COGNITION IN CHILDREN WITH ATTENTION DEFICIT HYPERACTIVE DISORDER: SYSTEMATIC REVIEW

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Absract

Background: The use of Transcranial Direct Current stimulation (tDCS) in cognition improvement in children with attention deficit hyperactivity disorder is new, and thus the scientific evidence for its effectiveness needs to be evaluated through a systematic review.

Objective: To provide updated evidence-based guidance for tDCS effects on cognition in children with attention deficit hyperactivity disorder. **Data synthesis:** Six studies included 133 participants in total. Best evidence synthesis was applied to summarize the outcomes, which were memory performance, intrinsic alertness, performing time and commission errors.

Conclusion: the available data demonstrated the efficacy of tDCS as a new modality on cognition in children with attention deficit hyperactivity disorder has an immediate and short term effect on improving cognition .Further studies are still needed, especially those involving both neurophysiological and functional evaluations and to cover further domain on attention deficit hyperactivity disorder.

Keywords:

transcranial direct current stimulation, tDCS, cognition, attention deficit hyperactivity disorder, ADHD, children and adolescents.

Introduction:

Attention deficit hyperactivity disorder (ADHD) is a childhood onset psychiatric disorder which is characterized by developmentally inappropriate levels of inattention, impulsivity and hyperactivity (DSM-IV). In ADHD cognitive control, the ability to control sensory processes and actions in a goal-directed manner (Bunge et al., 2002)[1] is severely compromised, affecting motor, emotional and cognitive domains (Wodka et al., 2007) [2]. ADHD patients are particularly impaired in different aspects of inhibition control, namely interference control, the suppression of task irrelevant, competing stimuli and response inhibition, the suppression of a prepotent response. Interference control has been effectively investigated using the Flanker task (Eriksen and Eriksen, 1974)[3] and the Simon task (Simon, 1990) [4], which has been shown to provide a reliable measurement of this cognitive ability (Wöstmann et al., 2013) [5]. In both tasks participants have to indicate the category of a target stimulus by a right or a left button press. In the Flanker task, the target is surrounded by distracting stimuli which must be ignored in order to give the right response. In the Simon task, the target stimulus is presented either on the left or on the right side. In this case, the position must be ignored to give the right response.

So far, ADHD patients have shown higher error rates and slower reaction times compared to healthy controls (Mullane et al., 2009).[6]

Successful interference control has been associated with the integrity of the right inferior frontal gyrus (rIFG) (Luks et al., 2010[7]; Zhu et al., 2010[8]). In children and adolescents with ADHD various studies have revealed structural (Sowell et al., 2003 [9]; Durston et al., 2004) [10] as well as functional alterations (Aron and Poldrack, 2005) [11] in the rIFG. For example during a Simon task, unmedicated ADHD patients showed less activity in the rIFG compared to healthy controls (Rubia et al., 2011) [12] whereas ADHD patients medicated with methylphenidate did not differ from healthy controls (Lee et al., 2010) [13]. Thus, increasing activity of the rIFG seems to facilitate interference control. Transcranial direct current stimulation (tDCS) is a non-invasive tool for modulating cortical excitability. To conduct tDCS a weak current is passing through the scalp mostly via two conductive rubber electrodes in sponges soaked in saline solution or covered with conductive gel. The modulation of cortical excitability depends on the polarity of electrodes. In general, the positively charged anode increases cortical excitability while the negatively charged cathode decreases it (Nitsche and Paulus, 2000) [14]. This modulation is due to a modification of the resting membrane potential in regions of current flow (Stagg and Nitsche, 2011) [15]. TDCS when applied for 30 min induces prolonged effects after the end of stimulation (Nitsche and Paulus, 2001) [16]. Studies showed tDCS induced improvements of symptom severity already in different psychiatric and neurologic disorders, for example depression (Kalu et al., 2012) [17], schizophrenia (Brunelin et al., 2012) [18], stroke (Chang et al., 2015) [19] and dyslexia (Heth and Lavidor, 2015) [20]. Castellanos and Proal (2012) suggested that tDCS may also be of therapeutic use for ADHD, especially due to its beneficial effect on larger scale networks (Keeser et al., 2011) [21]. The development of non-pharmaceutical treatment approaches is particularly relevant in ADHD, since even though many patients benefit from medical treatment, a substantial number report remarkable side effects and parents as well as children and adolescents often wish for alternative treatment strategies (Halperin and Healey, 2011) [22]. Effects of stimulant treatment persist only for the time of active medication (Chronis et al., 2003) [23], whereas beneficial effects of repetitive tDCS have been reported to last for several month (Cohen Kadosh et al., 2010) [24]. Even though tDCS has been predominantly employed in adults, studies in children and adolescents have confirmed that this method is also well tolerated and save in younger age groups (Mattai et al., 2011[25]; Andrade et al., 2014[26]; Moliadze et al., 2014[27]; Krishnan et al., 2015) [28].

Studies testing modulatory effects of tDCS in ADHD are, however, sparse. Using oscillatory tDCS during slow wave sleep, Prehn-Kristensen et al. (2014) [29] demonstrated an improvement of declarative memory performance on the next day as well as improved reaction times in a go/nogo task in children with ADHD (Munz et al., 2015) [30].

Purpose:

The purpose of this study is to systematically review the clinical effectiveness of transcranial direct current stimulation on cognition in children and adolescents with attention deficit hyperactivity disorder.

Methods:

Search strategy:

This study included studies that examine the effect of transcranial direct stimulation current on cognition in children and adolescents with attention deficit hyperactivity disorder. Literature search was performed independently by the three authors using an inclusive electronic literature search of Cochrane library, Pubmed, Physiotherapy Evidence Database (Pedro) Web of Science, Google scholar databases from their earliest records to February 2019, using a number of key words: Transcranial Direct Stimulation current, attention deficit hyperactivity disorder, cognition, children, adolescents. These key words were used individually and/or were combined. All references from the selected articles were also cross-checked by the authors to identify relevant studies that may have been missed in the search.

Study selection:

Before the beginning of the study selection procedures, duplicated searches were excluded by two authors. independently reviewed the studies for eligibility based on title and abstract. Studies deemed potentially eligible by at least one author then the full text versions were retrieved and independently screened by two authors to determine whether they met inclusion criteria. Disagreement between the two authors in any stage was resolved by discussion until consensus was reached or, where necessary, the third author made the final decision.

Eligibility criteria:

The inclusion criteria for studies to be included in this systematic review were as follows: participants in the study were children and adolescents who had ADHD and were aged between 7.2 and 17 years old; the outcome measures used in the study were related to cognition, such as memory performance, alertness, performing time in addition to behavior and selective attention; and the study was written in English. Studies were excluded if the participants had oppositional defiant disorder, conduct disorder, any psychiatric abnormalities, average intelligence quotient (IQ < 85), profound memory impairment or self-reported sleep-disturbances; if the study not published as a full text article.

Data-extraction and management:

Data were extracted by one author and checked by an other one through a self-made extraction form. Disagreements between the two reviewers were resolved by discussion until consensus was reached. Key details of each study were extracted using the specific data extraction format. The format includes: research design, participants, eligibility criteria, intervention, outcomes of interest and results of each study.

Assessment of methodological quality:

Two reviewers independently assessed the methodological quality of the included studies, according to the Physiotherapy Evidence Data base (PEDro) scale Appendix (1). The PEDro scale is a valid measure of the methodological quality of clinical trials and is based on the Delphi list developed by Verhagen et al [31]. The scale is used to rate studies from 0–11 according to following 11 methodological criteria: specified eligibility criteria, random allocation, concealed allocation, baseline comparability, blinded subjects, blinded therapists,

blinded assessors, adequate follow-up, intention-to-treat analysis, between group comparisons, and point estimates and variability. Each item was scored as 1 (yes) or 0 (no). The studies were ranked as 'high quality' if their score is 7, studies with a score of 5 or 6 were considered of 'moderate quality' and those with a score of 4 or less were deemed of 'poor quality' [32, 33]. PEDro scores were not used as inclusion/exclusion criteria, but rather as a basis for data-analysis and to discuss the strengths and weaknesses of studies.

Data collection and analysis:

We used the standard methods of the Cochrane Collaboration. Two review authors searched for and considered trials for inclusion, evaluated methodological quality and extracted data independently. Differences in interpretation were resolved by discussion with the third review author.

Quality assessment:

We conducted quality assessment according to the methods described in section six of the Cochrane Handbook for Systematic Reviews of Interventions (Handbook 2007). We considered four major sources of potential bias and methods of avoidance when assessing the trial quality:

- (1) selection bias - blinding of randomization;
- (2) performance bias - blinding of intervention;
- (3) attrition bias - complete follow-up;
- (4) detection bias - blinding of outcome assessment.

A quality rating was assigned to each trial for the criterion of blinding of randomization as follows: (A) adequate, (B) unclear, (C) inadequate, or (D) not used. A quality rating of (A) yes, (B) can't tell, or (C) no, was assigned to the other quality components (completeness of follow-up and blinding of outcome assessment). High quality trials were defined as those receiving an A rating for blinding of randomization (central computerized randomization service or sealed opaque envelopes). The quality assessment rating included in the Table of 'Characteristics of Included Studies' refers to blinding of randomization (allocation concealment) only.

Data synthesis and analysis:

Descriptive analysis was used to represent the extracted data from the selected studies.

RESULTS

Flow of studies through the review:

The literature search identified a total of 2400 potentially relevant articles. After the removal of duplicates (n= 168), rejection based on title and abstract (n=1247), and inclusion and exclusion criteria (n=6). were included for the quality assessment and best evidence synthesis.

Types of participants

A total of 140 children were randomized in the six included trials investigating ADHD. Participant recruitment and inclusion criteria varied between the five trials; Alexander 2014 [34] included 24 participants aged from 10 to 14 years old, Manuel 2015 [35] recruited 14 participants with age from 11 to 13.7 years old, Vahid 2017 [36] included 25 participants aged from 7.2 to 12.3 years old, Carolin 2016 [37] included 42 participants aged from 13 to 17 years old. The primary diagnosis for enrolled participants is attention deficit hyperactivity disorder. Alexander 2014 [38] and Manuel 2015 [39]; participants met the diagnostic criteria for ADHD according to DSM-IV-TR. in Vahid 2017 [40]; diagnosed with ADHD according to the diagnostic and statistical manual of mental disorders. Carolin 2016 [41]; met the diagnostic criteria for ADHD according to DSM-IV.

Types of interventions

The type of interventions is the same in all the studies; tDSC. There are just little different in procedure, time, duration and intensity. two studies (Alexander 2014) and (Manuel 2015) were applied during sleep.

Types of outcome measures

Some studies have the same type of outcome measures; (Vahid, 2017) and (Sotnikova 2017) used Go/No-go task to measure the effect tDCS on memory performance. To measure inhibitory control and response inhibition; (Vahid 2017) used N-Back test and WCST. Moreover, (Carolin 2016) used Flanker Task to measure interference control.

Discussion

Transcranial direct current stimulation is probably beneficial for improving cognition in children and adolescents with attention deficit hyperactivity disorder. The main objective of this review was to critically evaluate articles that demonstrate this assumption. Combining all outcome measures of all studies, transcranial direct current stimulation intervention generally demonstrated strong effects in improving cognitive abilities in children and adolescents with attention deficit hyperactivity disorder, in addition to reduction of clinical symptoms of ADHD;

inattention, hyperactivity and impulsivity. It helps in improvement of working memory, intrinsic alertness, inhibitory control and interference control.

AUTHORS' CONCLUSIONS

Implications for practice

The results of this review provide sufficient evidence to guide clinical practice on the use of tDCS in children and adolescents with ADHD symptoms.

Although concern for the safety of tDCS in children and adolescents has been reported, possible adverse effects of tDCS could be evaluated.

Available data from seven reviewed studies demonstrated the efficacy of transcranial direct current stimulation as a new modality in improving cognition and clinical symptoms in children and adolescents with ADHD with immediate and short term effect.

Implications for research

Further RCTs are required to assess long lasting effect of tDCS in improving cognition and reducing clinical symptoms in children with ADHD. Further trials are required to know and assess the exact washout period to be available to researchers that want to do accumulating studies. Costs also need to be considered.

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Alexander 2014

Methods	Blinding of randomisation - yes Blinding of intervention - yes Blinding of outcome measure - unclear Complete follow-up – yes
Participants	24 children; 12 normal, 12 with ADHD Main diagnosis: ADHD Age: 9-14 years old Conducted in: sleep laboratory (children with ADHD), at home (normal children)
Interventions	A double-blind crossover study with two groups: Study group and control group (sham stimulation). Each of the two techniques are performed during sleep.

outcomes	Memory performance
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Manuel 2015

Methods	Blinding of randomisation - yes Blinding of intervention - yes Blinding of outcome measure - yes Complete follow-up - yes
Participants	14 children with ADHD Main diagnosis: ADHD Age: 10-14 years Conducted in a sleep lab
intervention	A randomized double-blind cross-over with one study group: Transcranial direct current stimulation Sham stimulation Each of them were performed during non-rapid eye movement sleep
outcomes	Reaction time Motor memory Alertness Behavioral inhibition Sleep parameters

Vahid 2017

methods	Blinding of randomisation - unclear Blinding of intervention - yes Blinding of outcome measure - unclear Complete follow-up – yes
participants	25 children Main diagnosis: ADHD Age: 7.2-12.3 years Conducted in: not mentioned
intervention	A randomized double-blind sham controlled cross-over study of two

	groups: Anodal, cathodal and sham tDCS Cathodal, anodal and sham tDCS
outcomes	Inhibitory control Response inhibition Working memory performance Cognitive flexibility Planning Task-switching abilities

Breitling 2016

methods	Blinding of randomisation - no Blinding of intervention - no Blinding of outcome measure - no Complete follow-up – yes
participants	46 male; 21 normal, 21 with ADHD Main diagnosis: ADHD Age: 13-17 years Conducted in: not mentioed
intervention	A randomized control trial with two groups (study and control): Anodal, cathodal and sham tDCS Each participant in both groups received all of them separated by at least one week.
Outcomes	Interference control

Sotnikova 2017

Methods	Blinding of randomisation - unclear Blinding of intervention - yes Blinding of outcome measure - yes Complete follow-up – yes
Participants	16 adolescents (13 boys, 3 girls)

	Main diagnosis: ADHD Age: 12-16 years Conducted in: not mentioned
Intervention	A double-blind sham-controlled study with two groups First group: was firstly treated with tDCS and then with sham stimulation Second group: received treatment in the reverse order The time between both stimulation sessions was at least 2 weeks.
Outcomes	Working memory Behavioral changes: Reaction time Reaction time variability Omission errors Accuracy False alarms

Cornelia 2017

Methods	Blinding of randomisation - unclear Blinding of intervention - yes Blinding of outcome measure - yes Complete follow-up – yes
Participants	15 adolescents (12 male, 3 female) Main diagnosis: ADHD Age: 12-16 years Conducted in: the Department of Child and Adolescent Psychiatry, Psychosomatic and Psychotherapy of the Philips-University in Marburg, Germany.
Intervention	A randomized double-blinded sham-controlled crossover study with One group; received both anodal tDCS as well as sham stimulation on five consecutive days with a washout period of 2 weeks.
Outcomes	Changes of the parents' version of a German adaptive ADHD Diagnostic Checklist, FBB-ADHD from baseline to 7 days after the end of stimulation. Working memory performance

Characteristics of excluded studies [ordered by study ID]

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study	Reason for exclusion
Cosmo Camila, 2015	Participants didn't match the included age

1-Bunge, S. A., Dudukovic, N. M., Thomason, M. E., Vaidya, C. J., and Gabrieli, J. D. (2002). Immature frontal lobe contributions to cognitive control in children: evidence from fMRI. *Neuron* 33, 301-311. doi: 10.1016/S0896-6273(01)00583-9.

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- 12-Rubia, K., Halari, R., Cubillo, A., Smith, A. B., Mohammad, A. M., Brammer, M., et al. (2011). Methylphenidate normalizes fronto-striatal underactivation during interference inhibition in medication-naive boys with attention-deficit hyperactivity disorder. *Neuropsychopharmacology* 36, 1575–1586. doi: 10.1038/npp.2011.30.
- 13-Lee, Y. S., Han, D. H., Lee, J. H., and Choi, T. Y. (2010). The effects of methylphenidate on neural substrates associated with interference suppression in children with ADHD: a preliminary study using event related fMRI. *Psychiatry Investig.* 7, 49–54. doi: 10.4306/pi.2010.7.1.49.
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